LBA4001 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Lapatinib in combination with capecitabine plus oxaliplatin (CapeOx) in HER2 positive advanced or metastatic gastric (A/MGC), esophageal (EAC), or gastroesophageal (GEJ) adenocarcinoma: The LOGiC trial.

J. Randolph Hecht, Yung-Jue Bang, Shukui Qin, Hyun-Chul Chung, Jian-Ming Xu, Joon Oh Park, Krzysztof Jeziorski, Yaroslav Shparyk, Paulo M. Hoff, Alberto F. Sobrero, Pamela Salman, Jin Li, Svetlana Protsenko, Marc E. Buyse, Karen Afenjar, Tomomi Kaneko, Allison Kemner, Sergio Santillana, Michael F. Press, Dennis J. Slamon; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Seoul National University Hospital, Seoul, South Korea; Nanjing Yanggongjing Hospital, Nanjing, China; Yonsei University College of Medicine Severance Hospital, Yonsei, South Korea; Cancer Center, 307 Hospital, Academy of Military Medical Science, Beijing, China; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Instytut im. Marii Sklodowskiej-Curie, Warsaw, Poland; Lviv State Oncology Regional Treatment and Diagnostic Centre, Lviv, Ukraine; Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil; Azienda Ospedaliera Universitaria San Martino, Genova, Italy; Fundación Arturo López Pérez, Santiago, Chile; Fudan University Shanghai Cancer Center, Shanghai, China; N. N. Petrov Research Institute of Oncology, St. Petersburg, Russia; International Drug Development Institute, Louvain la Neuve, Belgium; Cancer International Research Group, Paris, France; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Collegeville, PA, United Kingdom; GlaxoSmithKline, Rio de Janeiro, Brazil; USC Norris Comprehensive Cancer Center, Los Angeles, CA; University of California, Los Angeles, School of Medicine/Translational Oncology Research Laboratory, Los Angeles, CA

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LBA4002 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

SAMIT: A phase III randomized clinical trial of adjuvant paclitaxel followed by oral fluorinated pyrimidines for locally advanced gastric cancer.

Kazuhiro Yoshida, Akira Tsuburaya, Michiya Kobayashi, Shigefumi Yoshino, Masazumi Takahashi, Nobuhiro Takiguchi, Kazuaki Tanabe, Naoto Takahashi, Hiroshi Imamura, Naokuni Tatsumoto, Akinori Hara, Kazuhiro Nishikawa, Ryoji Fukushima, Akira Kurita, Hiroshi Kojima, Yumi Miyashita, Koji Oba, Marc E. Buyse, Satoshi Morita, Junichi Sakamoto; Department of Surgical Oncology, Gifu University School of Medicine, Gifu, Japan; Kanagawa Cancer Center, Yokohama, Japan; Kochi Medical School, Nankoku, Japan; Yamaguchi University Graduate School of Medcine, Ube, Japan; Yokohama Municipal Citizen's Hospital, Yokohama, Japan; Chiba Cancer Center, Chiba, Japan; Hiroshima University, Hiroshima, Japan; The Jikei University Hospital, Minato, Japan; Sakai City Hospital, Sakai, Japan; Miyoshi Central Hospital, Miyoshi, Japan; Saiseikai Suita hospital, Suita, Japan; Osaka General Medical Center, Osaka, Japan; Teikyo University, Itabashi, Japan; Shikoku Cancer Center, Matsuyama, Japan; Aichi Cancer Center Hospital, Okazaki, Japan; NPO Epidemiological and Clinical Research Information Network, Okazaki, Japan; Hokkaido University, Sapporo, Japan; International Drug Development Institute, Louvain la Neuve, Belgium; Yokohama City University Medical Center, Yokohama, Japan; Tokai Central Hospital, Kagamihara, Japan

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LBA4003 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study.

Pascal Hammel, Florence Huguet, Jean-Luc Van Laethem, David Goldstein, Bengt Glimelius, Pascal Artru, Ivan Borbath, Olivier Bouche, Jenny Shannon, Thierry André, Laurent Mineur, Benoist Chibaudel, Franck Bonnetain, Christophe Louvet; Hôpital Beaujon, Clichy, France; Hopital Tenon, Paris, France; Hôpital Universitaire Erasme, Brussels, Belgium; Prince of Wales Hospital, Sydney, Australia; Akademiska University Hospital, Uppsala, Sweden; Hôpital Privé Jean Mermoz, Lyon, France; Cliniques Universitaires Saint-Luc, Brussels, Belgium; Centre Hospitalier Universitaire Robert Debré, Reims, France; Nepean Cancer Care Centre, Kingswood, Australia; Hôpital Saint Antoine, Paris, France; Institut Sainte Catherine, Avignon, France; GERCOR, Paris, France; Centre Hospitalier Universitaire, Besançon, Besançon, France; Department of Oncology, Institut Mutualiste Montsouris, Paris, France

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LBA4004 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

A phase III randomized trial of chemoimmunotherapy comprising gemcitabine and capecitabine with or without telomerase vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer.

Gary William Middleton, Juan W. Valle, Jonathan Wadsley, David Propper, Fareeda Y. Coxon, Paul J. Ross, Srinivasan Madhusudan, Tom Roques, David Cunningham, Philippa Corrie, William Greenhalf, Victoria Shaw, Trevor F. Cox, Paul Silcocks, Gemma Nanson, John P. Neoptolemos; University of Birmingham, Birmingham, United Kingdom; The Christie Hospital NHS Foundation Trust; European (ENETS) Centre of Excellence, Manchester, United Kingdom; Department of Clinical Oncology, Weston Park Hospital, Sheffield, United Kingdom; Institute of Cancer, Centre for Medical Oncology, St Bartholomew's Hospital, London, United Kingdom; Northern Centre for Cancer Care, Newcastle Upon Tyne, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; School of Molecular Medical Sciences, Nottingham University Hospitals, Nottingham, United Kingdom; Norfolk and Norwich University Hospital, Norwich, United Kingdom; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Oncology Centre, Addenbrooke's Hospital, Cambridge, United Kingdom; University of Liverpool, Liverpool, United Kingdom; University Of Liverpool, Liverpool, United Kingdom

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4005^ **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Results of a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates.

Daniel D. Von Hoff, Thomas J. Ervin, Francis P. Arena, E. Gabriela Chiorean, Jeffrey R. Infante, Malcolm J. Moore, Thomas E. Seay, Sergei Tjulandin, Wen Wee Ma, Mansoor N. Saleh, Marion Harris, Michele Reni, Ramesh K. Ramanathan, Josep Tabernero, Manuel Hidalgo, Eric Van Cutsem, David Goldstein, Xinyu Wei, Jose Luis Iglesias, Markus Frederic Renschler; Virginia G. Piper Cancer Center Clinical Trials at Scottsdale Healthcare/TGen, Scottsdale, AZ; Florida Cancer Specialists, Englewood, FL; Arena Oncology Associates, Lake Success, NY; University of Washington, Seattle, WA; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Princess Margaret Hospital, Toronto, ON, Canada; Atlanta Cancer Care, Atlanta, GA; N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; Roswell Park Cancer Institute, Buffalo, NY; Georgia Cancer Specialists PC, Atlanta, GA; Southern Health, East Bentleigh, VIC, Australia; Ospedale San Raffaele, Istituto di Ricovero e Cura a Carattere Scientifico, Milan, Italy; Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGen, Scottsdale, AZ; Vall d'Hebron University Hospital, Barcelona, Spain; Centro Integral Oncológico Clara Campal, Madrid, Spain; University Hospitals Leuven, Leuven, Belgium; Prince of Wales Hospital, Sydney, Australia; Celgene Corporation, Summit, NJ; Bionomics Ltd., Thebarton, Australia

Background: *nab*-paclitaxel (*nab*-P; 130 nm albumin-bound paclitaxel) has demonstrated both single-agent activity and synergy with gemcitabine (G) in preclinical models of pancreatic cancer (PC). *nab*-P + G also demonstrated promising efficacy in a phase I/II study in metastatic PC (*J Clin Oncol.* 2011:4548-4554), warranting a phase III study of *nab*-P + G vs G for metastatic PC. **Methods:** 861 patients (pts) with metastatic PC and a Karnofsky performance status (KPS) $\geq$ 70 were randomized at 151 community and academic centers 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^{2}weekly for 7 weeks followed by 1 week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle $\geq$ 2). The primary endpoint was OS; secondary endpoints were PFS and ORR by independent review. **Results:** The median age was 63 years (range 27 - 88). KPS was 100 (16%), 90 (44%), 80 (32%), and 70 (7%). Pts had advanced disease with liver metastases (84%), $\geq$ 3 metastatic sites (46%), and CA19-9 $\geq$ 59 $\times$ ULN (46%). *nab*-P + G was superior to G for all efficacy endpoints: median OS was 8.5 vs. 6.7 mo (HR 0.72; 95% CI, 0.617 - 0.835; $P = 0.000015$); median PFS was 5.5 vs. 3.7 mo (HR 0.69; 95% CI, 0.581 - 0.821; $P = 0.000024$), and ORR was 23% vs. 7% ($P = 1.1 \times 10^{-10}$) by RECIST v1.0. Metabolic response by PET in 257 patients was 63% for *nab*-P + G vs 38% for G ($P = 0.000051$). CA19-9 response ($\geq$ 90% decrease) was 31% for *nab*-P + G vs. 14% for G ($P < 0.0001$). Grade $\geq$ 3 AEs with *nab*-P + G vs. G included neutropenia (38% vs. 27%), fatigue (17 % vs. 7%), diarrhea (6% vs 1%), and febrile neutropenia (3% vs. 1%). Grade $\geq$ 3 peripheral neuropathy (PN) occurred in 17% vs. 1% of pts who received *nab*-P + G vs. G, respectively; for *nab*-P + G, PN improved to grade $\leq$ 1 in a median 29 days, and 44% of patients resumed *nab*-P treatment. The median duration of treatment was 3.9 mo for *nab*-P + G and 2.8 mo for G. **Conclusions:** MPACT was a large, international study performed at community and academic centers. *nab*-P + G was superior to G across all efficacy endpoints, had an acceptable toxicity profile, and is a new standard for the treatment of metastatic PC that could become the backbone for new regimens. Clinical trial information: NCT00844649.

HENT1 tumor levels to predict survival of pancreatic ductal adenocarcinoma patients who received adjuvant gemcitabine and adjuvant 5FU on the ESPAC trials.

John P. Neoptolemos, William Greenhalf, Paula Ghaneh, Daniel H. Palmer, Trevor F. Cox, Elizabeth Garner, Fiona Campbell, John Robert Mackey, Malcolm J. Moore, Juan W. Valle, Alec Mcdonald, Niall C. Tebbutt, Christos Dervenis, Bengt Glimelius, Richard M. Charnley, Francois Lacaine, Julia Mayerle, Charlotte Louise Rawcliffe, Claudio Bassi, Markus W. Buchler, The European Study Group for Pancreatic Cancer; University of Liverpool, Liverpool, United Kingdom; The University of Liverpool, Liverpool, United Kingdom; Department of Oncology, Cross Cancer Institute, Edmonton, AB, Canada; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada; University of Manchester, Manchester Academic Health Science Centre; Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Austin Health and University of Melbourne, Heidelberg, Australia; Aiga Olga Hospital, Athens, Greece; Akademiska University Hospital, Uppsala, Sweden; Freeman Hospital, Newcastle-upon-Tyne, United Kingdom; Hospital Tenon, Paris, France; Department of Medicine, University Hospital Greifswald, Greifswald, Germany; Surgical Department, University of Verona, Verona, Italy; University of Heidelberg, Heidelberg, Germany

Background: Some studies in patients with resected pancreatic cancer have suggested that expression of the human equilibrative nucleoside transporter (hENT1) may be predictive of improved survival from gemcitabine but these have either been based on retrospective non-randomized studies or in one study the principal treatment was chemoradiation. The samples collected from the adjuvant ESPAC1/3 randomized trials have provided a unique opportunity to assess to REMARK standards the therapeutic predictability of hENT1 in patients undergoing resection for pancreatic cancer. **Methods:** Tissue Microarrays (TMAs) were prepared using paraffin embedded tumor specimens from patients randomized to gemcitabine or 5FU/ Folinic acid in the ESPAC-1 and -3 trials. Cores were given an H-Score depending on the level of staining with the 10D7G2 anti-hENT1 antibody. Groups were compared using Kaplan-Meier and Cox proportional hazards. **Results:** Scores were obtained for 176 gemcitabine treated and 176 5FU treated patients. The overall median H-Score was 48 and patients were classified as having high hENT1 if the mean score for their cores was above this. Median overall survival for gemcitabine treated patients was 23.4 (95% CI: 18.3, 26.0) months versus 23.5 (95% CI: 19.8, 27.3) months for 5FU treated patients ($\chi^2_1 = 0.24$, $P = 0.623$). In the gemcitabine group A significantly lower survival ($\chi^2_1 = 9.87$, $P = 0.002$) was noted with low hENT1 (median survival 17.1 (95% CI: 14.3, 23.8) versus 26.2 (95% CI: 21.2, 31.4) months). Median survival was 25.6 (95% CI: 20.1, 27.9) and 21.9 (95% CI: 16.0, 28.3) months respectively for high and low hENT1 in the 5FU group, a non-significant difference ($\chi^2_1 = 0.83$, $P = 0.362$). Multivariate analysis confirmed hENT1 expression as a predictive marker in gemcitabine (Wald $\chi^2 = 7.10$, $P = 0.008$) but not 5-fluorouracil (Wald $\chi^2 = 0.34$, $P = 0.560$) groups. **Conclusions:** The study supports use of gemcitabine in patients with high tumor hENT1 expression and 5-fluorouracil in patients with low hENT1.

4007 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

Randomized multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) and a prospective evaluation of the of the association between tumor hENT1 expression and clinical outcome with gemcitabine treatment.

Elizabeth Poplin, Harpreet Wasan, Lindsey Rolfe, Mitch Raponi, Tone Ikdahl, Ihor Bondarenko, Irina Davidenko, Volodymyr Bondar, August Garin, Stefan Hubert Boeck, Volker Heinemann, Claudio Bassi, T. R. Jeffry Evans, Cynthia Voong, Paramjit Kaur, Jeffrey D. Isaacson, Andrew R. Allen; The Cancer Institute of New Jersey, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; Imperial College Healthcare NHS Trust, London, United Kingdom; Clovis Oncology, Inc., Boulder, CO; Clovis Oncology, Inc., San Francisco, CA; Department of Oncology, Oslo University Hospital, Oslo, Norway; Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine; Krasnodar City Oncology Center, Krasnodar, Russia; Donetsk Regional Anti-Tumor Centre, Donetsk, Ukraine; N. N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; Department of Hematology and Oncology, Klinikum Grosshadern and Comprehensive Cancer Center, LMU Munich, Munich, Germany; Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Munich, Germany; Surgical Department, University of Verona, Verona, Italy; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom

Background: Gemcitabine requires membrane transporter proteins to cross the cell membrane. Low expression of the human equilibrative nucleoside transporter-1 (hENT1) may play a role in gemcitabine resistance in PDAC. CO-101 (also known as CP-4126), a lipid-drug conjugate of gemcitabine, was rationally designed to enter cells independently of hENT1 and to circumvent transporter-mediated resistance. We conducted a randomized, controlled trial (LEAP) in patients with mPDAC to determine whether CO-101 improved survival vs gemcitabine in patients with low hENT1 tumors. The study also prospectively tested the hypothesis that gemcitabine is more active in patients with hENT1 high than hENT1 low tumors in metastatic disease. **Methods:** Patients were randomized to CO-101 or gemcitabine. An immunohistochemistry test measuring tumor hENT1 expression was developed in parallel with the recruitment phase of LEAP. To dichotomize the population, a hENT1 cut-off was defined using primary PDAC tumor samples from an adjuvant trial. LEAP participants provided a metastasis sample during screening for blinded hENT1 assessment, and the cut-off was applied to these samples. The primary endpoint of the study was overall survival in the low hENT1 subgroup. **Results:** 367 patients were enrolled, with metastasis hENT1 status available for 358/367 (97.5%). 232/357 (65%) were hENT1 low. There was no difference in overall survival between CO-101 and gemcitabine in the hENT1 low subgroup, or overall, with hazard ratios of 0.994 [95% CI 0.746, 1.326] and 1.072 [95% CI 0.856, 1.344] respectively. Within the gemcitabine arm, there was no difference in survival between the hENT1 high and low subgroups (HR 1.147 95% CI 0.809, 1.626). The observed side effect profile was typical of gemcitabine and was similar in both treatment arms, in the hENT1 low subgroups and overall. **Conclusions:** CO-101 is not superior to gemcitabine in patients with mPDAC and low tumor hENT1 expression. Metastasis hENT1 expression did not predict gemcitabine treatment outcome in patients with mPDAC. Clinical trial information: NCT01124786.

4008 **Oral Abstract Session, Mon, 9:45 AM-12:45 PM**

JASPAC 01: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 for patients with resected pancreatic cancer.

Akira Fukutomi, Katsuhiko Uesaka, Narikazu Boku, Hideyuki Kanemoto, Masaru Konishi, Ippei Matsumoto, Yuji Kaneoka, Yasuhiro Shimizu, Shoji Nakamori, Hirohiko Sakamoto, Soichiro Morinaga, Osamu Kainuma, Koji Imai, Naohiro Sata, Shoichi Hishinuma, Takayuki Nakamura, Michio Kanai, Satoshi Hirano, Yukinobu Yoshikawa, Yasuo Ohashi; Shizuoka Cancer Center, Shizuoka, Japan; St. Marianna University School of Medicine, Kawasaki, Japan; National Cancer Center Hospital East, Kashiwa, Japan; Kobe University Graduate School of Medicine, Kobe, Japan; Ogaki Municipal Hospital, Ogaki, Japan; Aichi Cancer Center Hospital, Nagoya, Japan; Osaka National Hospital, Osaka, Japan; Saitama Medical University International Medical Center, Saitama, Japan; Kanagawa Cancer Center, Yokohama, Japan; Chiba Cancer Center, Chiba, Japan; Asahikawa Medical University, Asahikawa, Japan; Jichi Medical University, Shimotsuke, Japan; Tochigi Cancer Center, Utsunomiya, Japan; Gunma Prefectural Cancer Center, Gunma, Japan; Kasugai Municipal Hospital, Kasugai, Japan; Hokkaido University Graduate School of Medicine, Sapporo, Japan; National Hospital Organization Kure Medical Center, Kure, Japan; The University of Tokyo, Tokyo, Japan

Background: Adjuvant chemotherapy with gemcitabine (G) has been standard treatment for resected pancreatic cancer (PC). In the GEST study, S-1 (S) had shown non-inferiority to G in overall survival (OS) for unresectable PC. The aim of this phase III study is to investigate non-inferiority of S to G on OS as adjuvant chemotherapy for resected PC. **Methods:** Patients (pts) after macroscopically curative resection of PC with an ECOG PS of 0-1 and adequate organ functions were randomly assigned to G (1000 mg/m^2, iv, d1, 8 and 15, q4w, for 6 courses) or S (80/100/120 mg/day based on BSA, po, d1-28, q6w, for 4 courses) with balancing by surgical margins (R), nodal status (N) and institution. Primary endpoint was OS. With 180 pts per arm, the study had 80% power to prove non-inferiority with a margin of hazard ratio (HR) 1.25 on the basis of expected HR 0.87, with 0.05 two-sided alpha. Secondary endpoints were relapse-free survival (RFS), safety, and quality of life (EQ-5D). One interim analysis was planned after 180 deaths. **Results:** From 4/2007 to 6/2010, 385 pts were enrolled from 33 hospitals in Japan. 378 pts (G/S: 191/187) were included in the full analysis set. Pts characteristics (G/S) were well balanced (PS0: 67%/70%, R0: 86%/88%, N0: 38%/36%). Based on the interim analysis with 205 OS events, IDMC recommended to publish the results. OS at 2-years were 53% for G and 70% for S. HR for S to G was 0.56 (95% CI, 0.42-0.74, $p<0.0001$ for non-inferiority, $p<0.0001$ for superiority). On subgroup analysis, HRs for R0/R1, N0/N1 pts were 0.57 (95% CI, 0.42-0.78)/0.53 (0.27-1.05), 0.48 (0.28-0.83)/0.58 (0.41-0.80), respectively. RFS at 2-years were 29% for G and 49% for S. HR of relapse for S to G was 0.56 (95% CI, 0.43-0.71, log-rank $p<0.0001$). Incidences of grade 3/4 toxicities in G/S were leukopenia 39%/9%, hemoglobin decrease 17%/13%, thrombocytopenia 9%/4%, elevated AST 5%/1%, fatigue 5%/5%, and anorexia 6%/8%. Relative dose intensity of G/S was 84%/97%. EQ-5D QOL score in S was significantly better than that in G ($p<0.0001$). **Conclusions:** S-1 adjuvant chemotherapy is shown non-inferior, and furthermore, even superior to GEM. S-1 is considered as the new standard treatment for resected PC pts. Clinical trial information: UMIN000000655.

4009 Poster Discussion Session (Board #1), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Phase II, randomized, double-blind placebo-controlled trial of nimotuzumab plus gemcitabine compared with gemcitabine alone in patients (pts) with advanced pancreatic cancer (PC).

Dirk Strumberg, Beate Schultheis, Matthias Philip Ebert, A. Kerkhoff, Ralf Dieter Hofheinz, Dirk M. Behringer, Wolfgang E. Schmidt, Erdem Goker, Sara De Dosso, Michael Kneba, Suayib Yalcin, Friedrich Overkamp, Frank Schlegel, M. Dommach, Robert Rohrberg, Tilman Steinmetz, Dirk Reuter, Ferdinand Bach; Marienhospital Herne, Herne, Germany; University of Bochum, Marienhospital Herne, Herne, Germany; Medical Department II, University Hospital Mannheim, Mannheim, Germany; University Hospital Münster, Münster, Germany; Department of Hematology and Medical Oncology, University Medical Centre Mannheim, Mannheim, Germany; Augusta-Kranken-Anstalt, Bochum, Germany; University Hospital Bochum, St. Josef Hospital, Med. Klinik I, Bochum, Germany; Ege University Medical School, Izmir, Turkey; Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; Department of Medicine, University Medical Center Schleswig-Holstein, Kiel, Germany; Hacettepe University Hospital, Ankara, Turkey; Medical Practice for Oncology and Hematology, Recklinghausen, Germany; St. Antonius Hospital, Eschweiler, Germany; Sana-Kliniken, Medizinisches Versorgungszentrum Onkologie, Dusseldorf, Germany; Gemeinschaftspraxis und Tagesklinik fuer Haematologie, Onkologie und Gastroenterologie, Halle, Germany; Group Practice Hematology/Oncology Cologne, Cologne, Germany; Oncoscience AG, Wedel, Germany

Background: FOLFIRINOX significantly increases survival in metastatic PC compared to gemcitabine, but its use is limited to selected pts, due its high toxicity. In the majority of cases, gemcitabine (gem) remains the mainstay of palliative treatment, although its modest impact on survival and disease progression. The addition of the EGFR tyrosine kinase inhibitor erlotinib prolonged median survival for only 2 weeks.This study was aimed to investigate the effect of adding Nimotuzumab (nimo), an anti-EGFR monoclonal antibody, to first-line gemcitabine, in PC. **Methods:** Pts with previously untreated, unresectable, locally-advanced or metastatic PC were randomly assigned to receive gem: 1000 mg/m2/ 30-min iv once weekly (d1, 8, 15; q28) and nimo: fixed dose of 400 mg once weekly as a 30-min infusion, or placebo, until progression or unacceptable toxicity. Primary endpoint was overall survival (OS) in the intention-to-treat (ITT) population. Secondary endpoints included PFS, safety, objective response rate (ORR), QoL. **Results:** Between 9/2007- 10/2011 a total of 192 pts were randomized (average age 63.6 ±10 years; 60% male; 69% ECOG PS 0), and 186 were evaluable at the ITT analysis. One-year OS was 19.5 % with gem+placebo and 34.4% with gem+nimo (HR=0.69; p=0.034). Median OS and PFS were 6.0 mo in the gem+placebo group, vs. 8.7 mo in gem+nimo (HR=0.83; p=0.21), and 3.7 vs. 5.4 mo, respectively (HR=0.73; p=0.06). One-year PFS was 9.5 % for gem+placebo, compared with 21.5% for gem+nimo (HR=0.71; p=0.05). Significantly, in pts ≥ 62 years (60% of the population), median OS and PFS were 5.2 mo in the gem+placebo group vs. 8.8 mo in gem+nimo (HR=0.66; p=0.034), and 3.2 in gem+placebo vs. 5.5 mo in gem+nimo group, respectively (HR=0.55; p=0.0096). Nimo was safe and well tolerated, and no grade 3/4 toxicities were observed. Thirteen % of pts experienced grade 1/2 skin toxicity. **Conclusions:** This randomized study clearly showed that nimo in combination with gem is safe and well tolerated. The 1-year survival rate is significantly improved. Especially pts ≥ 62 years seem to benefit, possibly due to a more aggressive biology in younger pts. Clinical trial information: NCT00561990.

4010 Poster Discussion Session (Board #2), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

A phase Ib study of gemcitabine plus PEGPH20 (pegylated recombinant human hyaluronidase) in patients with stage IV previously untreated pancreatic cancer.

Sunil R. Hingorani, William Proctor Harris, J. Thaddeus Beck, Boris A. Berdov, Stephanie Ann Wagner, Eduard M. Pshevlotsky, Sergei Tjulandin, Oleg Gladkov, Randall F. Holcombe, Ping Jiang, Daniel C. Maneval, Joy Zhu, Craig E. Devoe; Fred Hutchinson Cancer Research Center, Seattle, WA; University of Washington School of Medicine, Seattle, WA; Highlands Oncology Group, Fayetteville, AR; Medical Radiological Research Center, Obninsk, Russia; Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; Omsk Regional Budget Medical Institution: Clinical Oncological Center, Omsk, Russia; Russian Oncology Research Center; N.N. Blokhin Cancer Research Center, Moscow, Russia; Chelyabinsk Regional Clinical Oncology Center, Chelyabinsk, Russia; Mount Sinai School of Medicine, New York, NY; Halozyme Therapeutics, San Diego, CA; Monter Cancer Center, Lake Success, NY

Background: PEGPH20 is a PEGylated version of human recombinant hyaluronidase. In preclinical studies, PEGPH20 depleted pancreatic cancers of their high hyaluronan (HA) content. In a genetically-engineered murine model of PDA, PEGPH20 + gemcitabine (Gem) significantly prolonged survival compared to Gem alone. In Ph1 PEGPH20 monotherapy studies, the MTD was 3.0 μg/kg. The most common AEs were musculoskeletal events (MSEs). **Methods:** This was a dose-escalation study to find the recommended Phase 2 dose (RP2D) of PEGPH20 in combination with Gem in patients (pts) with Stage IV previously untreated pancreatic cancer. Pts received PEGPH20 at 1, 1.6, or 3 μg/kg IV twice a week for Wks 1-4, weekly for Wks 5-7, then 1 wk rest. Dose escalation was based on safety. Gem was given at 1000 mg/m^2 IV once a week for Wks 1-7, then 1 wk rest. Thereafter, PEGPH20 + Gem were given once a week for 3 wks in 4-wk cycles. Dexamethasone was given pre and post PEGPH20 doses. **Results:** Of the 28 pts enrolled, the majority had a Karnofsky performance status of 80%, and 85%/19%/26% of pts had liver/lung/visceral metastases. The median age was 58 yrs. Four pts received PEGPH20 at 1 μg/kg, 4 at 1.6 μg/kg, and 20 at 3 μg/kg. The RP2D was 3 μg/kg. Treatment duration ranged from 1-274 days; 5 pts remain on study. Treatment was generally well tolerated. Ten pts had 1 Gem dose reduction, 2 pts had 1 PEGPH20 dose reduction (3 to 1.6 μg/kg), but no pt had a DLT. The most common PEGPH20-related AEs were MSEs (25% Gr1; 18% Gr2) and fatigue (21% Gr1; 11% Gr2). Objective response was assessed by an independent central radiologist using RECIST 1.1. Of the 21 pts evaluable for efficacy, 7 had partial response (PR) for an overall response rate (ORR) of 33%, and 9 had stable disease for $\geq$ 2 mo. Tumor biopsies from 12 pts were evaluable for HA staining. HA was high in 9 and low in 3. Of the 9 with high HA staining, 5 had PR (56% ORR); HA data were not available for the other 2 PR pts. PK results show dose-dependent exposure consistent with data from PEGPH20 monotherapy studies. **Conclusions:** PEGPH20 in combination with Gem is generally well tolerated in advanced pancreatic cancer and shows promising efficacy, especially in pts with high intratumoral HA content. Clinical trial information: NCT01453153.

4011 Poster Discussion Session (Board #3), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Vismodegib (V), a hedgehog (HH) pathway inhibitor, combined with FOLFOX for first-line therapy of patients (pts) with advanced gastric and gastroesophageal junction (GEJ) carcinoma: A New York Cancer Consortium led phase II randomized study.

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Background: The HH pathway is overexpressed in gastroesophageal (GE) tumors. Pre-clinically, HH inhibitors have demonstrated a reduction in GE tumor growth, cell motility and invasiveness. V, an oral small-molecule antagonist of the Hh pathway, has previously been safely combined with FOLFOX chemotherapy. **Methods:** Pts with untreated metastatic or locally advanced gastric or GEJ adenocarcinoma were randomized 1:1, stratified by institution and disease status (with or w/o distant mets) to FOLFOX (ox 85 mg/m^2, LV 200 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2400 mg/ m^2 over 48 hrs) q14d plus V or placebo (P) (150mg PO daily). Cycle defined as 2 weeks and no crossover allowed at progression. FFPET and blood were collected for biomarker analyses. Response assessed every 8 weeks (RECIST 1.1). Primary endpoint was progression-free survival (PFS), secondary objectives were overall survival (OS), response rate (RR), and toxicity. **Results:** 124 pts enrolled at 20 sites between 10/09-2/12. 123 pts eligible for analysis (V/P 60/63). Pt characteristics (V/P): median age 58/62; ECOG PS 0: 24 (40%) / 30 (48%); male 39 (65%) / 52 (83%); GEJ 37 (62%) / 39 (61%); diffuse or mixed histology 19 (32%) / 10 (16%), recurrent disease 10(17%) / 16 (25%). Median number of FOLFOX cycles 10/11. Most common Grade $\geq$3 toxicities: (% pts V/P) neutropenia 50/32 (p=0.07), neuropathy 19/13 (p=0.49), fatigue 15/10 (p=0.50), thrombosis 14/11 (p=0.92), anemia 10/10 (p=0.99), hemorrhage-GI 8/11 (p=0.77), hypokalemia 10/5 (p=0.76), nausea 8/8 (p=0.99). Death on or within 30 days of treatment 6.7%/15.6% (p=0.20). Median PFS in intent to treat population 7.3/8.0 mo (95% CI 4.6-10.1/5.1-11.0; p=0.64) and median OS 11.5/14.9 mo (95% CI 9.6-13.4/11.3-18.4; p=0.23). Overall RR (%) 35/35 (p=0.99). **Conclusions:** Addition of V to FOLFOX did not improve PFS in an unselected advanced GE carcinoma population. Blood and tissue biomarker analyses are ongoing to determine if there is a subset of patients who may derive benefit from V. Supported by: N01-CM-62204, -62201, -62207, -62206, -62209, -62208 and 2UL1 TR000457-06. Clinical trial information: NCT00982592.

4012 Poster Discussion Session (Board #4), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Final analysis of a phase IB/randomized phase II study of gemcitabine (G) plus placebo (P) or vismodegib (V), a hedgehog (Hh) pathway inhibitor, in patients (pts) with metastatic pancreatic cancer (PC): A University of Chicago phase II consortium study.

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Background: Sonic Hh (SHh), the ligand for the Hh pathway, is over-expressed in >80% of PC. V had activity in preclinical murine PC models leading to increased tumor perfusion, enhanced tumor delivery of G, and an improvement in survival. **Methods:** We conducted a placebo-controlled, phase IB/randomized phase II trial of GV or GP. Eligible pts, KPS 80-100, had untreated metastatic PC, or had completed adjuvant therapy > 6 months (mo) prior. Primary endpoint: progression-free survival (PFS). Correlatives: serial SHh serum levels; serial perfusion CT imaging. All pts received G 1000mg/m^2over 30 minutes, days (D) 1, 8, 15, Q28D. A lead-in phase IB was performed. Pts, stratified by KPS (80 v 90/100), and disease status (newly diagnosed/recurrent), were randomized to V (150 mg PO daily) or P. For pts on P, cross-over was allowed at progression. Assuming a mPFS of 3.5 months for GP and 5.7 months for GV (HR=0.61), a sample size of 106 subjects (53 per group) provided 85% power to detect this difference, using a one-sided test at the 0.10 significance level. **Results:** No safety issues were identified in 7 pts enrolled in the phase IB study. The phase II study enrolled 106 evaluable pts (V/P 53/53) at 13 sites 2/10-6/12. Pt characteristics: median age 65/64 (range 52-82/39-83); KPS (% pts) 80: 38/30; 90: 26/38; 100: 36/32; newly diagnosed 91%/91%; recurrent: 9%/9%. Grade 3/4 toxicity (V/P, % pts, >5% in either arm): neutropenia 32/28; lymphopenia 4/15; thrombocytopenia 9/11; anemia 9/23; hyponatremia 4/15; fatigue 13/8; hyperglycemia 23/19; elevated ALT 13/9; hyperbilirubinemia 11/6; nausea 11/11. Response (%): CR 0/2, PR 8/11, SD 51/38. mPFS: 4.0/2.5 mo (95% CI: 2.5-5.3/1.9-3.8; HR 0.81 [0.54-1.21], p=0.30). 22 pts (42%) on GP crossed over to GV at progression. mOS: 6.9/6.1 mo (95% CI:5.8-8.0/5.0-8.0, HR 1.04, [0.69-1.58], p=0.84). Updated laboratory/radiological correlatives will be presented. **Conclusions:** Toxicity between the groups was similar. The addition of V to G in an unselected cohort does not improve response, PFS, or OS in pts with metastatic PC. Funding NCI N01-CM-62201. Clinical trial information: NCT01064622.

4013 Poster Discussion Session (Board #5), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: A randomized, double-blind phase II study.

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Background: Our multicenter study compared the efficacy of the oral PARP inhibitor olaparib plus paclitaxel (O/P) vs paclitaxel alone (P) as second-line therapy in pts with recurrent/metastatic gastric cancer (GC) (NCT01063517). As initial preclinical data suggested that responsiveness of GC cell lines to olaparib was associated with low ATM protein levels, our study was enriched for pts with low ATM tumors (ATM–) by IHC (50% randomized vs 14% screening prevalence). **Methods:** Eligible pts were randomized 1:1 (stratified by ATM status) to receiveolaparib 100 mg bid (tablet form) plus paclitaxel (80 mg/m^2 iv on days 1, 8, 15 per 28-day cycle) or placebo plus paclitaxel until progression or investigator decision. After combination therapy, pts could take olaparib 200 mg bid monotherapy or placebo until progression. Co-primary endpoints: progression-free survival (PFS; RECIST v1.1) in all pts and ATM– pts. Secondary endpoints: overall survival (OS), objective response rate (ORR), safety. **Results:** 123/124 randomized pts were treated (O/P=61; P=62). Baseline characteristics were generally well balanced. Use of post-progression therapy was similar in both arms (O/P=48.4%; P=43.5%) as was median paclitaxel duration (O/P=17 wks; P=16 wks); 18 pts received monotherapy (O/P=11; P=7). More pts in the O/P than P arm had delays (79 vs 63%) and reductions (41 vs 27%) in paclitaxel dosing. The most common grade ≥3 AEs in the O/P and P arms were neutropenia (56 vs 39%) and anemia (11 vs 11%). **Conclusions:** Olaparib plus paclitaxel was well tolerated and led to a statistically significant improvement in OS, but not PFS, vs paclitaxel alone in both all pts and ATM– pts, with a larger benefit in ATM– pts. Clinical trial information: NCT01063517.

	O/P	P	
All pts	n=62	n=62	
PFS, m	3.9	3.6	HR=0.80; 95% CI 0.54, 1.18 P=0.261
OS, m	13.1	8.3	HR=0.56; 95% CI 0.35, 0.87 P=0.010
EFR	n=53	n=47	
ORR %	26.4	19.1	OR=1.65; 95% CI 0.61, 4.68 P=0.323
PD %	26.4	44.7	
ATM– pts	n=31	n=32	
PFS, m	5.3	3.7	HR=0.74; 95% CI 0.42, 1.32 P=0.315
OS, m	NC	8.2	HR=0.35; 95% CI 0.17, 0.71 P=0.003
EFR	n=26	n=23	
ORR %	34.6	26.1	OR=1.76; 95% CI 0.49, 6.89 P=0.390
PD %	15.4	34.8	

EFR, evaluable for response; m, median (months); NC, not calculable; PD, best response of progressive disease. HR<1, OR>1 favor O/P. P values: 2-sided.

4014 Poster Discussion Session (Board #6), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Dual MEK/EGFR inhibition for advanced, chemotherapy-refractory pancreatic cancer: A multicenter phase II trial of selumetinib (AZD6244; ARRY-142886) plus erlotinib.

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Background: Pharmacologic inhibition of MEK leads to enhanced signaling through EGFR with hyperactivation of a parallel oncogenic pathway (PI3K) independent of mutant KRAS, supporting a therapeutic strategy of combined target inhibition in PDAC to overcome this negative feedback loop. Based on preclinical evidence of synergistic activity between EGFR and MEK inhibitors, we conducted a non-randomized phase II trial of erlotinib plus selumetinib, a selective, allosteric inhibitor of MEK1/2, in patients with PDAC who had received one prior line of chemotherapy. **Methods:** A Simon 2-stage design was used, with planned n = 46. Study treatment consisted of erlotinib 100 mg + selumetinib 100 mg daily in 3-week cycles, with CT evaluation every 2 cycles. 1^{o} objective was overall survival (OS). Correlative studies include detection of circulating tumor cells using a novel nonenrichment high definition immunofluorescence assay, and tissue- and serum proteomic-based predictive biomarkers. **Results:** 46 patients enrolled at 2 sites between 1/2011 and 1/2013 (median age 67 y.o. [range 40-84]; ECOG PS (0/1): 31/15; prior gemcitabine-based vs. FOLFIRINOX vs. other 1^{st}-line chemo: 34/10/2). Patients received a median of 2 cycles (range, 1-7). Of 41 evaluable patients to date, disease control rate is 51% (0 PR; 21 with stable disease (SD) $>$ 6 weeks, 10 with SD $>$ 12 weeks; 11 minor responses). 9/31 patients (29%) had CA19-9 decline $>$ 50%. Estimated median PFS and OS by Kaplan-Meier are 2.6 and 7.5 months, respectively, with 21 patients still alive. Grade 3/4 AEs likely attributable to study treatment include rash (10 patients), hypertension (6), anemia (5), diarrhea (4), and nausea/vomiting (4); no study-related deaths have occurred. 38% of patients have required dose reduction of one/both agents. **Conclusions:** Dual targeting of MEK/EGFR signaling shows antitumor activity in PDAC in a subset of patients and warrants further exploration, possibly in combination with, or comparison to, cytotoxic therapy. Companion efforts are ongoing to assess candidate predictive markers of benefit to this combination. Supported by CTEP and NIH R21 CA149939. Clinical trial information: NCT01222689.

4015 Poster Discussion Session (Board #7), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

A Bayesian network meta-analysis of systemic regimens for advanced pancreatic cancer.

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Background: For advanced pancreatic cancer, many regimens have been compared with gemcitabine (G) in randomized control trials (RCTs). Few have been compared with each other directly in RCTs and the relative efficacy and safety among them are unclear. **Methods:** A systematic review was performed through MEDLINE, EMBASE, Cochrane Central Register of Contorlled Trials and ASCO meeting abstracts up to Jan 2013 to identify RCTs that included metastatic pancreatic cancer comparing the following regimens: G, G+5-flourouracil (GF), G+capecitabine (GCap), G+S1 (GS), G+cisplatin (GCis), G+oxaliplatin (GOx), G+erlotinib (GE), G+Abraxane (GA) and FOLFIRINOX. Studies were reviewed by two authors and discrepancies were resolved by consensus or by a third author. Data including overall survival (OS), progression-free survival (PFS), response rate (RR), and side-effects were extracted. A Bayesian network meta-analysis with random effects was performed using WinBUGS to compare all regimens simultaneously. **Results:** Twenty-two studies involving 6,252 patients were identified, with 21 RCTs involving G, 4 with GF, 3 with GCap, 2 with GS, 6 with GCis, 3 with GOx, 1 with GE, 1 with GA and 1 with FOLFIRINOX. Median OS, PFS and RR for G arms from all trials were similar, suggesting the absence of significant clinical heterogeneity among RCTs. For OS, the results of the Bayesian network meta-analysis found that the probability that FOLFIRINOX was the best regimen was 71%, while it was 19% for GS, 7% for GA and 2% for GE respectively. The OS hazard ratio (HR) for FOLFIRINOX vs. GS was 0.82 (95% credible region (CR): 0.53-1.35), the OS HR for FOLFIRINOX vs. GA was 0.77 (95% CR: 0.51-1.23), and the OS HR for FOLFIRINOX vs. GE was 0.67 (95% CR: 0.45-1.08). Similar ranking and probabilities were observed for the best regimen for PFS. **Conclusions:** FOLFIRINOX appeared to be the best regimen for advanced pancreatic cancer probabilistically, with a trend towards improvement in OS and PFS when compared with GS, GA, or GE by indirect comparisons. In the absence of direct pairwise comparisons of these regimens from RCTs, network meta-analysis helps synthesize evidence and inform decision making.

4016 Poster Discussion Session (Board #8), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

SPARC in pancreatic cancer: Results from the CONKO-001 study.

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Background: Previous investigations in pancreatic cancer suggested an important prognostic role for SPARC (secreted protein acidic and rich in cysteine) expression in the peritumoral stroma but not for cancer-cell cytoplasmic SPARC expression. So far no data from prospective studies in patients after curatively intended surgery are available. **Methods:** CONKO-001, a prospective randomized phase III study, investigated the role of adjuvant gemcitabine as compared to observation. Tissue samples of 160 patients were collected and analysed by immunohistochemistry for the expression of SPARC in the peritumoral stroma (*strong* versus *not strong* [=moderate to negative]) and in the tumor cell cytoplasm (immunoreactive score IRS 0-12, 0-2 = *negative*, 3-12 = *positive*) by a pathologist blinded to clinical outcome. Kaplan-Meier analyses for disease-free survival (DFS) and overall survival (OS) were performed in dependence of SPARC expression. **Results:** Strong stromal SPARC expression was associated with worse DFS and OS in the overall study population (strong vs not-strong DFS 9.0 vs 12.6 months, p=0.005*;* OS 19.8 vs 26.6 months (p=0.033). It was highly prognostic in the subgroup treated with gemcitabine (strong vs not-strong DFS 12.1 vs. 18.4 months; p=0.007, OS 17.9 vs 30.2 months, p=0.006), but not in the observation group (strong vs not strong DFS 6.6 vs 7.3 months p=0.767; OS 21.5 vs 18.2 months, p=0.765). Cytoplasmic SPARC expression in the adenocarcinoma cells was also associated with worse patient outcome (positive vs negative DFS 7.4 vs 12.1 months, p=0.041; OS 14.1 vs 25.6 months, p=0.011), again the effect was restricted to patients treated with gemcitabine (positive vs negative DFS 8.3 vs 15.3 months, p=0.002; OS 11.0 vs 28.8 months, p= 0.003; control group DFS 5.8 vs 7.6 months, p=0.844; OS 14.9 vs 20.8 months, p=0.519). **Conclusions:** Our data confirm the prognostic significance of SPARC expression and demonstrate a significant prognostic factor of SPARC in patients with pancreatic cancer after curatively intended resection. The prognostic impact was restricted to patients who received adjuvant treatment with gemcitabine. In difference to former published data this was found for peritumoral SPARC as well as for SPARC expression in tumor cells.

4017 Poster Discussion Session (Board #9), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Use of pharmacogenomic modeling in pancreatic cancer for prediction of chemotherapy response and resistance.

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Background: Pancreatic adenocarcinoma (PDAC) is uniformly lethal and is the 4th leading cause of cancer mortality. Despite this, modern cytotoxics (C) can induce tumor responses and extend life. Xenograft models have shown that pharmacogenomic (PGx) modeling of C can predict efficacy. Chemo-sensitivity and gene expression profiling of circulating tumor and invasive cells (CTICs) isolated from peripheral blood may predict tumor response, progression and resistance. **Methods:** A prospective MSKCC study has completed planned accrual of 50 patients. 10 mL of peripheral blood is collected from patients with unresectable PDAC prior to C and at disease progression. Clinical data is prospectively collected. CTICs are isolated (Vita-Cap, Vitatex Inc.), total RNA is extracted and gene-expression analysis is performed. PGx models for twelve chemotherapy drug combinations used in PDAC were created from the GI50 data obtained from the NCI-60 cell lines (CellPath Therapeutics, Inc., Baltimore, MD). Expression data were normalized through GCRMA then probed to identify expression differences between patients with short v long TTP and within patients at baseline v at time of progression. The analysis was performed at the pathway and individual gene level. **Results:** CTICs were isolated, and gene expression and chemo-sensitivity patterns were obtained in all 50 patients prior to initiating C and in 20 patients at 1st line disease progression. Preliminary analysis demonstrates clinical benefit for patients treated with C predicted to be effective versus ineffective (TTP 7.3 mo v 3.7 mo, $p=0.017$, HR 0.30). Changes in chemo-sensitivity patterns were evident at disease progression, reflecting treatment resistance. Pathway analysis revealed that E2F1 and NFκB pathways are associated with prognosis, PLC and RB1 pathways become disrupted with disease progression. **Conclusions:** Isolation and gene expression profiling of CTICs can be performed reliably in unresectable PDAC. Preliminary analysis suggests that C profiling can predict response. Repeat PGx profiling identifies key pathways associated with treatment resistance. Clinical trial information: NCT01474564.

4018 Poster Discussion Session (Board #10), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

KRAS mutation status-stratified randomized phase II trial of GEMOX with and without cetuximab in advanced biliary tract cancer (ABTC): The TCOG T1210 trial.

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Background: Gemcitabine/platinum combination is considered as globally acceptable standard care in patients with ABTC. Two recently published randomized trials showed adding EGFR antagonist, either erlotinib or cetuximab, does not further improve the clinical outcomes of gemcitabine/oxaliplatin (GEMOX)-treated ABTC patients. However, the impact of KRAS mutation status on the results of both studies was not properly addressed. **Methods:** A prospective, multicenter randomized, phase II trial to evaluate the therapeutic efficacies of adding cetuximab to GEMOX in patients with ABTC, in which eligible patients were stratified by status of KRAS mutation and ECOG PS, and tumor location then randomized to receive either GEMOX (gemcitabine 800 mg/m^2, fixed-rate infusion and oxaliplatin 85 mg/m^2, i.v., Q 2 weeks) or GEMOX plus cetuximab (500 mg/m^2, i.v., Q 2 weeks, C-GEMOX). The primary endpoint was overall response rate (ORR). As an exploratory trial, 120 (60 per arm) patients was estimated to detect a two-tailed 10% difference in ORR (20% in GEMOX and 30% in C-GEMOX) with a significant level of a=0.2 and b=0.5. **Results:** Between Nov 2010 and May 2012, a total of 122 patients were accrued. The demography was male: 47.5%, median age: 60 y/o, ECOG PS 0/1: 28.7%/71.3%, IHCC/EHCC/GBC: 71.3%/16.4%/12.3%, KRAS mutation: 36.1%, with locally advanced/metastatic diseases: 32.0%/68.0%, and prior surgical resection: 41.8%. On intent-to-treat analysis, the ORR and DCR in the C-GEMOX (N=62) and GEMOX (N-60) arms was 27.3% vs 15.0% (p=0.1223) and 82.2% vs 60.0% (p=0.0090), respectively (Fisher's exact test); while the median PFS was 7.1 vs 4.0 months (p= 0.0069) and median OS was 10.3 vs 8.8 months (p=0.4057), respectively (log-rank test). Planned subgroup analysis showed the 43 patients with KRAS mutated tumors benefited more from cetuximab therapy, with a DCR of 78.3% vs 38.1% (p=0.0132), median PFS of 7.0 vs 1.9 months (p=0.0351) and median OS of 10.3 vs 6.6 months (p=0.6924). **Conclusions:** Adding cetuximab significant improves the DCR and PFS of GEMOX in ABTC patients, notably in subpopulation with KRAS mutated tumors. Larger-scale phase III trial is warranted. Clinical trial information: NCT01267344.

4019 Poster Discussion Session (Board #11), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Association of gene expressions of TOP2A, GGH, and PECAM1 with hematogenous, lymph-node, and peritoneal recurrence in patients with stage II/III gastric cancer enrolled in the ACTS-GC study.

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Background: Exploratory biomarker analysis was conducted to identify factors related to relapse sites in the ACTS-GC study, a randomized controlled trial comparing postoperative adjuvant S-1 therapy with surgery alone in 1,059 patients (pts) with stage II/III gastric cancer. **Methods:** Formalin-fixed, paraffin-embedded surgical specimens were retrospectively examined in 829 pts (78.3%), and 63 genes involved in pyrimidine metabolic pathway, growth factor signaling pathway, apoptosis, DNA repair, etc., were analyzed by quantitative RT-PCR after TaqMan assay-based pre-amplification. Gene expression levels were normalized to the geometric mean expressions of *GAPDH*, *ACTB*, and *RPLP0*, used as reference genes. The expression of each gene was categorized as lower or higher than the median value. The impact of gene expression on relapse site was analyzed using the 5-year relapse-free survival (RFS) data of the ACTS-GC. **Results:** Among the 829 pts, hematogenous, lymph-node, and peritoneal recurrence developed in 72, 105, and 138 pts, respectively. The hazard ratios (HR) (S-1 vs. surgery alone) were 0.79 (95%CI, 0.54-1.16) for hematogenous, 0.51 (95%CI, 0.31-0.82) for lymph-node, and 0.60 (95%CI, 0.42-0.84) for peritoneal recurrence. Among 63 screened genes, topoisomerase II alpha (*TOP2A),* gamma-glutamyl hydrolase *(GGH),* and platelet/endothelial cell adhesion molecule 1 (*PECAM1)* most strongly correlated with hematogenous, lymph-node, and peritoneal recurrence, respectively. Hematogenous RFS was significantly worse in *TOP2A* high pts than in low pts (HR, 2.35; 95% CI, 1.55-3.57). Lymph-node RFS was significantly worse in *GGH* high pts than in low pts (HR, 1.87; 95% CI, 1.13-3.08). Likewise, peritoneal RFS was significantly worse in *PECAM1*high pts than in low pts (HR, 2.37: 95% CI, 1.65-3.41). These factors were independent and stronger risk factors than tumor histological type on multivariate analysis. **Conclusions:** Expression levels of the *TOP2A, GGH,* and *PECAM1* genes in primary tumors are respectively linked to high risks of hematogenous, lymph-node, and peritoneal recurrence in pts with stage II/III gastric cancer.

4020 Poster Discussion Session (Board #12), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

MAGIC trial gene expression profiling study.

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Background: The MRC MAGIC trial established perioperative epirubicin, cisplatin and 5FU (ECF) chemotherapy as a standard of care for patients (pts) with operable oesophagogastric (OG) cancer (Cunningham NEJM 2006). We performed transcriptomic profiling of archival MAGIC tissue to evaluate an existing intrinsic gastric cancer (GC) gene signature, to describe expression patterns of biologically informative genes and to identify prognostic or predictive markers. **Methods:** RNA was extracted from formalin fixed paraffin embedded (FFPE) resections and analysed with the NanoString nCounter system. Our panel comprised 151 genes including intrinsic GC (G-INT and G-DIFF) signature genes (Tan Gastroenterology 2011), and genes amplified/deleted in GC including the therapeutic targets *FGFR2*, *EGFR*, *ERBB2* and *c-MET* (Deng Gut 2012). Data was preprocessed using nsolver analysis software with 2-step normalisation and log2 transformed. G-INT and G-DIFF subtype classification used the nearest template prediction algorithm; these were then correlated with pt characteristics and survival. The overexpression threshold was defined as deviation above the normal quantile-quantile plot. **Results:** Sufficient RNA for analysis was available for 209 resected pts. A pilot study (n=23) confirmed RNA quality and correlation between NanoString and Affymetrix results. RNA was more often available for pts with GC ($p<0.001$) and pts in the surgery alone arm ($p=0.049$). 70% of pts were classified into G-INT or G-DIFF intrinsic signature subtype (false discovery rate (FDR) <0.05); 61 (30%) were ambiguous. Predominantly mutually exclusive overexpression of receptor tyrosine kinase (RTK) targets *EGFR*, *ERBB2*, *FGFR*, and *c-MET* was seen in 5%, 12%, 9% and 6% of pts respectively. **Conclusions:** Although bias may exist in tissue availability for chemosensitive pts, transcriptomic profiling of archival FFPE from this mature phase 3 study provides powerful insight into the molecular heterogeneity of OG cancer. 70% of evaluable MAGIC pts were classified unambiguously into intrinsic GC subtypes. Mutually exclusive overexpression of targetable RTKs supports a personalized approach in OG cancer evaluating targeted drugs in relevant biological subgroups. Survival analyses are ongoing.

4021 Poster Discussion Session (Board #13), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Clinical outcome according to tumor HER2 status and EGFR expression in advanced gastric cancer patients from the EXPAND study.

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Background: In the EXPAND study adding cetuximab to first-line capecitabine and cisplatin chemotherapy (CT) failed to improve clinical outcome in patients (pts) with advanced gastric or gastroesophageal junction cancer. This analysis assessed treatment outcome according to tumor HER2 status (a pre-defined subgroup) and EGFR expression in EXPAND study pts. **Methods:** Tumor HER2 status was determined primarily by immunohistochemistry (IHC), HER2 +ve tumors were IHC 3+ or IHC 2+ and fluorescence in situ hybridization (FISH) +ve. EGFR expression was assessed by IHC. A continuous scoring system (scale of 0–300) was used to determine the level of EGFR expression. Biomarker status was correlated with clinical outcome. **Results:** In both treatment arms, pts with HER2 +ve tumors (n=144) vs HER2 -ve tumors (n=535) had a longer median overall survival (OS): 13.3 (95% CI 10.9–15.5) vs 9.2 (95% CI 8.1–10.5) months in the CT + cetuximab arm and 14.0 (95% CI 11.3–17.1) vs 9.7 (95% CI 8.6–11.0) months in the CT arm, and a better overall response rate, 51.4 (95% CI 39.3–63.3) vs 27.0 (95% CI 21.9–32.6) % and 37.5 (95% CI 26.4–49.7) vs 26.4 (95% CI 21.1–32.3) % respectively. In stepwise multivariable models, pts with HER2 -ve vs HER2 +ve tumors showed an increased risk of death (adjusted hazards ratio 1.552, 95% CI 1.244–1.936) and reduced odds of response (adjusted odds ratio 0.477, 95% CI 0.316–0.720). EGFR tumor expression was evaluable in 774 pts from the intent to treat population (n=904). The EGFR IHC score was low (median 0, range 0–300). No discriminating threshold for the IHC score was identified. However in pt subgroups defined by a series of cut-off points from an IHC score of 10 upwards (rising incrementally by 10), there was a tendency for improved OS, progression-free survival, and tumor response when adding cetuximab to CT in pts with high tumor EGFR IHC scores. **Conclusions:** In this analysis of EXPAND study pts, those with HER2 +ve tumors were associated with better outcome irrespective of the treatment arm compared with pts with HER2 -ve tumors. Tumor EGFR expression was generally low. Adding cetuximab to CT failed to improve outcome overall, but may benefit a small proportion of pts with high EGFR tumor expression. Clinical trial information: 2007-004219-75.

4022 Poster Discussion Session (Board #14), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

25-hydroxyvitamin D levels and survival in patients with advanced pancreatic cancer (APC): Findings from CALGB 80303.

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Background: Data from animal and cell line models suggest that vitamin D metabolism is important in pancreatic tumor maintenance and may contribute to this tumor's chemoresistance. While vitamin D has been implicated in a variety of cancers, the prevalence of vitamin D deficiency among patients with advanced pancreatic cancer (APC) and the effect of baseline vitamin D levels on survival outcomes are unknown. **Methods:** CALGB 80303 was a randomized controlled trial of patients with APC which demonstrated no difference in OS among patients treated with gemcitabine (GEM) vs. GEM + bevacizumab. We retrospectively measured baseline serum 25(OH)D levels and examined associations between baseline 25(OH)D levels and selected patient characteristics. Using the Cox rank score test, we examined the association between 25(OH)D level and PFS and OS. The differences in the levels among racial populations were tested using the Kruskal-Wallis test. **Results:** Of 256 patients with available serum, the median 25(OH)D level was 21.7 (range 4–77). 44.5% of patients were vitamin D deficient (25(OH)D $<$20), 32.4% were insufficient (25(OH)D $\geq$20 and $<$30), and 23% were sufficient (25(OH)D$\geq$30). Serum 25(OH)D levels were lower in patients self-reported as black compared to white patients and patients of other/undisclosed race (median 10.7 [4.0–36.3] vs. 22.4 [4.0–77.0] vs. 20.9 [12.6 – 31.8], respectively; $p<0.00001$). Adjusting for race, baseline 25(OH)D levels were not associated with PFS (HR 1.00, 95% CI 0.98–1.01) or OS (HR 1.00, 95% CI 0.99-1.01). **Conclusions:** Vitamin D deficiency was highly prevalent among patients with a new diagnosis of APC. Black patients had significantly lower 25(OH)D levels than white patients. In this cohort of patients with APC receiving GEM-based chemotherapy, baseline 25(OH)D levels were not associated with PFS or OS.

4023 Poster Discussion Session (Board #15), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Cougar-02: A randomized phase III study of docetaxel versus active symptom control in patients with relapsed esophago-gastric adenocarcinoma.

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Background: Survival in patients who relapse after first-line chemotherapy (CT) for advanced esophago-gastric adenocarcinoma (EGC) is poor though recently randomised trials (RCT) have suggested a small benefit for second line chemotherapy with taxanes or irinotecan. There is very little data on health related quality of life (HRQL) or overall survival (OS), particularly in patients who progress shortly after first-line therapy. **Methods:** COUGAR-02 was a multicentre open-label, phase III RCT for patients with locally advanced or metastatic EGC of performance status (PS) 0-2 who had progressed within 6 months of previous platinum/fluoropyrimidine CT. Patients were randomised (1:1) to receive either docetaxel 75mg/m^{2}every 3 weeks for up to 6 cycles or active symptom control (ASC). The primary endpoint was OS. The secondary endpoint of HRQL, assessed using EORTC QLQ-C30 and QLQ-ST022, was analysed using standardised area under a curve and compared using Wilcoxon rank sum test. Sensitivity analysis adjusting for dropouts due to death were performed using quality adjusted survival. **Results:** 168 patients (84 patients in each arm) were recruited between April 2008 and April 2012. Median age was 65 years (range 28-84); 81% were males. PS at randomisation was 0 for 27%, 1 for 57% and 2 for 15%. 86% had metastatic disease. 43% progressed during previous CT, 28% progressed within 3 months of end of previous CT and 29% progressed between 3 and 6 months. Median number of cycles of docetaxel was 3. 23% completed 6 cycles. Docetaxel was well tolerated and resulted in a significantly improved OS over ASC alone (HR=0.67 (95% CI 0.49-0.92); p=0.01). Objective response rate was 7%. For QLQ-C30, patients on docetaxel arm reported significantly less pain (p=0.0008) and trend for less nausea and vomiting (p=0.02) and constipation (p=0.02) than those on ASC arm. Similar global HRQL seen (p=0.53).For QLQ-ST022, trend seen for less dysphagia (p=0.02) and pain symptoms (p=0.01) for patients on docetaxel arm than ASC **Conclusions:** Docetaxel provided a significant OS benefit over ASC with improvements in symptom scores and no loss in overall HRQL. Docetaxel can be considered a standard of care in this setting. Clinical trial information: NCT00978549.

LBA4024 Poster Discussion Session (Board #16), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Phase III trial of a 3-weekly versus 5-weekly schedule of S-1 plus cisplatin (SP) combination chemotherapy for first-line treatment of advanced gastric cancer (AGC): SOS study.

Min-Hee Ryu, Eishi Baba, Kyung Hee Lee, Narikazu Boku, Young Iee Park, Ichinosuke Hyodo, Byung-Ho Nam, Taito Esaki, Baek-Yeol Ryoo, Eun-Kee Song, Sanghee Cho, Sung Sook Lee, Won Ki Kang, Sung Hyun Yang, Dae Young Zang, Dong Bok Shin, Sook Ryun Park, Katsunori Shinozaki, Toshimi Takano, Yoon-Koo Kang, on behalf of SOS Investigators; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Department of Comprehensive Clinical Oncology, Kyushu University, Fukuoka, Japan; Department of Hemato-oncology, Yeungnam University Hospital, Daegu, South Korea; Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan; Center for Gastric Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Gyeonggi, South Korea; Division of Gastroenterology, University of Tsukuba, Tsukuba, Japan; National Cancer Center, Goyang, South Korea; Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan; Division of Hematology/Oncology, Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, South Korea; Department of Hematology-Oncology, Chonnam National Univeristy Hwasun Hospital, Gwangju, South Korea; Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; Department of Internal Medicine, Korea Cancer Center Hospital, Seoul, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Medical Center, Hallym University College of Medicine, Anyang, South Korea; Division of Hematology/Oncology, Department of Internal Medicine, Gachon University Gil Hospital, Incheon, South Korea; Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan; Department of Medical Oncology, Toranomon Hospital, Tokyo, Japan

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Monday, June, 3, 2013, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2013, issue of *Journal of Clinical Oncology*. Onsite at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

4025 Poster Discussion Session (Board #17), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

A phase III study of S-1 plus cisplatin versus fluorouracil plus cisplatin in patients with advanced gastric or gastroesophageal junction adenocarcinoma.

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Background: A combination of S-1 and cisplatin (DDP) has been shown to be effective and safe for the first-line treatment of advanced gastric cancer in Japan. This is the first randomized phase III trial to compare S-1 plus DDP with 5-fluorouracil (5-Fu) plus DDP in Asia. **Methods:** This is an open-label, multicenter, phase 3, randomized controlled study. Patients with gastric or gastro-oesophageal junction adenocarcinoma were eligible for inclusion. Patients were randomly assigned in a 1:1 ratio to receive S-1 plus DDP (experiment group) or 5-Fu plus DDP (control group) for 6 cycles. In the experiment group, the dose of S-1 was 80 mg/m^2/day, po, twice daily on day 1-21 and DDP was 20mg/m^2 iv on day 1-4, repeat every 5 weeks. In the control group, 5-Fu was given as 0.8g/m^2/d CI 120h ,and the dose of DDP was the same with the experiment group, while repeat every 4 weeks. Allocation was by block randomization stratified by Eastern Cooperative Oncology Group performance status, sites of metastasis and prior gastrectomy. The primary endpoint was time to progression (TTP). Secondary end points included time to failure (TTF), overall survival (OS), and quality of life. **Results:** Totally 255 patients were enrolled into the study, of whom 236 were included in the analysis (n=120; n=116). Median TTP was 5.51 months (95% CI 4.59-6.26) in those assigned to experiment group compared with 4.62 months (95% CI 4.00-6.33) in the control group (hazard ratio [HR] 1.03; 95%CI 0.76-1.39, p=0.86). In the experiment and control groups, response rates were 22.5% vs 21.5%; P=0.86. Median OS was 10.00 months (95% CI 8.59-14.52) in the experiment group compared with 10.46 months (8.92-13.84) in the control group (HR 1.05; 95%CI 0.71-1.54, p=0.82). The most common adverse events in both groups were anemia (S-1 plus cisplatin, 80.17% vs 5-Fu plus cisplatin, 71.19%), leukopenia (71.90% vs 62.71%), neutropenia (68.60% vs 55.93%), nausea (50.41% vs 60.17%), thrombocytopenia (44.63% vs 26.27%), vomiting (42.98% vs 42.37%) and anorexia (38.02% vs 41.53%). **Conclusions:** S-1 plus DDP is an effective and tolerable option for patients with advanced gastric or gastro-oesophageal junction adenocarcinoma. Clinical trial information: NCT01198392.

4026 Poster Discussion Session (Board #18), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Randomized phase II trial of extended versus standard neoadjuvant therapy for esophageal cancer, NCCTG (Alliance) trial N0849.

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Background: Patients (pts) with locally advanced esophageal or gastroesophageal junction (GEJ) adenocarcinoma commonly receive neoadjuvant chemoradiotherapy (chemo-RT). Despite this approach the rate of recurrence remains high. Given the difficulties of postoperative therapy, the efficacy of extended neoadjuvant therapy was assessed. **Methods:** Eligibility criteria included T3-4,N0 – T_{any},N(+) disease amenable to radiation and surgery. Pts were randomized to either arm A (docetaxel 60 mg/m^2 day 1 , oxaliplatin [Oxal] 85 mg/m^2 day 1, and capecitabine 1250 mg/m^2/day days 1-14 x 2 cycles [DOC] followed by 5-FU 180 mg/m^2/day continuous IV through radiation + Oxal 85 mg/m^2 days 1,15,29 + 50.4 Gy radiation (chemo-RT)) or arm B (chemo-RT alone). Randomization was stratified by ECOG PS (0/1 vs 2) and stage (II vs III/IVA). Primary endpoint was pathologic complete response (PCR) rate, defined as no gross or microscopic tumor identified in the surgical specimen. Interim analysis assessed efficacy and futility of the experimental intervention. Wilcoxon rank sum and Fisher's exact tests were used to compare clinical/pathologic factors between arms. **Results:** Baseline and stratification factors were well balanced between arms. Of 42 pts included in the interim analysis (86% male; age [median 63, range 38-88], 100% PS 0/1; 71% stage III; 55% esophagus, 40% GEJ; 36% measurable disease), 4 and 1 pts in arms A and B, respectively, did not have surgery due to death (A, 2), progressive disease (A, 1), alternative treatment (A, 1) or adverse event (B, 1). Among 21 arm A pts, 21, 20, and 19 pts started 1st cycle of DOC, 2nd cycle of DOC and chemo-RT, respectively. All arm B pts received chemo-RT. 33% (7/21) of arm A and 48% (10/21) of arm B pts achieved PCR (p=0.53). Among pts undergoing surgery, 94% (16/17) and 100% (20/20) of arm A and B pts had complete resection (p=0.46). 38% and 24% of arm A and B pts experienced at least one grade 4+ adverse event at least possibly related to treatment (p=0.51). **Conclusions:** Extended neoadjuvant therapy in pts with locally advanced esophageal or GEJ adenocarcinoma failed to improve the PCR rate. Follow-up in regard to survival and rate of recurrence is ongoing. Clinical trial information: NCT00938470.

4027 Poster Discussion Session (Board #19), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Effectiveness of D2 gastrectomy for lymph node positive and advanced gastric cancer: Survival results of the Italian Gastric Cancer Study Group (IGCSG) randomized surgical trial on D1 versus D2 dissection for gastric carcinoma.

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Background: It is still unclear whether D2 lymphadenectomy can significantly improve survival of gastric cancer and therefore should be applied routinely or performed in selected cases. We conducted a multicenter randomized trial to compare the efficacy of D2 and D1 lymphadenectomy for gastric cancer. Primary outcome was overall survival; secondary endpoints were disease specific survival, morbidity and in-hospital mortality. **Methods:** Between June 1998 and December 2006 patients with gastric adenocarcinoma were randomly assigned to either D1 or D2 lymphadenectomy. Intraoperative randomization was implemented centrally by telephone. **Results:** A total of 267 eligible patients were allocated to either D1 (133) or D2 group (134). Morbidity (12·0% vs 17·9%, p=0·18) and mortality (3·0% vs 2·3%; p=0·72) were similar. There was no difference in the overall 5-year survival (66·5% vs 64·2%, p = 0.70). Subgroups analyses showed a 5-years disease specific survival benefit for pT1 cases treated with D1 dissection (98.0% vs 82.9%, p = 0.01) and of pT>1 LN+ patients treated with D2 resection (38·4% vs 59·5%, p = 0.05 at five years). **Conclusions:** In intention to treat analysis we observed no overall 5-year survival benefit from D2 resection. The trial showed a survival benefit of D1 procedure in early stages. On the opposite, despite evidence of contamination in the D1 arm, a survival advantage was documented in patients with advanced disease and lymph node metastases submitted to D2 procedure. Clinical trial information: ISRCTN11154654.

Survival results.

		Follow-up					
		At 5 years					Complete
		Survival (%)	Diff.	I.C. 95%		P value*	P value *
Survival	All	65.4 (59.8-71.4)					
	D1	66,5	-2,3	-14,0	9,3	0,69	0,36
	D2	64,2					
	D1 T1	91,7	-11	-26,1	4	0,12	0,17
	D2 T1	80,7					
	D1 T2+	51,2	7,3	-7,8	22,3	0,35	0,59
	D2 T2+	58,5					
	D1 LN+	42,5	11,8	-5	28,4	0,20	0,33
	D2 LN+	54,3					
	D1 T2+ LN+	35,0	16	-2	34	0,09	0,19
	D2 T2+ LN+	51,0					
Disease-specific survival	All	71.8 (66.3-77.7)					
	D1	71,0	1,6	-9,8	12,9	0,88	0,92
	D2	72,6					
	D1 T1	98,0	-15,1	-28,2	-2	0,014	0,019
	D2 T1	82,9					
	D1 T2+	54,5	14,2	-0,9	29,3	0,10	0,14
	D2 T2+	68,7					
	D1 LN+	46,0	15,1	-2,0	32,1	0,15	0,19
	D2 LN+	61,1					
	D1 T2+ LN+	38,4	21,1	2,5	39,6	0,05	0,08
	D2 T2+ LN+	59,5					

* Log-rank test.

4028 Poster Discussion Session (Board #20), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Sorafenib (S) alone versus S combined with gemcitabine and oxaliplatin (GEMOX) in first-line treatment of advanced hepatocellular carcinoma (HCC): Final analysis of the randomized phase II GONEXT trial (UNICANCER/FFCD PRODIGE 10 trial).

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Background: HCC is a vascular tumor with poor prognosis. Although S has been shown to improve survival, its ability to induce tumor shrinkage is very low. Given the activity of Gemcitabine and Oxaliplatin (GEMOX) in HCC, a phase II trial combining S with GEMOX was undertaken to define efficacy and safety profile. **Methods:** Patients with inoperable advanced and/or metastatic HCC (BCLCC B or C), with or without prior palliative chemoembolization, Child pugh score A, WHO performance status (PS) 0-1, were eligible for this two-stage, randomized phase II trial. Patients received S (400 mg BID) alone (arm A) or in combination with GEMOX every 2 weeks (gem. 1000 mg/m² [10 mg/m²/min] on D1; oxaliplatin, 100 mg/m² on D2) (arm B). Randomization was stratified according to CLIP score (0-1 vs. 2-3) and center. Primary endpoint was crude 4-mo Progression-Free Survival (PFS) rate (H0, $< 50\%$; H1, $\geq 70\%$; $\alpha = 10\%$; 1- $\beta = 90\%$). **Results:** From Dec 2008 to Oct. 2011, 94 pts were enrolled: median age, 64 yrs; male, 88%; PS 0 (69%) 1(31%), CLIP 0-1 (48%) 2-3 (52%), cirrhosis (63%), portal vein thrombosis (29%), extra liver metastasis (69%). These characteristics were well balanced in both arms. Median duration and dose intensity of S were 4 mo (1-27) and 81% in both arms, respectively. Median number of GEMOX cycles was 7 (1-12) in arm B. Main severe (grade 3-4) toxicity (arm A/B) consisted of neutropenia (grade 3-4: 0%/7%), fatigue (18%/24%), thrombocytopenia (0%/9%), diarrhea (grade 2-4: 10%/21%), peripheral neuropathy (grade 2-3: 0%/10%), and hand foot syndrome (grade 2-3: 13%/7%). For evaluable pts (n = 83), ORR was 9% / 16% and DCR was 70%/77% in arms A/B, respectively. For all pts (median follow-up, 17.6 mo), 4-mo PFS rate was 54%/61%, median PFS was 4.6 (3.9-6.2)/6.2 (3.8-6.8) mo, and median OS was 13.0 (10.4-22.2) /13.5 (7.5-19.1) mo in arms A/B, respectively. **Conclusions:** S plus GEMOX was feasible in HCC. This trial met its primary endpoint (4-mo PFS $\geq 50\%$) and ORR, median PFS and OS were encouraging data. Exploratory analyses are underway to identify subgroups of patients likely to derive most benefit from this combination. Clinical trial information: NCT00941967.

4029 Poster Discussion Session (Board #21), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

The impact of diabetes on HCC.

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Background: The incidence of hepatocellular carcinoma (HCC) in the UK has increased by 40% over the last 20 years, with a corresponding increase in mortality rate. The rising incidence of obesity and type II diabetes are believed to be contributing factors due to the association with non-alcoholic fatty liver and steatohepatitis. We aimed to examine if diabetes was as an independent risk factor for the development of HCC and to assess the impact of diabetes on overall survival (OS). **Methods:** Data from 724 patients with HCC and a control group comprising 340 patients with chronic liver disease were collected prospectively between 2007 and 2012. The odds ratio (OR) for HCC in diabetic versus non-diabetic patients was calculated. Univariate and multivariate analysis was performed using logistic regression. Cox proportional hazards analysis was used to estimate hazard ratio (HR) for death for HCC patients, with and without diabetes and for the impact of variation in diabetic treatments. **Results:** The prevalence of diabetes was 39% within the HCC population and 10.3% within the chronic liver disease group. Univariate analysis demonstrated increased risk of HCC associated with age, sex, diabetes, haemochromatosis, cirrhosis, alcohol abuse and Child's score. In patients with diabetes OR for HCC was 5.74 (CI 3.9-8.3; $p<0.001$). Age, sex, cirrhosis, Child's score, diabetes and diabetes treatment with insulin, retained significance as independent risk factors in multivariate analysis. There was no survival difference for HCC patients with and without diabetes. In diabetic patients with HCC, treatment of diabetes with metformin, compared against other diabetic treatment options, was associated with a significantly longer OS (31 versus 24 months, $p = 0.016$; HR 0.74, $p = 0.027$). **Conclusions:** This study has demonstrated that diabetes is an independent risk factor for the development of HCC in a high risk population and that treatment with insulin appears to confer further independent risk. Diabetes has no effect on survival following the development of HCC but treatment of diabetes with metformin is associated with prolonged survival. In considering the optimal treatment for diabetes in chronic liver disease the beneficial effects of metformin on OS, if HCC develops, should be taken into account.

4030 Poster Discussion Session (Board #22), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Placebo controlled, double blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): Results on long-term survival.

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Background: Octreotide LAR (O) compared to placebo (P) lengthens significantly time to tumor progression (TTP) in patients with metastatic midgut neuroendocrine tumors (Rinke et al. 2009). The antiproliferative response was more pronounced in patients with low ($\leq$ 10%) hepatic tumor load (HL). To investigate whether this beneficial effect also affects overall survival (OS), patients included in the PROMID trial were followed until January 2013 at least once a year. **Methods:** Between July 2001 and January 2008, 42 and 43 patients were randomly assigned to receive O or P. Post study treatment was at the discretion of the local investigator. Data on cause of death and on post study treatment were documented. OS was analyzed using the Kaplan-Meier method. Treatment groups (O vs. P; HL at study entry $\leq$ 10% vs. $>$10%) were compared using the log rank test and hazard ratios were estimated with the use of the Cox proportional hazards model. **Results:** 41 of 85 patients died until January 2013. 19 in the octreotide and 22 in the placebo arm. Median OS for all 85 patients was 85 months, "not reached" in the O arm and 84 months in the P arm (p=0.59, HR=0.85 [CI 0.46; 1.56]). Cause of death was unrelated to the tumor disease in 8 patients. 26 of 64 patients (10 in the O vs. 16 in the P arm) died in the HL $\leq$ 10% subgroup and 15 of 21 patients (9 in the O vs. 6 in the P arm) in the HL $>$ 10 % (p=0.002, HR=2.7). Median OS in the HL $\leq$ 10% subgroup was "not reached" (octreotide) vs 80.5 months (placebo) (p=0.14, HR=0.56 [CI 0.25; 1.23]). In the HL $>$ 10% subgroup the respective numbers were 35 vs. 84 months (p=0.14, HR=2.18 [CI 0.75; 6.33]). Post study treatment in the O and P groups included octreotide LAR (29 vs. 38 patients), hepatic CHE (5 vs. 12 patients), PRRT (13 vs. 13 patients) and CHT (4 vs. 5 patients). **Conclusions:** Octreotide LAR not only prolongs TTP but also extends OS in the subgroup of patients with metastatic midgut NETs and a low HL ($\leq$ 10% at study entry) but not in the high (HL $>$ 10%) subgroup. Almost all patients who were randomized at study entry in the P group received octreotide LAR after disease progression, but these experienced a less favourable OS in the low HL subgroup. Clinical trial information: NCT00171873.

4031 Poster Discussion Session (Board #23), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

A multicenter, randomized, blinded, phase III study of pasireotide LAR versus octreotide LAR in patients with metastatic neuroendocrine tumors (NET) with disease-related symptoms inadequately controlled by somatostatin analogs.

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Background: The novel somatostatin analog (SSA) pasireotide has a broader binding profile than currently available SSA (octreotide and lanreotide). Results from a phase III study (NCT00690430) of pasireotide LAR (P) vs octreotide LAR (O) in patients (pts) with NET and disease-related symptoms uncontrolled by the maximum approved dose of available SSA are shown. **Methods:** Pts (N=110) were randomized and stratified by predominant symptom at baseline (diarrhea [D], flushing [F], or D+F) 1:1 to P (60 mg IM) or O (40 mg IM) q28d. Primary objective was symptom response at month (M) 6. Secondary objectives included tumor response and safety. Progression-free survival (PFS) was an exploratory analysis. **Results:** 53 and 57 pts were enrolled in the P and O arms when the study was halted due to an interim analysis suggesting futility for symptom response. Baseline characteristics were similar between arms. Majority of primary tumor locations were small intestine (72% and 81% in the P and O arms). Symptom response at M6 was 9/43 (21%) and 12/45 (27%) in the P and O arms, odds ratio 0.73 (95% CI, 0.27-1.97; p=0.53). Median numbers of D/day and F/2 weeks and change in symptom from baseline to M6 are in Table. Hyperglycemia (11% vs 0%), diarrhea (9% vs 7%), and abdominal pain (2% vs 9%) were the most common grade 3/4 AEs in the P vs O arms in the core phase, and 7 (13%) and 4 (7%) pts discontinued due to AEs. Median investigator-assessed PFS was 11.8 months and 6.8 months in the P and O arms (HR=0.46; p=0.045). **Conclusions:** P and O showed a similar safety profile except for the higher frequency of hyperglycemia in P. Pts on P had PFS 5 months longer than pts on O (investigator assessment), despite no differences in symptom response rates. These results warrant a large phase III trial to clarify the role of P as a therapy for NET. Clinical trial information: NCT00690430.

	Pasireotide LAR N=53		Octreotide LAR N=56*		Between treatment Least-squares mean (95% CI)	
	D	F	D	F	D	F
n	26	28	32	29		
Baseline mean±SD	4.9±1.4	74.0±50.3	6.7±3.3	76.6±64.5		
M6 mean change, %±SD	-25.1±24.0	-42.1±38.8	-36.5±29.1	-49.4±36.7	6.9 (-8.0, 21.9)	4.5 (-15.9, 24.8)

* One pt in the O arm had no baseline information.

4032 Poster Discussion Session (Board #24), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Multicenter phase II trial of temsirolimus (TEM) and bevacizumab (BEV) in pancreatic neuroendocrine tumor (PNET).

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Background: PNET has long had few effective therapies other than chemotherapy. Placebo-controlled phase III trials of the mTOR inhibitor everolimus and the VEGF/PDGF receptor inhibitor sunitinib noted improved progression-free survival (PFS). However, objective response rates (RR) with these agents are still $<10\%$. Preclinical studies suggest enhanced anti-tumor effects with combined mTOR and VEGF targeted therapy. **Methods:** We conducted a phase II trial of the mTOR inhibitor TEM (25 mg IV q week) and the VEGF-A monoclonal antibody BEV (10 mg/kg IV q 2 weeks) in patients (pts) with well or moderately differentiated PNET and progressive disease by RECIST within 7 months of study entry. Co primary endpoints were RR and 6-month PFS. Planned enrollment was 50 patients, with interim analysis for futility after the first 25 evaluable pts. Pts had no prior mTOR or VEGF targeted agents, ECOG PS 0-1, and adequate hematologic and organ function. Continued octreotide was allowed, but not required. Prior interferon, embolization, and $\leq$ 2 chemotherapy regimens were allowed. **Results:** 55 pts were eligible for response assessment. Confirmed PR was documented in 20 of 55 patients (37%). 44 of 55 (80%) patients were progression-free at 6 months. Of 49 pts evaluable for this endpoint, 12 month PFS is 49%. 15 patients remain on therapy. For evaluable patients, the most common grade 3-4 adverse events attributed to therapy were hypertension (18%), hyperglycemia (13%), fatigue (11%). leukopenia (9%), headache (9%), proteinuria (7%), and hypokalemia (7%). **Conclusions:** The combination of TEM/BEV has substantial activity in a multi-center phase II trial with RR of 37%, well in excess of single targeted agents in PNET. 6-month PFS was a notable 80% in a population of patients with RECIST criteria progression within 7 months of study entry. Phase III trials of combined VEGF/mTOR inhibition in PNET should be pursued. Clinical trial information: NCT01010126.

4033 Poster Discussion Session (Board #25), Mon, 1:15 PM-5:15 PM and 4:45 PM-5:45 PM

Effectiveness of peptide receptor radionuclide therapy for neuroendocrine neoplasms: A multi-institutional registry study with prospective follow-up.

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Background: Peptide receptor radionuclide therapy targets somatostatin receptors expressed on well differentiated neuroendocrine neoplasms. Retrospective monocentric studies indicate that peptide receptor radionuclide therapy is an effective treatment for patients with neuroendocrine neoplasms. **Methods:** We initiated a multi-institutional, prospective and board reviewed registry study for patients treated with peptide receptor radionuclide therapy. 450 patients were included and followed for a mean of 24.4 months. Patients were treated with Lutetium-177 (54%), Yttrium-90 (17%) or both radionuclides (29%). Primary neuroendocrine neoplasms were derived of pancreas (38%), small bowel 30%), unknown primary (19%), lung (4%) and colorectum (3,5%). Most neuroendocrine neoplasms were well differentiated with a proliferation rate below 20% in 54% and were pretreated by 1 or more therapies in 73%. **Results:** Overall survival of all patients from the beginning of therapy was 59 months in median. Median survival depended on radionuclides used (Yttrium-90: 38 months; Lutetium-177: not reached; both: 58 months), proliferation rate (G1: median not reached; G2: 58 months; G3: 33 months; unknown: 55 months) and origin of primary tumors (pancreas: 53 months; small bowel: not reached; unknown primary: 47 months; lung: 38 months) but not upon number of previous therapies. Median progression-free survival measured from last cycle of therapy accounted to 41 months for all patients. Progression-free survival of pancreatic neuroendocrine neoplasms was 39 months in median. Similar results were obtained for neuroendocrine neoplasms of unknown primary with a median of 38 months whereas neuroendocrine neoplasm of small bowel were progression-free for a median of 51 months. Side effects like G3-G4 nephrotoxicity or hematological function were observed in 0.2% and 2% of patients. **Conclusions:** Peptide receptor radionuclide therapy is effective for patients with G1-G2 neuroendocrine tumors irrespective of previous therapies with a survival advantage of several years compared to other therapies and only minor side effects.

4034 General Poster Session (Board #15D), Sun, 8:00 AM-11:45 AM

DOCOX: A phase II trial with docetaxel and oxaliplatin as a second-line systemic therapy for patients with advanced and/or metastatic adenocarcinoma of the pancreas.

Thomas Jens Ettrich, Goetz von Wichert, Thomas M. Gress, Patrick Michl, Michael Geissler, Holger Frithjof Hebart, Andreas W. Berger, Marc Porzner, Bettina Danner, Rainer Muche, Thomas Seufferlein; Department of Internal Medicine I, University of Ulm, Ulm, Germany; Department of Gastroenterology, Philipps-University Marburg, Marburg, Germany; Department of Gastroenterology and Oncology, Klinikum Esslingen, Esslingen, Germany; Klinikum Schwäbisch-Gmünd, Schwäbisch-Gmünd, Germany; Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

Background: In Europe and the USA, pancreatic ductal adenocarcinoma (PDAC) is the fifth most common cause of cancer-related death. For patients with metastatic disease, palliative cytostatic systemic treatment is the only option. There is no established standard for 2nd-line treatment. Fluoropyrimidines either alone or in combination with Oxaliplatin or other chemotherapeutic agents are increasingly used. There are interesting data regarding the combination of Gemcitabine with Oxaliplatin or Docetaxel with respect to progression free survival (PFS) and tumor response in 1st-line. For the first time, the DocOx-trial investigates the combination of Oxaliplatin with Docetaxel as 2nd-line treatment after progression under palliative first-line systemic treatment with Gemcitabine. **Methods:** Prospective, single arm, non-randomized, multicenter, Simon´s two stage phase II trial using Docetaxel (75 mg/m^2, 60 min, d 1) plus Oxaliplatin (80 mg/m^2, 120 min, d 2, qd 22). Duration of the trial is scheduled up to 8 cycles. Primary endpoint: tumor response (RR) according to RECIST 1.0. Secondary endpoints: PFS, OS, safety/toxicity, QoL/clinical benefit. **Results:** Here we present the data on response rate (RR), median progression free survival (mPFS) and median overall survival (mOS) as of February 4th, 2013. Data represents the Intention to treat-analysis of the 44 patients included between 2009 and 2012. 5 patients did not obtain any treatment. RR was 16% (7 partial remissions, no complete remission) with a disease control rate (DCR) of 48% after the first two treatment cycles. Median PFS was 7 weeks (95%-CI: 6-16 w.) and median OS after start of 2nd-line therapy was 36 weeks (95%-CI: 19-55 w.). **Conclusions:** In this single-arm 2nd-line trial for the treatment of PDAC, the combination of Doxcetaxel and Oxaliplatin shows very promising results compared to other 2nd-line-protocols such as OFF. Some patients seem to benefit particularly as indicated by long periods of treatment in this setting. Even after 8 cycles of treatment with DocOx, partial response was observed in 2 patients and stable disease in another 6 patients corresponding a disease control rate of 18%. Clinical trial information: NCT00690300.

4035 General Poster Session (Board #15E), Sun, 8:00 AM-11:45 AM

Prospective randomized phase II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer: A study of the CESAR Central European Society for Anticancer Drug Research-EWIV.

Heike Richly, Luise Maute, Gerhard Heil, Jörn Rüssel, Elke Jäger, Dieter Koeberle, Stefan Fuxius, Karin Weigang-Koehler, Walter Aulitzky, Bernhard Woehrmann, Gernot Georg Hartung, Berta Moritz, Iris Burkholder, Max E. Scheulen, Lothar Bergmann; West German Cancer Center, University Duisburg-Essen, Essen, Germany; Medical Clinic II, University Hospital, Frankfurt, Germany; Kreiskrankenhaus Lüdenscheid, Luedenscheid, Germany; Department of Oncology and Hematology, Martin Luther University Halle-Wittenberg, Halle, Germany; Krankenhaus Nordwest, UCT University Cancer Center, Frankfurt, Germany; Department of Medical Oncology, Kantonsspital St. Gallen, St. Gallen, Switzerland; Onkologische Schwerpunktpraxis, Heidelberg, Germany; Klinikum Nürnberg Nord, Nürnberg, Germany; Robert Bosch Klinik, Stuggart, Germany; Klinikum Braunschweig, Braunschweig, Germany; Klinikum Oldenburg, Oldenburg, Germany; CESAR Central European Society for Anticancer Drug Research - EWIV, Vienna, Austria; STABIL, Statistische und Biometrische Lösungen, Zweibrücken, Germany; Innere Klinik (Tumorforschung), West German Cancer Center, University of Essen Medical School, Essen, Germany

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most common malignant tumours, but PDAC is still associated with a poor prognosis in advanced disease with an overall 5-year survival of only about 15%. Therefore there is a need for new treatment strategies. To improve the standard therapy with gemcitabine we initiated a prospective randomized phase-II trial with gemcitabine (GEM) vs. gemcitabine plus sunitinib (SUNGEM) based on data of in vitro trials and phase-I data for the combination treatment. **Methods:** Patients (N=113) with locally advanced or metastatic PDAC were prospectively randomized to receive gemcitabine alone (GEM) at a dosage of 1000 mg/m² day 1, 8, 15 q28 or to a combination of gemcitabine and sunitinib (SUNGEM) at a dosage of GEM 1000 mg/m² d1+8 and sunitinib 50mg p.o. d1-14, qd21 (based on a phase-I trial). The primary endpoint was progression-free survival (PFS), secondary endpoints were overall survival (OS), time to progression (TTP), overall response rate (ORR) and toxicity. **Results:** The confirmatory analysis of PFS was based on the ITT population (N=106). The median PFS was 13.3 weeks (95 %-Cl: 10.4-18.1 weeks) in the GEM group and 11.6 weeks in the SUNGEM arm (95 %-Cl: 7.0-18.0 weeks) (one-sided logrank: p=0.74). The 6-month PFS rate was 26.8 % (95 %-Cl: 15.4-39.5 %) in GEM arm and 25.0 % in SUNGEM arm (95 %-Cl: 14.0-37.8 %). The overall response rate was 6.1 % (95 %-Cl: 0.7-20.2 %) in the GEM arm and was a slightly but not significantly higher for the SUNGEM arm with 7.1% (95%-Cl: 0.9 – 23.5%).The median time to progression (TTP) was 14.0 weeks (95 %-Cl: 12.4-22.3 weeks) for the GEM arm and 18.0 weeks (95 %-Cl: 11.3-19.3 weeks) for the SUNGEM arm (two-sided logrank: p=0.60). The median OS was 30.4 weeks (95 %-Cl: 18.1-37.6 weeks) for the SUNGEM and 36.7 weeks (95 %-Cl: 20.6-49.0 weeks) for the GEM arm (two-sided logrank: p=0.44). With regard to toxicities, at least one AE of grade 3 or 4 was reported in 78.8% in the SUNGEM arm and 72.2% in the GEM arm. **Conclusions:** The combination of gemcitabine plus sunitinib (SUNGEM) did not improve the PFS in locally advanced or metastatic PDAC compared to gemcitabine alone. Clinical trial information: NCT00673504.

4036 General Poster Session (Board #15F), Sun, 8:00 AM-11:45 AM

Predictive value of phase II clinical trials in pancreatic cancer: Rethinking the road to progress.

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Background: Few new therapies for pancreatic adenocarcinoma (PC) have been approved by the Food and Drug Administration (FDA) or recommended by the National Comprehensive Cancer Network (NCCN), reflecting frequent failures in phase III trials. We hypothesize that the high failure rate in large trials is due to a low predictive value for "positive" phase II studies. **Methods:** Given a median time from initiation of clinical trials to FDA approval of 6.3 years, we conducted a systematic search of the clinicaltrials.gov database for phase II interventional trials of antineoplastic therapy in PC initiated from 1999-2004. We reviewed drug labels and NCCN guidelines for FDA approval and guideline recommendations. **Results:** We identified 70 phase II trials that met our inclusion criteria. Forty-five evaluated compounds without preexisting FDA approval, 23 evaluated drugs approved in other diseases, and 2 evaluated cellular therapies. With a median follow-up of 12.5 years, none of these drugs gained FDA approval in PC. Four trials, all combining chemotherapy with radiation, eventually resulted in NCCN recommendations. Forty-two of the trials have been published. Of 16 studies providing pre-specified type I error rates, these rates were ≥ 0.1 in 8 studies, 0.05 in 6 studies and <0.025 in 2 studies. Of 21 studies specifying type II error rates, 7 used >0.1, 10 used 0.1, and 4 used <0.1. Published studies reported a median enrollment of 47 subjects. Fourteen trials reported utilizing a randomized design. **Conclusions:** The low rate of phase II trials resulting in eventual regulatory approval of therapies for PC reflects the challenge of conquering a tough disease as well as deficiencies in the statistical designs. New strategies are necessary to quantify and improve odds of success in drug development. Statistical parameters of individual or coupled phase II trials should be tailored to achieve the desired predictive value prior to initiating pivotal phase III studies. Positive predictive value of a phase II study assuming a 1%, 2%, or 5% prior probability of success and 10% type II error rate.

Type I error	1% Prior	2% Prior	5% Prior
0.1	0.08	0.16	0.32
0.05	0.15	0.27	0.49
0.01	0.48	0.65	0.83
0.0025	0.78	0.88	0.95

4037 General Poster Session (Board #15G), Sun, 8:00 AM-11:45 AM

A phase I trial of a local delivery of siRNA against k-ras in combination with chemotherapy for locally advanced pancreatic adenocarcinoma.

Talia Golan, Ayala Hubert, Amotz Shemi, Amiel Segal, Alan Dancour, Elina Zorde Khvalevsky, Eliel Ben-David, Stephen Raskin, Yuri Goldes, Yael Inbar, Maor Lahav, Avi Domb, Eithan Galun; Sheba Medical Center, Tel HaShomer, Israel; Hadassah Hebrew University Hospital, Jerusalem, Israel; Silenseed, Ltd., Jerusalem, Israel; Shaare Zedek Medical Center, Jerusalem, Israel; Sheba Medical Center, Ramat Gan, Israel; Chaim Sheba Medical Center, Ramat Gan, Israel; The Hebrew University of Jerusalem, Jerusalem, Israel

Background:K-Ras mutation G12D is most prevalent in pancreatic adenocarcinoma (PDAC). siRNA against the K-Ras^{G12D}(siG12D) mutant had showed significant preclinical anti-tumor effects. siG12D LODER - miniature biodegradable polymeric matrix that encompasses anti-K-RasG12D siRNA drug, is placed with Endoscopic US biopsy and designed to continuously release the drug regionally over a period of 4 months. **Methods:** Open label phase I study of patients with locally advanced non-operable PDAC in the first-line setting. Patients were assigned to receive siG12D LODERs in dose escalation cohorts: 0.025mg, 0.75mg and 3.0mg. Gemcitabine 1000 mg/m^{2}IV was given weekly, following siG12D LODER insertion. The RP2D (recommended phase II dose) was further examined in 3.0 mg dose cohort in combination with modified Folfirinox (Oxaliplatin 85mg/m2, Irinotecan 150mg/m2, Fluorouracil infusion 2,400mg/m2 46 hours, every 2 weeks). Follow up period was 8 weeks and survival follow up until death. Primary study objectives were to determine the dose-limiting toxicities (DLT) and maximum tolerated doses (MTD). **Results:**15 patients have been enrolled. 2 patients were omitted from study due to metastatic disease detected on day 1 post siG12D LODER implant imaging . Median age = 70 (range 52-85); male:female 8:7. Among 13 treated patients, the most frequent adverse events observed in the study were typically grade 1-2 in severity; 4 patients experienced serious adverse events (SAE), one procedure related. No DLTs were observed. MTD was not reached. CT performed 8-10 weeks following the procedure showed stable disease in all patients. Reduction in tumor marker CA 19-9 was observed in 64% (7/11) of patients. The median survival of 13 patients was 16 months (8/13 patients still alive at analysis). **Conclusions:** The combination of siG12D LODER and chemotherapy is well tolerated. The combination has demonstrated promising efficacy in locally advanced PDAC with durable responses. Phamocodynamic endpoints are currently being examined in an expansion cohort in operable patients. A phase II randomized trial is planned in order to investigate efficacy of siG12D LODER in locally advanced non-operable PDAC. Clinical trial information: NCT01188785.

4038 General Poster Session (Board #15H), Sun, 8:00 AM-11:45 AM

A pilot phase II multicenter study of nab-paclitaxel (Nab-P) and gemcitabine (G) as preoperative therapy for potentially resectable pancreatic cancer (PC).

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Background: Nab-P plus G is a new option for advanced PC. This combination was evaluated as a preoperative regimen for potentially resectable PC. **Methods:** Patients (pts, n=25) with resectable PC (NCCN criteria) were treated with 3 cycles of Nab-P (125mg/m^2) & G (1000mg/m^2) on day 1, 8, and 15, followed by surgical resection. The chosen endpoint was Grade III/IV histological changes (Arch Surg.127:1335-39:1992) in > 30% of resected tumor specimens. **Results:** Accrual is complete with 25 pts (median age 65, 10 F:15 M), 14/25 completed 3 cycles of treatment. Early drug discontinuation or drug interruption prior to the completion of 3 cycles occurred in 11 pts due to azotemia, cholangitis, pneumonia, catheter infection and pt decision. One pt had a fatal (grade 5) non-neutropenic aspergillus pneumonia. There was one episode of neutropenic fever (4%), and 3 episodes of cholangitis (12%) due to biliary stent malfunction. Other adverse events (grade 3/4) include neutropenia 64%, anemia 20%, dehydration 12%, nausea 12% and thrombocytopenia 12%. Dose reductions due to AEs were required in 5 pts, (3-neutropenia, 2-rash). Surgical resection was successful in 20/25 pts: 12- Pancreaticoduodenectomy, 8- Distal Pancreatectomy, 19/20 pts underwent an R0 resection. Surgical resection was not done in 5/25 pts due to: pre-operatively identified metastatic disease (2), blood vessel involvement at surgery (1), pt declined (1) and a pre-operative death (1).Post-operative tumor staging identified a complete response (n=1); stage IA (n=1); stage IIA (n=6); and stage IIB (n=12). Radiological partial response (PR) was documented in 4 pts prior to surgery. CA19-9 levels decreased from baseline by > 50% in 60% (n=15) of pts and by > 90% in 16% (n=4). Post-operative > 90% histological tumor response (Grade 3/4) was seen in 6 of 20 (30%) resected specimens. **Conclusions:** Preoperative therapy with Nab-P plus G is feasible with evidence of activity by radiological (PR in 16%), CA19-9 (decrease > 50% in 60% of pts) and pathological down staging (Grade 3/4 in 30% in resected tumor specimens). A larger study is warranted. Supported by Abraxis/Celgene Pharmaceuticals and the TGen foundation. Clinical trial information: NCT01298011.

4039 General Poster Session (Board #16A), Sun, 8:00 AM-11:45 AM

Hemoglobin-A1c level to predict for clinical outcomes in patients with pancreatic cancer.

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Background: An association between diabetes mellitus (DM) and pancreatic ductal adenocarcinoma (PDA) has long been recognized. While long-standing DM may be a risk factor for developing PDA, new-onset DM may be a manifestation of the cancer. Here we assess the role of an objective and quantifiable measure of glucose intolerance, hemoglobin-A1c (HbA1c), in predicting clinical outcomes in PDA. **Methods:** HbA1c values were prospectively collected on 656 consecutive patients presenting to the Johns Hopkins Pancreas Multidisciplinary Cancer Clinic from 2009-2012. Patients were diagnosed with benign pancreatic disease (BPD) or biopsy-confirmed resectable (R), borderline/locally advanced (BL), or metastatic (M) PDA. Patients with prior treatment for PDA or a history of DM greater than a 1-year were excluded. Univariate Cox regression analyses and multivariable proportional hazards models were used to identify poor prognostic factors for overall survival. **Results:** Of 284 patients included, 44 had benign disease, 62 R-PDA, 115 BL-PDA, and 63 M-PDA. Patients with malignant disease (R-, BL-, and M-PDA) collectively had higher HbA1c values on average at presentation than patients with BPD (6.1% vs. 5.6%, $p<0.001$). There was a trend towards higher HbA1c at presentation in patients with advanced PDA (BL and M) compared to patients with R-PDA (6.2% vs. 5.9%, $p=0.100$); moreover, the proportion of patients with HbA1c levels in the diabetic range (>6.4%) increased with more advanced stage of disease. Among patients with PDA ($n=240$), univariate analyses showed HbA1c≥6.5, age≥65, ECOG≥1, CA19-9>90, tumor size >3cm, and advanced stage to be significantly associated with inferior survival (all HR>1, $p<0.05$). After multivariate analysis with backward elimination, all of the above factors except for tumor size >3cm remained in the model for inferior survival. **Conclusions:** HbA1c level at presentation appears to correlate with disease stage and, moreover, to predict for survival among all stages of PDA. Patients with PDA have significantly higher HbA1c levels at presentation than patients with BPD. This study highlights the potential utility of HbA1c as a screening tool and prognostic factor.

4040^ General Poster Session (Board #16B), Sun, 8:00 AM-11:45 AM

Interim safety and efficacy analysis of a phase II, randomized study of GVAX pancreas and CRS-207 immunotherapy in patients with metastatic pancreatic cancer.

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Background: GVAX is composed of GM-CSF-secreting allogeneic pancreas cancer cell lines and administered with low-dose cyclophosphamide (CY) to inhibit regulatory T cells. In prior studies, GVAX induced mesothelin-specific T cell responses that correlated with survival. CRS-207 is a live-attenuated *Listeria monocytogenes* engineered to express human mesothelin. CRS-207 stimulates potent innate and adaptive immunity and has shown synergy with GVAX in mouse tumor models. Anecdotal survival benefit was observed in the CRS-207 phase I study in patients who received prior GVAX. **Methods:** Patients were enrolled with metastatic pancreatic ductal adenocarcinoma (PDA) who received or refused $\geq$ 1 prior chemotherapy, had ECOG $\leq$ 1 and adequate organ function. Patients were randomized 2:1 to receive 2 doses of CY/GVAX followed by 4 doses of CRS-207 (Arm A) or 6 doses of CY/GVAX (Arm B) every 3 weeks. Clinically stable patients were offered additional 20-week courses. The primary endpoint was comparison of OS between treatment arms. Secondary endpoints were to evaluate safety, clinical and immune responses. **Results:** 90 patients were treated (Arm A: 61, Arm B: 29). As of Jan 2013, 27 patients completed 1 course (A: 24, B: 3) and 17 patients (A: 15, B: 2) initiated a 2nd course. Median age was 63. Median number of prior regimens was 3. No treatment-related serious adverse events (SAEs) or unexpected toxicities were observed. The most frequent Grade (G) 3/4 related toxicities were fever, lymphopenia, hypophosphatemia, elevated liver enzymes, and fatigue following CRS-207 in $<$5% of subjects. Of 51 patients evaluated post-treatment, 34% had stable disease in Arm A vs. 19% in Arm B. OS for all patients treated was 6 months in Arm A vs. 3.4 months in Arm B (two-sided, p=0.0114). **Conclusions:** Combined CY/GVAX pancreas and CRS-207 was generally well-tolerated with no treatment-related SAEs or unexpected G3/4 toxicities. The significant difference in OS between treatment arms met the criteria for early stopping. This indicates that the combination immunotherapy may extend OS for metastatic PDA patients with minimal toxicity and should continue to be developed as an effective therapy. Clinical trial information: NCT01417000.

4041 General Poster Session (Board #16C), Sun, 8:00 AM-11:45 AM

Pimasertib plus gemcitabine in metastatic pancreatic adenocarcinoma: Results of a safety run-in part of a phase II trial.

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Background: Activating MAPK pathway mutations (predominantly *RAS)* occur with a high incidence in metastatic pancreatic adenocarcinoma (mPaCa). Pimasertib is a MEK1/2 inhibitor with potent activity in cell lines and xenografts with an activated MAPK pathway. This two-part trial in patients (pts) with mPaCa comprises a dose-escalation safety run-in and a randomized phase II part (EudraCT 2009-011992-61). We defined the maximum tolerated dose (MTD), safety, pharmacokinetics (PK) and antitumor activity of two pimasertib dosing schedules (S), and the recommended phase II dose (RP2D). **Methods:** Dose-escalation (3+3 design) in two dosing S of oral pimasertib: once-daily (qd) - 5 days on, 2 days off (S1); and twice-daily (bid) - continuous (S2) combined with the standard dose of gemcitabine (gem). **Results:** 53 pts (median age 61 years and ECOG performance status 0-1) have been treated at six dose levels in S1 (15 to 120 mg qd) and at 60 and 75 mg bid in S2. MTDs were defined as 120 mg qd and 75 mg bid. Two pts had a dose-limiting toxicity (DLT) in the DLT observation period: a grade (G) 3 confusion with ataxia and disorientation at 60 mg bid and a G4 suicidal ideation at 75 mg bid. G3-4 adverse events (AEs) in >5% of pts were: neutropenia (32%), thrombocytopenia (25%), asthenia (19%), dyspnea (9%), transaminitis (9%), anemia (8%), and diarrhea, pulmonary embolism, pulmonary sepsis (6% each). Most common AEs were asthenia (70%), ocular AEs (68%), skin rash (62%), nausea (58%), diarrhea (58%), peripheral edema (51%), thrombocytopenia (49%), vomiting (45%), mucositis (43%), neutropenia (38%), decreased appetite (36%) and anemia (34%). The main ocular AE was serous retinal detachment (58%); manageable retinal vein occlusion occurred in five pts. PK data were comparable to pimasertib monotherapy and published gem data. Partial responses were noted in 10 pts and stabilisation ≥3 months in 13 pts. Hot spot mutations in genes activating the MAPK and PI3K/AKT pathway and correlation with clinical outcome are being investigated. **Conclusions:** Pimasertib MTDs were reached. The RP2D was defined as 60 mg bid. PK was dose proportional and associated with target inhibition. Sustained responses were seen in both dosing schedules. Clinical trial information: 2009-011992-61.

4042 General Poster Session (Board #16D), Sun, 8:00 AM-11:45 AM

Circulating cytokines and angiogenic factors (CAF) as markers of clinical response in the study of trametinib (T) plus gemcitabine (G) versus placebo (P) plus gemcitabine for patients (pts) with untreated metastatic adenocarcinoma of the pancreas (MEK113487).

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Background: T is a reversible and highly selective allosteric inhibitor of MEK1/MEK2. The addition of T to G did not improve overall survival (OS) as first-line treatment for pts with metastatic adenocarcinoma of the pancreas (ASCO GI 2013 #291). CAF profiles have shown potential for identification of prognostic and predictive markers in cancer pts (Tran, *Lancet,* 2012). **Methods:** Plasma samples (n = 144 baseline [BL]; n = 112 day 15) from pts who consented to participate in MEK113487 study were analyzed for 30 CAFs (ANG2, IGFBP3, IL2R, IP10, MMP2, MMP9, OPN, PDGFBB, SCF, TIMP1, IL6, MIP1B, SDF1, TRAIL, VEGF, MIP3A, MCP2, FGFB, IL8, VEGFR1, IL10, IL1A, IL12P40, PIGF, EGF, IL1B, TNFA, IL4, MIP1A, MCP3) using SearchLight multiplex assays in a CLIA-certified laboratory. Change from BL was assessed using either paired *t* tests or Wilcoxon tests. BL and change from BL CAF levels were tested for association with clinical outcome using proportional hazards regression within arm ($P < .01$ for significance) and between arms (treatment arm by CAF level interaction, $P < .05$ for significance). **Results:** Lower levels (< median) of BL ANG2, IL6, TIMP1, and IL8 were associated with an average of 5 mo longer OS in both the T+G and G arms. Lower BL levels (less than first quartile) of IGFBP3 and PDGFBB were associated with 6 mo longer OS in the T+G arm, while higher levels (greater than third quartile) of IGFBP3 and PDGFBB were associated with 4.8 mo longer OS in the G arm. A combined model of low IGFBP3 and/or PDGFBB showed improved survival for T+G vs G (median OS, 10.3 vs 5.6 mo). Decreases of ANG2 and IL2R levels at day 15 from BL were observed in the T+G arm only; additional results will be presented. **Conclusions:** This study suggests that plasma CAF profiling may aid in the prognostic evaluation of pts, assessing therapeutic response, and identifying pathways modulated by treatment in pancreatic cancer pts. Low IGFBP3 and PDGFBB may identify patients who receive greater benefit from T+G compared with G in this population and merit further investigation as predictive markers. Clinical trial information: NCT01231581.

4043 General Poster Session (Board #16E), Sun, 8:00 AM-11:45 AM

Extended neoadjuvant chemotherapy (CT) in borderline resectable pancreas cancer (BRPC).

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Background: The optimal surgical (S) approach to BRPC is unknown. We evaluated an approach to BPRC using extended course chemotherapy (CT) without routine neoadjuvant chemoradiation (CRT). Clinical outcomes were evaluated on an ″intent to treat″ basis. **Methods:** Patients (pts) were identified from a prospectively-maintained database started in 2008. Pts required 1) Dx BRPC with non-tail primary per radiographic staging using AHPBA/NCCN guidelines 2) No prior therapy (Rx) 3) Negative staging/exploratory laparoscopy prior to S 4) All cancer Rx at VMMC prior to S. Pts received gemcitabine/docetaxel (G/D) as initial CT. Pts with systemic progression/comorbid complication prior to 24 wks were not offered local Rx; pts with localized cancer at 24 wks judged likely to achieve R0 resection were offered S; all other pts were offered fluoropyrimidine-based CRT. **Results**: Of 76 identified pts (median age 66), 12 (16%) are on initial CT and not fully evaluable. G/D as sole CT achieved 24 wk disease control in 46/64 (72%) pts and >50% decline in baseline CA 19.9 in 39/55 pts (71%). 53/64 fully evaluable pts (83%) completed 24 wks CT, 11/64 pts (17%) did not (4 systemic progression, 3 Rx- related, 4 intercurrent illness). 50/53 pts attempted local Rx (40 S, 10 CRT, 2 unfit, 1 refused). 30/40 pts (75%) had successful S (all R0), 10/40 pts (25%) had inoperable disease (4 local-subsequently received CRT, 6 systemic). 23/30 pts (77%) have received some form Rx post R0 resection. With median f/o of 20 mo, 23/44 (52%), 17/30 (57%), and 6/14 (43%) receiving any local Rx, S, and CRT-only remain progression free. 13/30 S pts recurred, 3 local (10%) and 10 systemic (33%). 1-yr, 2-yr, 3-yr, and median overall survivals (OS) for fully evaluable pts respectively are 82%, 50%, 36%, and 27 mo. Median OS for pts receiving CT-only (20 pts), CT+CRT (14 pts), and R0 pts are 12 mo, 17 mo, and >20 mo, respectively. 25/30 R0 pts remain alive (range 6-54 mo). **Conclusions:** 1) Extended neoadjuvant CT without routine neoadjuvant CRT is a feasible approach to BRPC. 2) G/D has significant activity in BRPC. 3) Pretreatment surgical staging combined with the above Rx yields a high probability of R0 resection. 4) OS for both resected and non-resected pt was superior to usual literature comparators.

4044 General Poster Session (Board #16F), Sun, 8:00 AM-11:45 AM

The impact of diabetes mellitus and metformin on survival of patients with advanced pancreatic cancer receiving chemotherapy.

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Background: A causal relationship between diabetes mellitus (DM) and pancreatic cancer (PC) is well established. However, in patients with advanced PC (APC) who receive palliative chemotherapy, the impact of DM on prognosis is unclear. **Methods:** Between 2003 and 2010, we enrolled consecutive patients with APC, all recipients of palliative chemotherapy, with the provision that DM disease status could be properly defined. Enrollees were stratified by diagnosis, in accordance with 2010 DM criteria (AHA/ADA). DM at least 2 years' duration prior to diagnosis of APC qualified as remote-onset DM (vs recent-onset). Clinical characteristics and outcomes were then analyzed. **Results:** Of the 349 enrollees with APC, 183 (52.4%) had DM. In patients with DM, 160 had DM at the time APC was diagnosed (remote onset, 87; recent onset, 73); and the remaining 23 developed DM during the course of APC treatment. Ultimately, 73.2% (134/183) of DM patients received antidiabetic medication (metformin (56), sulfonylurea (62), insulin (43)). By multivariate analysis, cancer extent (HR, 1.792; $p < 0.001$) and weight loss during chemotherapy (HR, 1.270; $p = 0.08$) were associated with diminished overall survival (OS), whereas a diagnosis of DM (HR, 0.788; $p = 0.05$) conferred a positive effect on OS (OS 8.4 months in DM patients vs 7.5 months in non-DM patients, $p = 0.04$). Among DM patients, recent-onset DM trended toward prolonged OS, compared with remote-onset/subsequent DM (9.8 months vs. 7.9 months, respectively; HR, 0.789; $p = 0.142$). Neither antidiabetic medication in general nor sulfonylurea or insulin specifically affected OS. However, recipients of metformin survived longer than non-recipients (HR, 0.693; 95% CI, 0.492-0.977; $p = 0.036$). Relative to the APC cohort overall including non-DM patients, metformin conferred better survival as well (11.0 months vs. 7.8 months, HR 0.712, $p = 0.067$), given similar baseline clinical characteristics. **Conclusions:** In patients with APC receiving palliative chemotherapy, recent-onset DM (within 2 years of APC diagnosis) and metformin treatment are positive prognosticators, associated with prolonged OS.

4045 General Poster Session (Board #16G), Sun, 8:00 AM-11:45 AM

Development and validation of a predictive model to assess an individual's risk of pancreatic cancer.

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Background: Due to the very low survival of pancreatic cancer (PC), early detection is a critical strategy to improve the outcome of PC.Screening individuals with genetic syndromes associated with a high incidence of PC or families predisposed to PC is increasing. However, those populations account for only 10% of all PC cases. A different approach for developing an effective surveillance tool is needed to identify high-risk individuals without hereditary risks. The goal of this study was to develop and validate risk prediction models for filtering purposes as part of the sporadic PC surveillance activities. **Methods:** Based on an eight-year follow-up of a cohort study involving 1,289,933 men and 557,701 women in Korea who had biennial examinations in 1996-1997, gender-specific risk prediction models were developed using the Cox proportional hazards model. The models were validated using independent data of 500,046 men and 627,629 women who had biennial examinations in 1998-1999. The models' performance was evaluated with respect to their discrimination and calibration abilities based on the C-statistic and the Hosmer-Lemeshow (H-L) type χ^2-statistic. **Results:** Age, height, BMI, fasting glucose, urine glucose, smoking, and age at smoking initiation were included in the model for men. In the model for women, height, BMI, fasting glucose, urine glucose, smoking, and drinking habits were included. Smoking was the most significant risk factor for developing pancreatic cancer in both men and women. Model validation showed excellent model performance with C-statistics (95% confidence interval) of 0.813 (0.800−0.826) and 0.804 (0.788−0.820) for men and women, respectively. The H-L type χ^2-statistics (P-values) were 7.478 (0.587) and 10.297 (0.327) for men and women, respectively. Five different risk groups could be identified with hazard ratios (HR) greater than 20 in the highest risk group compared to the lowest risk group in both the men and women. **Conclusions:** Gender-specific individualized risk prediction models for PC were developed and validated with a high level of performance. These models can be used to identify high-risk individuals who may benefit from increased surveillance of PC.

4046 General Poster Session (Board #16H), Sun, 8:00 AM-11:45 AM

Circulating tumor cells in locally advanced pancreatic adenocarcinoma: The ancillary study Circe 07 of the LAP 07 trial.

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Background: Pancreatic carcinoma is one of the leading causes of cancer-related mortality. At time of diagnosis, 30% of patients present with a locally advanced unresectable but non metastatic carcinoma (LAPC). Theoretically, patients with micrometastatic dissemination at diagnosis should benefit from systemic treatments, whereas radiation therapy should be favored in the others. Based on the hypothesis that circulating tumor cells (CTC) count is a surrogate of the cancer metastatic abilities, CTC detection rates and prognostic value were studied in a prospective cohort of LAPC patients. **Methods:** LAP07 international multicenter randomized study assesses in patients whose LAPC is controlled after 4 months of gemcitabine-based chemotherapy whether to administrate a chemoradiotherapy could increase overall survival versus continuation of chemotherapy alone. A subgroup of patients included in LAP 07 trial were prospectively screened for CTC before the start of the chemotherapy and after two months of treatment, using the CellSearch technique. Clinico-pathological characteristics and survival of patients were obtained prospectively and were correlated with CTC detection. **Results:** Seventy-nine patients were included in this ancillary study. One or more CTC/7.5ml were detected in 5% of patients before treatment and in 9% of patients after two months of chemotherapy (overall detection rate: 11% of patients). CTC positivity was associated with poor tumor differentiation ($p=0.04$), and with shorter overall survival in multivariable analysis ($RR=2.5$, $p=0.01$), together with anemia ($p=0.005$). **Conclusions:** The evaluation of micrometastatic disease using CTC detection appears as a promising tool which could help to personalize treatment modalities in LAPC patients. Clinical trial information: NCT00634725.

4047 General Poster Session (Board #17A), Sun, 8:00 AM-11:45 AM

Genetic, tissue, and plasma biomarkers of outcomes from a prospective study of neoadjuvant short course proton-based chemoradiation for resectable pancreatic ductal adenocarcinoma (PDAC).

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Background: The prognosis of resectable PDAC reflects a complex interaction between genotype, growth factor levels, and tumor microenvironment. We performed genetic, plasma, and tissue-based biomarker analysis for a phase I/II study of neoadjuvant short course proton-based chemoradiation. **Methods:** Patients with radiographically resectable PDAC were treated on an IRB approved, phase I/II trial of neoadjuvant short course-proton-based chemoradiation. Genotyping included KRAS, BRAF, NRAS, TP53, and PIK3CA. Tissue-based IHC on resection specimens included DPC4, CXCR4, CXCR7, and SDF1a in the central and peripheral regions of PDAC. The trial was amended to evaluate plasma biomarkers, drawn before and after chemoradiation, including HGF, VEGF, sVEGFR2, SDF1α, bFGF, PlGF, TNF-α, CAIX, sFLT1, IL-6, IL-8, and IL-1β. Correlation with OS was evaluated by the Wald test in a univariable Cox regression using log-transformed covariates. **Results:** Surgical specimens from all 38 patients who underwent resection and serial plasma samples from the last 12 patients enrolled were analyzed. Disease-specific results were previously reported (ASCO 2012, abs 4021). DPC4 intact (37% of evaluated patients) was associated with oligometastatic disease ($p<0.05$) but not OS. KRAS mutation 31/38 patients (82%), did not affect OS (HR=1.57, p=0.88) , but the specific KRAS G12D mutation (14/38, 37%) had a worse OS (HR=2.44, $p<0.05$). SDF1α and CXCR7 expression was higher and CXCR4 expression was lower in the tumor center versus periphery. Higher CXCR7 expression in the periphery was associated with poor OS (HR=2.29, $p<0.05$). High baseline plasma HGF was associated with a worse OS (HR=6.60, $p<0.05$), with a trend for association between high post-treatment plasma HGF and poor OS (HR=9.28, p=0.08). No other biomarker evaluated was significantly associated with OS. **Conclusions:** In this exploratory analysis, KRAS G12D status, CXCR7 expression, and plasma HGF level were associated with worse OS. DPC4 status correlated with oligometastatic disease. Additional IHC evaluations, including c-MET expression, are ongoing and will be reported. Clinical trial information: NCT00438256.

4048 General Poster Session (Board #17B), Sun, 8:00 AM-11:45 AM

Whole-transcriptome paired-end sequencing and the pancreatic cancer genetic landscape.

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Background: A deeper knowledge of the pancreatic cancer (PDAC) biology is needed to improve the prognosis of the disease. **Methods:** 17 PDAC samples were collected by ultrasound-guided biopsy used for DNA and RNA extraction. 14 samples were analyzed by high resolution copy number analysis (CNA) on Affymetrix SNP array 6.0 and with segmentation algorithm against a reference of 270 Ceu HapMap individuals (Partek Genomic Suite). 17 samples were analyzed by whole transcriptome massively parallel sequencing, performed at 75x2 bp on a HiScanSQ Illumina platform. An average of 7, 3x107 reads per sample were generated, with a mean read depth of 50X. Single nucleotide variants (SNVs) were detected with SNVMix2 and compared with genetic variation databases (dbSNP, 1000genomes, Cosmic). Non-synonimous SNVs were analyzed with the predictors SNPs and GO and PROVEAN. **Results:** CNA results in 9/14 samples exhibited both macroscopic and cryptic cytogenetic alterations, with a mean of 10 CNA per patient. Most frequent gains were observed in 18q11.2 involving GATA6 (3/14) and 19q13 targeting AKT2 (3/14) while hotspot deletions were found on 18q21 (7/14), 17p13 (6/14), 9p21.3 (6/14), 15q (5/14) and 1q35 (4/14). RNAseq showed that samples exhibited a mean of 145 (range: 61-240) non-synonimous SNVs, of which 16 on average are potentially disease-related. Merging copy number and RNAseq data we highlighted the major oncogenic hits of PDAC, confirming the prevalence (14/17) of KRAS mutations, in one case also NRAS (G13D), and the three oncosuppressor CDKN2A (mutated in 3 cases and deleted in 6 cases, in hetero- or homozygosity), SMAD4 (altered by point mutation or gene deletion in 7/14), and TP53 (lost in 6/14 and mutated in 5/17). The signaling pathways affected were: KRAS/MAPK, TGFbeta and integrin signaling, proliferation and apoptosis, DNA damage response, and epithelial to mesenchymal transition. Moreover we found new oncogenic alterations, such as HMGCR, that displayed mutations in 17% of the analyzed patients (3/17). **Conclusions:** NGS combined with high resolution cytogenetic analysis can improve the understanding of pancreatic carcinogenesis.

4049 General Poster Session (Board #17C), Sun, 8:00 AM-11:45 AM

Clinical characterization of hypoxia in pancreatic ductal adenocarcinoma (PDAC) by ^{18}F-FAZA PET and pimonidazole.

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Background: We previously demonstrated correlation between hypoxia and aggressive tumor biology in orthotopic, patient-derived pancreatic xenografts (Chang et al. Cancer Res 2011). With the development of hypoxia-directed therapies, there is a need to understand the range and relevance of hypoxia in PDAC patients. We therefore launched two complementary clinical trials using 2-nitroimidazole-based hypoxia probes. **Methods:** PIMO-PANC involves pre-operative administration of pimonidazole to patients (pts) undergoing PDAC resection. Hypoxic percent (HP) of tumors is determined by semi-automated image analysis (on Aperio's Genie) of multiple histological sections stained for pimonidazole by immunohistochemistry (IHC). FAZA-PANC uses the positron emission tomography (PET) tracer fluoroazomycin arabinoside (^{18}F-FAZA) to evaluate hypoxia by functional imaging. 2 hours post-injection of (5.2 MBq/kg) ^{18}F-FAZA, static scans are acquired followed by computed tomography for anatomic registration. Skeletal muscle is a non-hypoxic reference tissue to define standardized uptake values (SUV), tumor to muscle uptake ratios (T/M's) and a threshold for hypoxia. **Results:** PIMO-PANC has enrolled 29 pts and FAZA-PANC 16. IHC analysis of the first 10 pt tumors demonstrates considerable intra- and inter-tumoral heterogeneity of hypoxia (HP: 1 to 26% across pt tumors); minimal hypoxia ($< 5\%$) was observed in 3 pts. ^{18}F-FAZA-PET in the first 11 pts demonstrates SUV_{max} from 1.02 to 1.83, median T/M's from 0.84 to 1.31. A threshold of 1.27 SUV_{max} defines HP of 0 to 60% with minimal hypoxia ($<10\%$) in 5 pts. **Conclusions:** There is significant heterogeneity of hypoxia across the spectrum of clinical PDAC (local to metastatic disease) using the 2-nitroimidazole hypoxia probes pimonidazole and ^{18}F-FAZA. Given the intra-tumoral heterogeneity of hypoxia by histopathology, functional imaging is the preferred method to assess hypoxia in PDAC patients. Importantly, both methods identified a group of PDAC tumors with low levels of hypoxia. This is relevant to the on-going development of hypoxia-targeting strategies. Accrual to PIMO-PANC is on-going and will address the prognostic relevance of hypoxia in PDAC. Clinical trial information: NCT01542177 and NCT01248637.

4050 General Poster Session (Board #17D), Sun, 8:00 AM-11:45 AM

A network meta-analysis (NMA) of randomized controlled trials (RCT) of chemotherapy regimens for metastatic pancreatic cancer (mPC).

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Background: Recent RCTs suggest a survival benefit for combination therapy in mPC compared to gemcitabine alone. Such combinations include FOLFIRINOX and gemcitabine plus nab-paclitaxel (G+nab-P). Survival and safety outcomes of these regimens were analyzed using gemcitabine as the reference comparator. **Methods:** Systematic review and NMA included data from reported phase III RCTs meeting quality standards and compared chemotherapy treatment to gemcitabine for mPC between 2000 and 2013. Excluded were trials assessing locally advanced pancreatic cancer. Following inter-trial heterogeneity assessment (patient characteristics, trial methodologies, treatment protocols), Bayesian NMAs were conducted for primary (overall survival [OS]) and secondary (progression free survival [PFS]) outcomes, overall response rate [ORR], and safety. **Results:** 27 studies were included involving 10 429 patients and 18 different treatments. No significant heterogeneity was observed between trials. When indirectly compared, FOLFIRINOX, PEFG and G+nab-P were top ranked for OS, PFS and ORR (Table). Comparing FOLFIRINOX and G +nab-P, there was no significant difference in odds ratios (OR) for febrile neutropenia, diarrhea or sensory neuropathy. FOLFIRINOX caused more gr3-4 neutropenia (OR 1.85 (95%Cl 1.1-3.4),$p<0.05$), and G+nab-P trended more gr3-4 fatigue (OR 2.03 95% Cl 0.95-3.8). **Conclusions:** Survival and safety outcomes were comparable amongst the three regimens identified from this network meta-analysis for mPC. FOLFIRINOX tended towards a greater survival benefit over G+nab-P and PEFG although comparisons did not reach statistical significance.Head-to-head trials between FOLFIRINOX, G+nab-P and PEFG are needed to further compare the survival benefits and safety profiles of these treatments.

Direct comparison	OS	PFS
FOLFIRINOX vs. Gem	0.57 (0.45-0.73)	0.47 (0.37-0.59)
G+nab-P vs. Gem	0.72 (0.62-0.835)	0.69 (0.581-0.821)
PEFG* vs. Gem	0.65 (0.43-0.99)	0.51 (0.42-0.96)
Indirect comparison		
FOLFIRINOX vs. G+nabP	0.81 (0.55-1.14)	0.70 (0.44-1.04)
FOLFIRINOX vs. PEFG*	0.90 (0.55-1.47)	0.95 (0.52-1.62)

* PEFG – cisplatin, epirubicin, 5FU, gemcitabine.

4051 General Poster Session (Board #17E), Sun, 8:00 AM-11:45 AM

Identifying targetable pathways in pancreatic cancer from endoscopic ultrasound-guided fine-needle aspirates (EUS/FNA): Providing a personalized approach to targeted therapy.

Andrea Wang-Gillam, Sachin Wani, Emma J. Langley, Feng Gao, Faris Murad, Daniel Mullady, Dayna S Early, Steven Alphonse Edmundowicz, David Linehan, Anne Kuller, Anjali Jain, Phillip Sangwook Kim, Sharat Singh, Riad Azar; Washington University School of Medicine in St. Louis, St. Louis, MO; University of Colorado Anschutz Medical Campus, Aurora, CO; Prometheus Laboratories Inc., San Diego, CA; Washington University in St. Louis, St. Louis, MO; Department of Surgery, Washington University School of Medicine, St. Louis, MO; Prometheus, San Diego, CA

Background: Targeted therapy trials in pancreatic cancer patients have either failed or, at most, provided only marginal benefit. Identification of activated key signaling pathways would allow the optimal selection of patients for kinase inhibitor trials. Hence, we launched a study to profile targetable pathways from EUS/FNA samples using an ultrasensitive multiplexed protein microarray platform (CEER, Prometheus). **Methods:** Patients who underwent routine diagnostic FNA for a suspicious lesion in the pancreas underwent two dedicated passes for CEER profiling of the following phosphorylated (activated) key molecules: HER1, HER2, HER3, c-met, IGF-IR, PI3K, AKT, MEK, ERK, and other signaling proteins. **Results:** Of 100 participants, final cytology results were: 73 carcinomas, 8 indeterminate, 13 negative, and 5 neuroendocrine. Pathway activation was heterogeneous in patients with carcinoma. Among 61 pancreatic cancer patients with adequate HER evaluation, a high prevalence of HER3 activation (62%) was observed, and concomitant activation of two or more HER pathways was seen in 52% of patients. In particular, activation of HER2 and HER3 was noted in 23% of carcinoma patients. High concordance of HER, PI3K and AKT activation was seen. **Conclusions:** Our study confirmed the feasibility of profiling targetable pathways from FNA samples. Furthermore, it illustrates highly variable and concomitant pathway activation among pancreatic cancer patients, suggesting the feasibility of a personalized approach to targeted therapy. Future trials will need to be designed to explore the clinical benefit of combinations of HER-targeted agents in defined subsets of pancreatic cancer patients, and further evaluation of the HER3 pathway is especially warranted. An analysis of pathway interactions and prognostic effects is in progress.

Activated HER pathways.

	p-HER (n=61)	p-PI3K	p-AKT
p-HER1	1	1	0
p-HER2	3	1	3
p-HER3	6	2	3
p-HER1/2	1	1	1
p-HER1/3	1	1	1
p-HER2/3	14 (23%)	14	13
p-HER1/2/3	16 (26%)	15	10
p-HER neg	19 (31%)	5	6

4052 General Poster Session (Board #17F), Sun, 8:00 AM-11:45 AM

MicroRNA biomarkers in whole blood for detection of pancreatic cancer.

Nicolai Aagaard Schultz, Christian Dehlendorff, Benny Vittrup Jensen, Jon K. Bjerregaard, Kaspar Nielsen, Stig Egil Bojesen, Dan Calatayud, Svend Erik Nielsen, Mette K. N. Yilmaz, Niels Henrik Hollander, Klaus Kaae Andersen, Julia S. Johansen; Department of Surgical Gastroenterology and Transplantation, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Statistics, Bioinformatics & Registry, Danish Cancer Society, Copenhagen, Denmark; Department of Oncology, Herlev Hospital, Copenhagen, Denmark; Odense University Hospital, Odense, Denmark; Department of Clinical Immunology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark; Copenhagen University Hospital Herlev, Herlev, Denmark; Departments of Oncology, Hilleroed Hospital, Hilleroed, Denmark; Department of Oncology, Aalborg Hospital, Aalborg, Denmark; Sygehus Syd Naestved, Naestved, Denmark; Department of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark; Department of Medicine and Oncology, Copenhagen University Hospital Herlev, Herlev, Denmark

Background: There is a great need for biomarkers for early diagnosis of patients with pancreatic cancer (PC) to improve their poor prognosis. The aims were (1) to describe differences in miRNA expression in whole blood between patients with PC, healthy subjects (HS) and patients with chronic pancreatitis (CP); and (2) to identify panels of miRNAs for early diagnosis of PC. **Methods:** Case-control study. 409 patients with PC, 33 patients with other periampullary cancers (PAC) and 25 patients with CP were included prospectively in the Danish BIOPAC biomarker study. 312 blood donors were included as HS. MiRNA expressions in pretreatment 2.5 ml whole blood samples collected in PAXgene RNA tubes were investigated in three independent cohorts: "Discovery Study" (PC n=143, CP n=18, HS n=69); "Training Study" (PC n=180, HS n=199); and "Validation Study" (PC n=86, PAC n=33, CP n=7, HS n=44). TaqMan Human MicroRNA assay was used to screen 754 miRNAs in the "Discovery Study". Fluidigm BioMark PCR System was used in the "Training Study" (38 miRNAs) and "Validation Study" (13 miRNAs). **Results:** The "Discovery Study" demonstrated that 38 miRNAs (out of a total of 754 miRNAs) in whole blood were significantly deregulated between patients with PC and controls. These miRNAs were tested in the "Training Study" and two diagnostic indexes were constructed including 4 miRNAs in bPANmiRC index I (= miR-150 + miR-636 – miR-145 – miR-223) or 10 miRNAs in bPANmiRC index II (= 6.9275 – 0.2134xmiR-122 – 0.3560xmiR-34a – 0.8577xmiR-145 + 1.0043xmiR-636 – 0.6725xmiR-223 + 0.7018xmiR-26b – 0.3233xmiR-885.5p + 1.1304xmiR-150 – 0.2204xmiR-126* - 0.1730xmiR-505) (AUC 0.86/0.93, sensitivity 85%/85% and specificity 64%/85%). **Conclusions:** We identified two diagnostic indexes, using 4 or 10 miRNAs in peripheral whole blood, with a potential clinical value in the evaluation of patients with uncharacteristic symptoms to identify PC at an early stage.

4053 General Poster Session (Board #17G), Sun, 8:00 AM-11:45 AM

Significance of baseline quality of life scores in predicting clinical outcomes in an international phase III trial of advanced pancreatic cancer: NCIC CTG PA.3.

Michael M. Vickers, Dongsheng Tu, Chee Lee, Paul Wheatley-Price, Wendy Parulekar, Michael Donald Brundage, Malcolm J. Moore, Heather-Jane Au, Christopher J. O'Callaghan, Derek J. Jonker, Jolie Ringash, David Goldstein; Tom Baker Cancer Centre, Calgary, AB, Canada; NCIC Clinical Trials Group, Kingston, ON, Canada; NHMRC Clinical Trials Centre, Sydney, Australia; Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Department of Medicine, University of Ottawa, Ottawa, ON, Canada; NCIC Clinical Trials Group, Cancer Research Institute, Queen's University, Kingston, ON, Canada; NCIC Clinical Trials Group, Queen's Division of Cancer Care and Epidemiology, Kingston, ON, Canada; Princess Margaret Hospital, Toronto, ON, Canada; Cross Cancer Institute, Edmonton, AB, Canada; The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; Princess Margaret Cancer Center, Toronto, ON, Canada; Prince of Wales Hospital, Sydney, Australia

Background: There is insufficient information regarding the prognostic significance of baseline Quality of life (QoL) scores on overall survival (OS) and adverse events (AEs) in advanced pancreatic cancer. **Methods:** QoL was assessed prospectively using the EORTC QLQ-C30 and AEs were graded using the NCI Common Toxicity Criteria version 2.0 as part of the PA.3 trial of gemcitabine + erlotinib (G+E) vs. gemcitabine + placebo (G+P). Relevant clinical variables, ECOG performance status (PS), and QoL scores at baseline were analyzed by Cox stepwise regression to determine predictors of OS and AEs. QoL scores were transformed by square root. **Results:** 222 of 285 patients (pts) (78%) treated with G+E and 220 of 284 pts (77%) treated with G+P completed baseline QoL assessments. In a multivariate Cox analysis (MVA) combining all pts, better QoL physical function (PF) score independently and incrementally predicted longer OS (HR 0.91; CI: 0.83-1.00), as did non-white race (HR 0.62; CI: 0.42-0.91), PS 0-1 (vs. PS 2 - HR 0.64; CI: 0.49-0.84), locally advanced pancreatic cancer (LAPC) (vs. metastatic - HR 0.54; CI: 0.42-0.69) and G+E (vs. G+P - HR 0.79; CI: 0.64-0.98). More financial difficulty (HR 0.92; CI: 0.87-0.98) and PS 0-1 (HR: 0.36; CI: 0.17-0.77) predicted a lower risk of grade 3 or higher AEs. In a MVA of pts treated with G+E, pain intensity <20 (vs. $\geq$ 20 - HR 0.68; CI:0.52-0.88) and LAPC (HR 0.67; CI: 0.48-0.91) were associated with longer OS, while better QoL cognitive (HR 0.71; CI: 0.50-1.00), worse constipation (HR 0.89; CI: 0.81-0.98) and worse financial scores (HR 0.86; CI: 0.78-0.94), better dyspnea score (HR 0.82; CI: 0.71-0.93) and PS 0-1 (HR 0.21; CI: 0.05-0.78) predicted for lower risk of AEs. In a MVA of pts treated with G+P, better global QoL score (HR 0.91; CI:0.85-0.98) and LAPC (HR 0.57; CI: 0.40-0.82) were predictors of longer OS while no variables predicted grade 3 or higher AEs. **Conclusions:** In addition to clinical variables (including physician assessed PS), patient reported QoL scores added incremental predictive information regarding survival and adverse events for advanced pancreatic cancer patients treated with systemic chemotherapy.

4054 General Poster Session (Board #17H), Sun, 8:00 AM-11:45 AM

Randomized, open-label, phase II trial of gemcitabine with or without bavituximab in patients with nonresectable stage IV pancreatic adenocarcinoma.

Shuchi Sumant Pandya, Lucas Wong, Andrea J. Bullock, Stephen A. Grabelsky, Merrill Kingman Shum, Joseph Shan, Kerstin B. Menander, Tony R. Reid; Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; Scott & White Cancer Research Institute, Temple, TX; Beth Israel Deaconess Medical Center, Boston, MA; Center for Hem Onc, Boca Raton, FL; Oncology Institute of Hope and Innovation, Whittier, CA; Peregrine Pharmaceuticals, Inc., Tustin, CA; UC San Diego Moores Cancer Center, La Jolla, CA

Background: Despite advances in the treatment of metastatic pancreatic cancer (PC), there is critical need to develop novel therapies.Median survival with combination chemotherapy is limited to less than one year and only the optimally conditioned patients can tolerate these therapies. Bavituximab (B) is a monoclonal antibody (mAB) directed againstphosphatidylserine (PS) that causes vascular shutdown and reactivation of the innate and adaptive immunity in animal models. Preclinical data in mouse PC models indicate that gemcitabine (G) increases PS exposure and the addition of a mAb targeting PS reduces tumor burden, visible liver metastases, microvessel density, and increases tumor macrophage infiltration compared to G alone (Beck et al. 2006). The purpose of this trial is to evaluate and compare the efficacy and safety of the combination of G+B vs. G alone as first line therapy in pts. with nonresectable Stage IV PC. **Methods:** Seventy patients were randomized (1:1) to receive G 1000 mg/m^2 on days 1, 8, and 15 every 28Edays with or without weekly B 3mg/kg IV until disease progression or unacceptable toxicities. Key eligibility criteria were Stage IV PC, ECOG $\leq$2, measurable disease, age$\geq$18 years, total bilirubin $\leq$1.5xULN, and adequate renal, hematologic, and hepatic function. The primary efficacy endpoint was overall survival (OS) and secondary endpoints included overall response rate (ORR) and progression free survival (PFS). **Results:** Of the 70 (G/G+B 34/36) patients randomized, 67 (G/G+B 33/34) received study treatment and 63 (G/G+B 31/32) were evaluable. No significant difference was seen in age, gender, race or ECOG. At analysis 87% deaths had been reported in G and 72% in G+B group. Median OS estimate is 5.2 months for G and 5.6 months for G+B. No difference between groups was observed in PFS (median 3.9 months for G and 3.7 months for G+B). ORR was 13% for G and 28% for G+B. Most AEs were grade 1-2 and typical of exposure to G. **Conclusions**: In this patient population with extensive disease burdens and limited treatment options, G+B was well tolerated and demonstrated moderate activity in tumor response and survival. Clinical trial information: NCT01272791.

4055 General Poster Session (Board #18A), Sun, 8:00 AM-11:45 AM

Willingness of patients with pancreatic cancer to participate in clinical trials.

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Background: Recruitment of oncology patients into clinical trials continues to be a challenge as <5% of patients are accrued. Low accrual rates may be due to reduced awareness of trial availability and eligibility by physicians/patients. Our objective was to study the attitudes of patients with pancreatic cancer (PC) regarding clinical trial participation and to identify possible barriers to recruitment. **Methods:** In this cross-sectional study, we collaborated with Pancreatic Cancer Action Network (PanCAN) and invited patients with PC or their caregivers to complete a survey. The survey that was developed consisted of 22 questions and inquired about patients' previous clinical trial enrollment experiences and their views on participation. The surveys were collected over a 6-month period via the PanCAN website and regional meetings. Comparison analyses between groups were done by Chi-square and Fisher's test using STATA software. **Results:** Of the390 surveys received, 149 were included in the final analyses. 30% of the patients were offered to participate in a trial by their physicians. When asked to participate, 62% of the patients agreed. Of the patients who were not enrolled in a clinical trial, 61% were offered to participate in a trial but did not agree. This suggests that these patients were eligible to participate but declined. **Conclusions:** Majority of the patients with pancreatic cancer were not offered to participate in clinical trials by their physicians but would have agreed if asked. While low clinical trial recruitment rates for PC may be multifactorial, further research may focus on the important role of physicians in clinical trial recruitment efforts.

	Patient n=70 n(%)	Caregiver n=79 n(%)
Gender		
Male	28(40)	8(10)
Female	42(60)	71(90)
Race		
White	63(90)	64(81)
Hispanic	2(3)	3(4)
African-American/Black	4(6)	3(4)
Asian/Pacific Islander	0	5(6)
Native American/Alaska Native	1(1)	1(1)
Other	0	3(4)
Histology		
Pancreatic adenocarcinoma	48(69)	62(79)
PNET	12(17)	6(8)
Unknown	9(13)	10(13)
IPMN	1(1)	1(1)
Stage		
Localized	27(39)	16(20)
Locally advanced	11(16)	12(15)
Metastatic	32(46)	51(65)
ECOG performance status		
0	23(33)	10(13)
1	33(47)	22(28)
2	10(14)	15(19)
3	3(4)	29(37)
4	1(1)	3(4)

4056 General Poster Session (Board #18B), Sun, 8:00 AM-11:45 AM

A randomized phase II trial of adjuvant chemotherapy with S-1 versus S-1 and gemcitabine (GS) versus gemcitabine alone (GEM) in patients with resected pancreatic cancer (CAP-002 study).

Hideyuki Yoshitomi, Hiroaki Shimizu, Hiroyuki Yoshidome, Masayuki Ohtsuka, Atsushi Kato, Katsunori Furukawa, Tsukasa Takayashiki, Satoshi Kuboki, Daiki Okamura, Daisuke Suzuki, Masayuki Nakajima, Toshiaki Aida, Masaru Miyazaki, Chiba Study Group of Adjuvant Chemotherapy for Pancreatic Cancer (CAP); Department of General Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

Background: Although the adjuvant therapy using GEM is now the standard therapy for patients with resected pancreatic cancer (PC), the prognosis still remains poor. Resent study demonstrated the non-inferiority of S-1 and superiority of GS to GEM with respect to progression free survival in patients with unresectable pancreatic cancer. **Methods:** Patients with invasive ductal PC who underwent radical surgery were enrolled. After stratification for R0/1, stage and institution, patients were randomized to receive GEM (GEM 1g/ $m^{2,}$ iv, d1, 8, and 15, q4w X12), S-1 (80/100/120mg/day based on BSA, po, d1-14, q3w X 16) or GS (S-1 60/80/100mg/day based on BSA po, d1-14 plus GEM 1g/ $m^{2,}$ iv, d8, 15, q3w X 16) within 8weeks after operation. Eligibility included histological residual tumor (R) 0 or 1, and no previous chemo- or/and radiation therapy. Primary endpoint was 2y disease free survival (DFS) rate and secondary endpoints included overall survival (OS), and safety. **Results:** Between January 2007 and October 2010, 96 patients were randomized into the three arms of the trial (32 pts to each group). Patients' characteristics were well balanced (GEM/S-1/GS) with regard to age (66/67/66y), tumor location (head 66/69/75%), tumor status (T3+4 88/78/91%), and nodal status (positive 75/69/75%). Until November 2012, 74 events (77%) have occurred for DFS. Two year DFS rate was 24.2%, 28.1% and 34.4% in GEM, S-1 and GS, respectively and there was no significant difference between groups. The median OS was 21m in GEM, 26m in S-1 and 27.9m in GS (Log rank test: N.S.). Grade 3/4 toxicities in GEM/S-1/GS were hematological 63/10/74% and non-hematological 17/10/23%, respectively. No treatment related death was observed during the study. **Conclusions:** S-1 and GS provided similar efficacy to GEM as the adjuvant chemotherapy for resected PC. According to the results, S-1 and GS is the adequate combination for phase III trial to examine the efficacy of adjuvant chemotherapy for PC. Clinical trial information: UMIN000002000.

4057 General Poster Session (Board #18C), Sun, 8:00 AM-11:45 AM

Is successful resection following neoadjuvant radiation therapy for borderline resectable pancreatic cancer dependent on improved tumor-vessel relationships?

Avani Satish Dholakia, Amy Hacker-Prietz, Aaron Tyler Wild, Siva P. Raman, Laura D. Wood, Daniel A. Laheru, Lei Zheng, Ana De Jesus-Acosta, Peng Huang, Dung T. Le, Richard D. Schulick, Barish H. Edil, Susannah G. Ellsworth, Timothy M. Pawlik, Christine A Iacobuzio-Donahue, Ralph H. Hruban, John L. Cameron, Elliot K. Fishman, Christopher Lee Wolfgang, Joseph M. Herman; Johns Hopkins University School of Medicine, Baltimore, MD; University of Colorado, Aurora, CO

Background: Margin-negative (R0) surgical resection is the only potentially curative therapy for pancreatic cancer. For patients deemed borderline resectable (BL), neoadjuvant chemoradiotherapy (NRT) increases the likelihood of subsequent R0 resection and improves overall survival. Prognostic factors for achieving resection following NRT have yet to be clearly identified. **Methods:** Fifty consecutive patients with BL-PDAC evaluated by a multidisciplinary tumor board who received NRT from 2007-2012 were retrospectively identified. Computed tomography (CT) scans pre- and post-radiation and surgical specimens were centrally reviewed. **Results:** 29 patients underwent resection following NCRT, while 21 remained unresectable. Between the two groups, age, gender, mean RT dose, and proportion of pancreatic head tumors were not significantly different. Smaller tumor volume and lack of the following factors was associated with selection for resection: superior mesenteric/portal vein encasement ($p=0.01$), superior mesenteric artery involvement ($p=0.02$), ascites ($p=0.01$), and questionable/overt metastases ($p=0.01$). Notably, celiac artery involvement/encasement, common hepatic artery encasement, and percentage change in tumor volume were not significant predictors of resection (all $p>>0.05$). Interestingly, tumor volume and degree of individual vessel involvement did not significantly change from scans before and after NCRT (all $p>>0.05$). Median OS was 22.9 vs.13.0 months in resected and unresected patients, respectively ($p<0.001$). Of resected patients, 93% had negative margins, 28% had positive nodes, 27% demonstrated $<10\%$ viable tumor, and 12% had pathologic complete response at surgery. Dpc4 expression was retained in 68% of specimens with viable tumor. **Conclusions:** Although the apparent radiographic extent of vascular involvement does not change significantly after NRT, subsequent R0 resection rates are high, nodal involvement is low, and outcomes are similar to resected patients who receive adjuvant therapy. Resection attempts should not be deferred solely based on lack of improvement in tumor-vessel interactions.

4058^ General Poster Session (Board #18D), Sun, 8:00 AM-11:45 AM

CA19-9 decrease at 8 weeks as a predictor of overall survival (OS) in a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel (*nab*-P) plus gemcitabine (G) versus G alone in patients with metastatic pancreatic cancer (MPC).

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Background: *nab*-P + G showed promising efficacy in a phase I/II study in MPC, and decreases in CA19-9 correlated with OS. In MPACT, patients (pts) who received *nab*-P + G vs G had improved median OS (8.5 vs 6.7 mo; HR 0.72; p = 0.000015), PFS (5.5 vs 3.7 mo; HR 0.69; p = 0.000024) and ORR (23% vs 7%; $p = 1.1 \times 10^{-10}$). Here we present a prespecified exploratory analysis of CA19-9 from the MPACT trial. **Methods:** 861 previously untreated pts with MPC were randomized 1:1 to receive *nab*-P 125 mg/m^2 + G 1000 mg/m^2 days 1, 8, and 15 every 4 weeks or G alone 1000 mg/m^2 weekly for 7 weeks followed by a week of rest (cycle 1) and then days 1, 8, and 15 every 4 weeks (cycle $\geq$ 2). CA19-9 was evaluated at baseline and then every 8 weeks. OS comparisons at different CA19-9 criteria were performed by stratified Cox proportional hazards model (*P* by stratified log-rank test using randomization criteria). **Results:** 750 pts had an evaluable CA19-9 at baseline. More pts in the *nab*-P + G arm vs the G arm demonstrated a best CA19-9 decrease from baseline of $\geq$ 20% and $\geq$ 90% (61% vs 44% and 31% vs 14%, respectively; Table). At the first postbaseline assessment (week 8), greater proportions of pts in the *nab*-P + G arm vs the G arm had CA19-9 decreases of $\geq$ 20% and $\geq$ 90% (Table). At that time point, for pts with a decrease of $\geq$ 20% in CA19-9, *nab*-P + G demonstrated a significantly longer OS vs G. The risk reduction for pts with a $\geq$ 90% decrease was greater than in pts with a $\geq$ 20% decrease. In pts with an 8-week CA19-9 decrease $<$ 20%, median OS for *nab*-P + G vs G was 8.3 vs 8.0 mo (HR 0.92; p = 0.705). The relationship of CA19-9 kinetics with OS will also be examined. **Conclusions:** Higher proportions of pts in the *nab*-P + G arm had CA 19-9 responses of $\geq$ 20% and $\geq$ 90% vs the G arm. Pts who achieved a CA19-9 decrease at 8 weeks of $\geq$ 20% or $\geq$ 90% had significantly longer OS with *nab*-P + G than with G. Clinical trial information: NCT00844649.

	nab-P + G n = 379		G n = 371
Best CA19-9 decrease ≥ 20%, n (%)	230 (61)		162 (44)
8-week CA19-9 decrease ≥ 20%, n (%)	196 (52)		140 (38)
Median OS, mo	13.2		9.4
1-year OS, %	53		34
HR		0.59	
p		< 0.001	
Best CA19-9 decrease ≥ 90%, n (%)	117 (31)		51 (14)
8-week CA19-9 decrease ≥ 90%, n (%)	59 (16)		33 (9)
Median OS, mo	13.4		9.4
1-year OS, %	57		20
HR		0.44	
p		0.0022	

4059^ **General Poster Session (Board #18E), Sun, 8:00 AM-11:45 AM**

Prognostic factors (PFs) of survival in a randomized phase III trial (MPACT) of weekly *nab*-paclitaxel (*nab*-P) plus gemcitabine (G) versus G alone in patients (pts) with metastatic pancreatic cancer (MPC).

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Background: In MPACT, pts who received *nab*-P + G vs G had improved overall survival (OS; median 8.5 vs 6.7 mo; HR 0.72; p= 0.000015). Here we assessed potential PFs of OS. **Methods:** 861 pts with MPC were randomized 1:1, stratified by region, presence of liver metastases, and Karnofsky performance status (KPS), to *nab*-P + G or G. OS was described in subgroups. A step-wise multivariate analysis (with significance level for entry of 0.20 and for stay of 0.10) was performed to evaluate the treatment effect and identify possible predictors of OS. **Results:** Pts with poorer PFs had a shorter median OS, consistent with the literature, and OS consistently favored *nab*-P + G in pts with these PFs (Table). Region of Eastern Europe, age ≥ 65 years, poorer KPS, presence of liver metastases, and number of metastatic sites all predicted OS (increased risk of death). The treatment effect remained significant (HR 0.72; 95% CI, 0.605 - 0.849; p < 0.0001, Cox proportional hazards [CPH] model). In another multivariate analysis in which baseline CA19-9 was added to the final model described above, the treatment effect HR was 0.67 (95% CI, 0.573 - 0.794; p < 0.0001, CPH model). Baseline CA19-9, a predictor of OS by univariate analysis, was not predictive after correction for the above factors. **Conclusions:** In MPACT, the most important predictors of OS were KPS, age, presence of liver metastases, number of metastatic sites, and region. After correcting for these factors, assignment to *nab*-P + G was an independent significant predictor of improved survival. Clinical trial information: NCT00844649.

Factors predictive of OS		HR		P value
Treatment (*nab*-P + G vs G)		0.72		0.0001
Region (E Europe vs N America)		1.22		0.0765
Age (< 65 vs ≥ 65 years)		0.81		0.0190
KPS (70 - 80 vs 90 - 100)		1.60		< 0.0001
Liver metastases (yes vs no)		1.81		< 0.0001
No. of metastatic sites (1, 2, 3, > 3)		1.08		0.0864
Pt subgroups		*nab*-P + G		G
	n	Median OS, mo	n	Median OS, mo
Region				
N America	268	8.7	271	6.8
E Europe	64	7.7	62	5.9
Age				
< 65	254	9.2	242	6.8
≥ 65 years	177	7.8	188	6.6
KPS				
70	30	3.9	33	2.8
80	149	8.1	128	5.6
90	179	8.9	199	7.1
100	69	12.6	69	10.9
Liver metastases				
Yes	365	8.3	360	5.9
No	66	11.0	70	10.7
No. of metastatic sites				
1	33	13.5	21	9.0
2	202	8.3	206	7.1
3	136	8.0	140	5.9
> 3	60	8.6	63	5.0

4060 General Poster Session (Board #18F), Sun, 8:00 AM-11:45 AM

Prognostic value of an immune score combining intra- and peritumoral T-cell subset density in patients with pancreatic adenocarcinoma.

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Background: Immune scoring based on T-cell subsets and density can add prognostic value to conventional TNM staging for patients with solid tumors, but limited data are available for pancreatic adenocarcinoma. **Methods:** Using tissue microarrays, CD3, CD4, CD8, CD45RO, and FOXP3 T-cells were quantified by immunohistochemistry in the intratumoral (IT) compartment and peritumoral (PT) parenchyma of 111 consecutively resected specimens. T-cell counts were correlated with patient overall survival, disease-free survival, and time to recurrence (OS, DFS, TTR) by Cox regression, controlling for clinicopathological factors. An immune score (IS) based on IT CD4 T-cell count $>$ median, PT CD8 T-cell count $\leq$ median, and IT/PT CD3 T-cell ratio >1, grouped patients into high, intermediate, or low categories if all 3, 1 to 2, or none of these immune features were present, respectively. **Results:** Median follow-up time was 20 months, and 85% of patients either died or recurred during the study period. By univariate analysis, PT CD8 T-cell count was associated with shorter OS ($p=0.02$), whereas both IT CD4 T-cell count and IT/PT CD3 T-cell ratio were associated with longer OS ($p=0.01$ and $p=0.05$, respectively). Alone, none of these immune features predicted TTR. Combined into an IS, patients in the high ($n=23$), intermediate ($n=60$), or low ($n=23$) categories had significantly different OS (respective medians 30, 17, and 13 months, log-rank $p=0.01$), DFS (28, 16, and 12 months, $p=0.01$), and TTR (21, 14, and 10 months, $p=0.02$). By multivariate analysis, the association between IS and clinical outcomes was independent of tumor size, extra-pancreatic invasion, and nodal metastases (TNM staging). The IS discriminated outcomes among patients with nodal metastases ($n=80$), such that node-positive patients with a high IS had a median survival similar to node-negative patients (30 and 33 months, $p=0.7$). FOXP3 and CD45RO T-cell counts did not appear to add prognostic value to the IS. **Conclusions:** An immune score that combines specific T-cell location and density may have prognostic value in patients with resected pancreatic adenocarcinoma, independently from pathologic features currently used for staging.

4061 General Poster Session (Board #18G), Sun, 8:00 AM-11:45 AM

Assessment of the association of the VeriStrat test with outcomes in patients (pts) with advanced pancreatic cancer (PC) treated with gemcitabine (G) with or without erlotinib (E) in the NCIC CTG PA.3 phase III trial.

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Background: VeriStrat is a mass spectrometry based assay performed on serum or plasma that has been shown to be prognostic in several tumor types, and may predict differential drug benefit in several settings. We investigated the association of VeriStrat with outcomes in the NCIC CTG PA.3 randomized phase III trial of G and E vs. G and placebo (P) in pts with advanced PC. **Methods:** Pre-treatment plasma samples were available for 499/569 (87.7%) enrolled pts. VeriStrat testing was performed in a CLIA-certified laboratory; pts were classified as either Good, Poor, or indeterminate. The relationship between VeriStrat results and overall survival (OS) and progression free survival (PFS) was assessed by Kaplan-Meier curves and log-rank test in univariate analysis and Cox model adjusting for gender, age [>60 vs. ≤ 60], race [Caucasian vs. other], ECOG [0-1 vs. 2], and pain intensity at baseline [≤ 20 vs. >20] in multivariate analysis. The predictive effect was assessed by interaction test. All statistical analyses were performed by the NCIC CTG. **Results:** Of the 499 samples, 11 were hemolyzed and 4 had acquisition failures. VeriStrat was performed on 484 samples, 9 failed quality control, 22 had indeterminate results. Of the remaining 452, 353 (78%) were classified as Good and 99 (22%) as Poor. In the G and P arm, median OS was 7.16 months (ms) for VeriStrat Good vs. 3.78ms for VeriStrat Poor ($p<0.0001$); Adjusted Hazard Ratio (AHR) 0.59 (0.43-0.82), $p=0.002$. In the G and E arm, median OS was 7.33ms for VeriStrat Good vs. 4.50ms for VeriStrat Poor $p<0.0001$; AHR 0.47 (0.32-0.70), $p=0.001$. A similar relationship was seen for PFS (G and P arm: median PFS 3.91 vs. 2.07ms ($p=0.001$); AHR 0.67 [0.49-0.92], $p=0.01$); G and E arm: median PFS 4.24 vs. 2.86ms ($p=0.0004$); AHR 0.54 [0.37-0.80], $p=0.002$). Tests of interaction of VeriStrat status and treatment for OS and PFS were not significant: AHR 0.78 (0.48-1.25), $p=0.30$ and AHR 0.80 (0.50-1.30), $p=0.37$ respectively. **Conclusions:** VeriStrat results were significantly associated with OS and PFS for both regimens in this study. VeriStrat was not predictive of benefit from the addition of E to G.

4062 General Poster Session (Board #18H), Sun, 8:00 AM-11:45 AM

Phase II study of neoadjuvant chemotherapy with modified FOLFOXIRI in borderline resectable or unresectable stage III pancreatic cancer.

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Background: FOLFIRINOX has shown high activity in metastatic pancreatic cancer (PC) patients and could be an interesting regimen also for patients with inoperable locally advanced disease. Our group had developed a similar schedule in metastatic colorectal cancer named FOLFOXIRI with good tolerance and activity. Therefore, we have decided to perform a phase II trial to prospectively evaluate the activity of modified FOLFOXIRI in borderline resectable or unresectable PC. **Methods:** Modified FOLFOXIRI consisted of a lower dose of irinotecan (150 mg/sqm) and of infusional 5-fluorouracil (2800 mg/sqm as a 48-hour continuous infusion on days 1 to 3) with no bolus 5-fluorouracil. Folinic acid and oxaliplatin (85 mg/sqm) remained unchanged. The study enrolled patients with diagnosis of pancreatic adenocarcinoma, stage III borderline resectable or unresectable disease (cT4,cN0-1,cM0), ECOG PS 0-1, age 18-75. The primary end-point of the study was the percent of patients who undergo radical surgical resection after chemotherapy. **Results:** Thirty-two patients have been enrolled; M/F=12/20; PS 0/1=16/16. Median age was 60 years (range 44-75). Median number of FOLFOXIRI cycles was 6 (range 2-14). Grade 3-4 toxicities was experienced by 20 patients during chemotherapy. Twelve partial responses (37%) and 14 stable diseases (45%) have been observed; 2 patients had progressive diseases (6%). The remaining 4 patients (12%) have not been yet evaluated because are still in the first months of treatment. A local treatment was received after chemotherapy by 18 patients until now: 13 (41%) received radical surgical resection and 5 received concomitant chemo-radiotherapy. Three explorative laparotomy showed occult metastases. In other 7 cases surgery is planned while 2 patients refused surgery. Median progression-free survival is 14.0 months and median overall survival is 24.2 months with a two-year survival rate of 54%. **Conclusions:** Chemotherapy with FOLFOXIRI seems active in locally advanced PC and may allow to obtain a downstaging of disease leading to achieve a curative surgical resection in some cases. Longer follow up is needed to better evaluate long-term outcome of this strategy.

4064 General Poster Session (Board #19B), Sun, 8:00 AM-11:45 AM

The effect of anti-IGF1 therapy on muscle mass in metastatic pancreatic cancer.

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Background: IGF-1 plays a role in the growth of multiple tumor types, including pancreatic cancer. IGF-1 also serves as a growth factor for muscle. The impact of therapeutic targeting of IGF-1 on muscle mass is unknown. **Methods:** We evaluated muscle mass at L3 in patients enrolled in a randomized phase II study of MK-0646 (M), a monoclonal antibody directed against the IGF-1 protein, in patients with metastatic pancreatic cancer (MPC). We used the Slice-o-matic (ver 4.3) software to segregate CT images into muscle and fat components and measured muscle area (cm2) at baseline and after 2 and 4 months of treatment. Patients received either gemcitabine with erlotinib (G+E), G+E+M, or G+M. Differences between the groups were compared using t-tests. **Results:** 58 patients had both baseline and 2 month imaging available for analysis. Of these, 44 received M and 14 had G+E only. Baseline muscle mass between the two groups was similar: 146 cm2 and 142 cm2, respectively (P=0.47). After two months of treatment, both groups demonstrated decrease in muscle mass: 134 cm2 (8% loss) vs. 130 cm2 (6% loss) (P= 0.19). Of the 37 patients who had either PR or SD at 2 months, there was a non-significant increase in muscle mass loss among the patients receiving M (7.8% vs. 4.5%, p=.31). At 4 months, those remaining patients in the M group lost 6% (n=14) of muscle mass compared to 3% in the non-M group (n=5) (P=0.54). Each 1% loss of muscle mass increased the odds of dropout by 13% (p=.03, CI 1.0-27%) and predicted for poor survival (p=HR 1.08, p=.02). **Conclusions:** MPC patients can be expected to lose muscle mass even while having clinical benefit (PR or SD) from chemotherapy. Muscle loss correlated with a risk of study drop-out and death. There was a non-significant trend towards greater muscle mass loss in patients on anti-IGF-1R therapy. However, it is unclear if this loss translates into functional differences between patients. Clinical trial information: NCT00769483.

4065 General Poster Session (Board #19C), Sun, 8:00 AM-11:45 AM

HPV status to predict outcome for anal cancer treated with radiochemotherapy.

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Background: Evaluation of the HPV infection- and transformation-status as a predictor of the response to definitive radio-chemotherapy for anal cancer. **Methods:** 80 patients (54 fm, 26 m) with histologically confirmed anal cancer and known HPV-Infection- (determined by PCR) and p16-expression-status (determined by immunohistochemistry) were analyzed. All pts. were treated with definitive radio-chemotherapy (RCT) with 5-FU/MMC, median age 60ys (35–86), median follow up 54mo (4–180). 41 pts. were HPV+ and p16+ (group 1), 10 pts. were HPV-/p16+ (group 2), 9 pts. were HPV+/p16- (group 3) and 17 pts. were HPV+/p16- (group 4). Endpoints were local control (LC) at 5ys and overall survival (OS) at 5ys. In addition to HPV/p16 status, the influence of T-stage and tumor localization (canal vs. margin) was analyzed. **Results:** More women than men were HPV+ (fm 77% vs. m 33%) while gender was evenly distributed among HPV-pts. (fm 48% vs. m 53%). Upon univariate analysis, gender, HPV+ and p16+ were significant predictors of both LC and OS ($p<0.05$) while T-Stage was predictive for LC ($p<0.05$). Upon multivariate analysis, gender and T-Stage significantly influenced LC (w85.2% vs. m54.9%, $p=0.028$; $<$T3 84.2% vs $\geq$ T3 48,1%, $p=0,019$). OS was significantly influenced by gender (w95% vs. m59.2%, $p=0.005$), while the influence of HPV/p16-status did not reach significance when all four groups were analyzed simultaneously in this moderately sized cohort. Upon direct univariate comparison of HPV+/p16+ und HPV-/p16-pts, both gender and combined HPV/p16-positivity had a significant influence on LC and OS. Upon multivariate analysis, combined HPV/p16-positivity resulted in better LC (HPV+/p16+: 85% vs. HPV-/p16-: 38.7%, $p=0.003$), while, as a consequence of moderate patient numbers, only gender significantly predicted OS (fm93.7% vs. m62.6%, $p=0.015$). Viral status, however, showed a trend for significance. **Conclusions:** The data from one of the largest monocentric series treated with a uniform treatment regimen suggest that HPV-status predicts response to RCT in pts. with anal cancer. Patients with tumors not associated with HPV whatsoever (HPV-/P16-) have both inferior LC and a clear trend for inferior OS and might require an intensified treatment regimen.

4066 General Poster Session (Board #19D), Sun, 8:00 AM-11:45 AM

Adjuvant chemoradiotherapy versus chemotherapy for resectable gastric cancer: A systematic review and meta-analysis.

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Background: The benefits of adjuvant chemo-radiotherapy (ChRT) over chemotherapy (Ch) for resectable gastric cancer are currently unclear. We performed a systematic review and meta-analysis (direct and indirect) of published randomized controlled trials (RCT) to compare the effects of adjuvant chemo-radiotherapy with chemotherapy on overall and disease-free survival for patients with resectable gastric cancer. **Methods:** We searched MEDLINE and CENTRAL from the date of inception and annual meeting proceedings of ASCO and ASTRO from 1999 to November 2012 for RCTs comparing adjuvant ChRT with Ch, adjuvant ChRT with surgery alone and adjuvant Ch with surgery alone. The primary outcome was overall survival (OS); secondary outcomes included disease-free survival (DFS) and toxicity. Hazard ratios (HR), confidence intervals (CI) and p values (p) were estimated with fixed effects models using Revman 5.1. **Results:** We found five trials comparing adjuvant ChRT with Ch (n = 1110), three trials comparing adjuvant ChRT with surgery alone (n = 651) and 31 trials comparing adjuvant Ch with surgery alone (n = 8273). Meta-analysis of direct comparison trials showed that adjuvant ChRT significantly improved both OS (HR 0.79, 95% CI 0.64-0.98, p = 0.03) and DFS (HR 0.76, 95% CI 0.64-0.92, p = 0.004) when compared with Ch. Subgroup analyses showed that the effects on OS and DFS were similar regardless of use of D2 nodal dissection, intensity modulated radiotherapy techniques, fluorouracil or platinum-based chemotherapy. There were no significant differences in toxicity between the two groups. The results for the direct and indirect comparisons were statistically consistent. **Conclusions:** There was a significant survival benefit of adjuvant chemo-radiotherapy over chemotherapy, with no increase in toxicity for patients with resected gastric cancer. Future efforts should also focus on predictive markers, and toxicity or quality-of-life assessments, to individualize adjuvant therapy and optimize the therapeutic ratio.

4067 General Poster Session (Board #19E), Sun, 8:00 AM-11:45 AM

Prognostic implications of signet ring cell histology in esophageal adenocarcinoma: A SEER database analysis

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Background: Signet ring cell esophageal adenocarcinoma histology has been difficult to study in a single institution series because of its relative rarity, yet has an anecdotal reputation for poor prognosis. We examined the Surveillance Epidemiology and End Results (SEER) database to assess the prognostic implications of this esophageal adenocarcinoma subtype. **Methods**: All patients with esophageal adenocarcinoma in the SEER database from 2004 – 2009 were included. Characteristics of patients with signet ring cell histology were compared to those without it. Univariate and multivariate analyses examining the relationship of signet ring cell histology with overall survival (censored at 72 months) were performed in all patients, as well as those undergoing surgical resection. **Results**: 597 of 11,838 (5%) study patients had signet ring cell histology. Patients with signet ring cell histology were similar in age, race, and gender distribution, but had a higher grade ($p<0.001$) and higher stage ($p<0.001$) at diagnosis. In both all-comers as well as those undergoing surgical resection, univariate analyses showed a worse survival in patients with signet ring cell esophageal cancer (HR = 1.24; 95% CI 1.13-1.37 and HR = 1.57; 95% CI 1.29-1.92 respectively). In multivariate analyses adjusting for age, gender, grade, stage, and race, patients with signet ring cell cancer had a worse prognosis than those with non-signet ring cell adenocarcinoma (HR = 1.20; 95% CI 1.09 -1.33). In surgically resected patients, this remained a trend, but did not reach statistical significance (HR = 1.16; 95% CI 0.94-1.42). **Conclusions:** This large study of esophageal adenocarcinoma confirms the clinical impression that signet ring cell variant of adenocarcinoma is associated with an advanced stage at presentation and a worse prognosis independent of stage of presentation.

4068 General Poster Session (Board #19F), Sun, 8:00 AM-11:45 AM

Search for biomarkers of stage II/III gastric cancer and development of individualized therapy.

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Background: Standard therapy for stage II/III gastric cancer is curative resection followed by adjuvant chemotherapy. Treatment outcomes are expected to be further improved by the development of individualized therapy based on new biomarkers. We have extracted mRNA from frozen specimens of gastric cancer to construct a cDNA bank and searched for new biomarkers of stage II/III gastric cancer. We report currently available results. **Methods:** The study group comprised 256 patients with stage II/III gastric cancer in whom at least 5 years had passed since surgery (among whom 149 received S-1 as adjuvant chemotherapy). A total of 130 genes were selected on the basis of the results of comprehensive DNA microarray analyses and extraction from serial analysis of gene expression (SAGE) libraries, and other studies. Relative expression levels of each gene in gastric cancer tissue and adjacent normal mucosa were measured by quantitative PCR, and the relations between clinicopathological factors and treatment outcomes were studied. In addition, using 9 types of gastric cancer cell lines, we knocked down the new cancer biomarkers obtained in this study with small interfering RNA (siRNA) and performed functional analysis. **Results:** In patients with resected stage II/III gastric cancer, INHBA, IGF-1R, CLDN7, and DPD genes were independent prognostic factors. In the subgroup of patients who received S-1-based adjuvant chemotherapy, IGF-1R, INHBA, SULF1, REG4, MMP11, and KIAA1199 genes were independent prognostic factors. Knockdown of the KIAA1199 gene with siRNA markedly inhibited the proliferative and invasive activities of the gastric cancer cell lines and lowered resistance to 5-fluorouracil. **Conclusions:** Investigatory studies of new biomarkers of gastric cancer identified prognostic factors for patients with resected stage II/III gastric cancer and those who received adjuvant chemotherapy with S-1. At present, the development of small molecule drugs that target KIAA1199 and the joint development of risk stratification tools with the goal of individualized therapy for stage II/III gastric cancer are ongoing.

4069 General Poster Session (Board #19G), Sun, 8:00 AM-11:45 AM

Comparison of HER2 expression in paired biopsies and surgical specimen of gastric and esophageal adenocarcinoma: Impact of neoadjuvant chemotherapy.

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Background: HER2 is overexpressed in 10 to 20% of gastro-esophageal adenocarcinoma (GE-ADK), and is a target for trastuzumab in metastatic patients. We conducted a study to compare HER2 expression between diagnostic biopsies (DB) and surgical specimens (SS) of GE-ADK, and to determine the influence of non-trastuzumab containing neoadjuvant chemotherapy (NAC) on this expression. **Methods:** Pathological specimens from biopsies of 228 patients operated on with a curative aim in two French hospitals between 2004 and 2011 were collected. Two cohorts treated (n=141) or not (n=87) with a NAC were constituted. Two blind independent pathological HER2 analyses on DB and on SS were performed using IHC and CISH. HER-2 overexpression (HER2 +) was defined by a score 3+ in IHC, or 2+ with a positive CISH test, and according to the specific HER2 scoring guidelines for GE-ADK. **Results:** Paired HER2 status could be determined for 218 out of the 228 patients (95.6%). HER2 + rates were 13.3% on DB (29/218) and 14.7% on SS (32/218). HER2 + tumors were mainly cardial or esophageal adenocarcinomas, with a well-differentiated, intestinal histological type. HER2 status differed between DB and SS in 13 patients (6%). When DB analyses were added to SS analyses, 5 additional patients were HER2 +, the relative increase in HER2 + cases being 13.5% (17.1% for patients with NAC versus 7.1% for patients without NAC, p=0.4, NS). Differences between DB and SS HER2 expression could be explained by the intratumoral heterogeneity and also by a possible HER2 expression decrease in SS after NAC. **Conclusions:** The determination of HER2 status on DB provides results that complete those obtained with SS. Combining the analysis of DB and of SS enables to optimize the selection of trastuzumab-eligible patients in case of metastatic relapse, especially in patients previously treated with NAC.

Diagnostic Biopsy / Surgical Specimen		No NAC (N = 83)		NAC (N = 135)		Total
HER2 +	HER2 -	HER2 +	HER2-			
No NAC	HER2 +	9	4			13 (15.7%)
(N = 83)	HER2 -	1	69			70
NAC	HER2 +			15	4	19 (14.1%)
(N = 135)	HER2 -			4	112	116
Total		10 (12.0%)	73	19 (14.1%)	116	218

4070 General Poster Session (Board #19H), Sun, 8:00 AM-11:45 AM

A phase II trial of definitive chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) in advanced esophageal cancer (KDOG 0501-P2).

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Background: Our previous phase I study (Radiother Oncol 2008,87:398) provided evidence that definitive chemoradiotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF-R) was tolerable and active in patients with advanced esophageal cancer (AEC). This phase II study was conducted to confirm the efficacy and toxicity of DCF-R in AEC. **Methods:** Patients with previously untreated carcinoma of the thoracic esophagus who had T4 tumors, M1 lymph-node metastasis, or both received an infusion of docetaxel (35 mg/m^2) and an infusion of cisplatin (40 mg/m^2) on day 1 and a continuous infusion of 5-fluorouracil (400mg/m^2/day) on days 1-5, every 2 weeks, plus concurrent radiation (RT). The total RT dose was initially 61.2, but was lowered to multiple-field irradiation with 50.4 Gy to decrease esophagitis and late toxicity. Consequently, the number of cycles of DCF administered during RT was modified from 4 to 3. After DCF-R, patients received at least 2 cycles of DCF (docetaxel 40 mg/m^2 on day 1, cisplatin 60 mg/m^2 on day 1, and 5-fluorouracil 600 mg/m^{2}on days 1-5, every 4 weeks). The primary endpoint was the clinical complete response rate (cCRR). Secondary endpoints were response rate (RR), progression free survival (PFS), overall survival, and safety. **Results:** 42 patients (36 men, 6 women) were enrolled. The median age was 62 years (range: 46-75). PS 0/1/2 was 14/25/3. TNM classification T4M0/non-T4M1LYM/T4M1LYM was 20/12/10. The total scheduled dose of RT 61.2Gy /50.4Gy was 12/30 patients. The RR was 90.5% and the cCRR was 52.4% (95% CI:37.3-67.5%). As of January 2013, the median PFS was 11.1 months and the median survival time was 23.1 months. Grade 3 or higher major toxicities comprised leukopenia (71.4%), neutropenia (57.2%), anemia (16.7%), febrile neutropenia (38.1%), anorexia (31.0%), and esophagitis (28.6%). There was one treatment-related death caused by aspiration pneumonia. Grade 3 or higher late toxicities comprised one pericardial effusion (Grade 4), one case of esophagitis (Grade 3), and one case of thoracic aortic aneurysm (Grade 3). **Conclusions:** DCF-R frequently caused myelosuppression, but was highly active and suggested be a promising regimen in AEC. Clinical trial information: 000002029.

4071 General Poster Session (Board #20A), Sun, 8:00 AM-11:45 AM

HER2 status in primary tumors and metastatic regional lymph nodes in patients with esophageal adenocarcinoma (EAC).

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Background: Selection of patients for HER2-targeted therapy is based on HER2 analysis in primary EACs. Since EACs metastasize via regional lymph nodes, concordance of *HER2* gene amplification results between primary tumors and their metastatic lymph nodes (MLN) is a clinically important issue. **Methods:** Resected EACs (N = 103) having at least three distinct regional MLNs (total 508 MLNs; median 4 [range 3-11]) were sectioned using routine procedures and tested for *HER2* amplification by fluorescence in situ hybridization (FISH). Primary tumors were also evaluated for HER2 protein expression by immunohistochemistry (IHC) and by FISH. Amplification was defined as *HER2/CEP17* $\geq$ 2. IHC was scored as 0, 1+, 2+, or 3+. Primaries whose HER2 status was positive by both FISH and IHC (ie, amplified and IHC3+), or negative by both (ie, nonamplified and IHC0-1+), were selected. HER2 status was compared between primaries and their MLNs (kappa). **Results:** Concordant HER2 results between primaries and their MLNs were found in 92% (95/103) of EACs (Table; κ = .76 [95% CI .60 - .92]). However, among patients with HER2-positive primaries, 19% (4/21) had *HER2*-nonamplified MLNs; among these cases, either all MLNs were *HER2*-nonamplified (n = 2), or both *HER2*-nonamplified and –amplified MLNs were present (n = 2). Among HER2-negative primary EACs, 5% (4/82) of cases had MLNs that were all *HER2*-amplified (n = 3) or both *HER2*-nonamplified and -amplified (n = 1). **Conclusions:** A patient subset whose primary EACs were HER2-positive (by both FISH and IHC) were unexpectedly found to lack *HER2* amplification in corresponding MLNs. Conversely, a subgroup with HER2-negative primaries had *HER2*-amplified MLNs, and would have been deemed ineligible for HER2-targeted therapy. These preliminary data suggest that evaluating MLNs in resected EACs has the potential to better identify patients who benefit from HER2-targeted therapy.

HER2 status in primary tumor (103 patients)	HER2 status in MLNs (≥3 MLNs tested per patient) No. patients (%)	
All MLNs amplified n=21	**All MLNs nonamplified n=82**	
Positive, n=21	17 (81)	4 (19)[a]
Negative, n=82	4 (5)[a]	78 (95)

[a] Includes patients with HER2-positive and -negative MLNs.

4072 General Poster Session (Board #20B), Sun, 8:00 AM-11:45 AM

A phase ll study of new combination regimen with trastuzumab, S-1, and CDDP in HER2-positive advanced gastric cancer (HERBIS-1).

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Background: S-1, a novel oral fluoropyrimidine, plus cisplatin (SP) regimen is one of the standard chemotherapy as first-line for advanced gastric cancer. ToGA study demonstrated that trastuzumab (T-mab) combination regimen improved the overall survival of patients with HER2-positive advanced gastric cancer. However, there was no study evaluating the efficacy and the safety of T-mab in combination with S-1 plus cisplatin (SP) regimen. Therefore, we planned this study to examine the efficacy and the safety of the SP plus T-mab. **Methods:** Patients confirmed to be HER2-positive by IHC and/or FISH (IHC 3+ or IHC 2+ and FISH positive) received S-1 at 80 mg/m^2 po, day 1-14, and cisplatin 60 mg/m^2 iv, day 1 plus trastuzumab 8 mg/kg iv, day 1 (6 mg/kg iv, d1 from 2nd course), repeated every 3 weeks until disease progression. Primary endpoint was response rate (RR). Secondary endpoints were progression-free survival, overall survival and safety. The threshold response rate was defined as 35%, and the expected rate was set at 50% with a 80% power and a 1-sided alpha value of 0.1 and the calculated sample size was 50 patients. **Results:** A total of 56 patients (median age 66) were enrolled in this study. The efficacy and the safety analyses were conducted in the full analysis set of 53 patients. (Two patients were excluded for ineligibility and one was for no treatment). The confirmed RR assessed by the independent review committee was 67.9% (95% CI: 53.7 – 80.1), and the disease control rate was 94.3%. The median PFS was 7.1 months (95% CI: 6.0 – 10.1). The median OS was not reached. (The median follow-up time: 9.2 months) The main grade 3/4 adverse events were as follows: neutropenia 34%, leucopenia 8%, anorexia 23%, diarrhea 8%, hypoalbuminemia 4%, vomiting 6%, and increased creatinine 6%. **Conclusions:** This tri-week regimen with SP plus T-mab showed promising results in patients with HER2-positive advanced gastric cancer. Clinical trial information: UMIN000005739.

4073 General Poster Session (Board #20C), Sun, 8:00 AM-11:45 AM

Nomogram for predicting the benefit of neoadjuvant chemoradiotherapy for esophageal cancer: A SEER-Medicare analysis.

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Background: The impact of neoadjuvant chemoradiotherapy for esophageal cancer remains difficult to establish for specific patient (pt) populations. The primary aim of this study was to create a web-based prediction tool that provides individualized survival projections based on clinically relevant tumor and treatment data. **Methods:** Pts diagnosed with esophageal cancer between 1997 and 2005 were selected from the Surveillance, Epidemiology, and End Results (SEER) Medicare database. The covariates chosen for retrospective analysis were: sex, T and N stage, histology, total lymph nodes examined, and receipt of neoadjuvant chemotherapy (CT), radiotherapy (RT), or chemoradiotherapy (CRT). After weighting correction by treatment groups, a log logistic regression model for overall survival (OS) was selected based on goodness of fit analysis. Based on bootstrap resampling with 100 repetitions the Concordance Index (CI) was 0.703. **Results:** 1,128 resected esophageal pts that either did or did not receive neoadjuvant treatment were appropriate for analysis. On log logistic multivariate analysis: age, sex, T stage, N stage, number of lymph nodes harvested, receipt of neoadjuvant CRT, and receipt of chemotherapy were significantly associated with OS. All T stages greater than 1 benefitted from neoadjuvant CRT ($p=<0.001$). No T stage benefitted from isolated neoadjuvant CT or RT. Patients with nodal metastases benefitted from neoadjuvant CRT ($p=<0.001$) and CT ($p=0.002$). **Conclusions:** SEER-Medicare pts with resected esophageal cancer can be used to produce a survival prediction tool that can: 1) serve as a counseling and decision aid to pts and caregivers regarding their postoperative prognosis and 2) assist in research protocol design. Patients T2 or greater or with lymph node metastases benefitted from neoadjuvant CRT based on our data. This nomogram may underestimate the benefit of neoadjuvant CRT due to its variable downstaging effect on final pathologic stage. This web based tool is available for use at http://skynet.ohsu.edu/nomograms.

4074 General Poster Session (Board #20D), Sun, 8:00 AM-11:45 AM

Phase I/II trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil (DCF) followed by concurrent chemoradiotherapy in locally advanced esophageal squamous cell carcinoma.

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Background: Standard of care for unresectable locally advanced esophageal squamous cell carcinoma (ESCC) is concurrent chemoradiotherapy (CRT). However, its survival remains limited. Neoadjuvant chemotherapy with docetaxel, cisplatin and 5-FU (DCF) demonstrated promising activity with pathological complete response (CR) of 22% for resectable stage II/III ESCC (Hara H et.al, ASCO 2012). This study was performed to assess the efficacy and safety of induction chemotherapy with DCF followed by CRT in patients with unresectable locally advanced ESCC. **Methods:** Eligibility criteria included clinically T4 and/or M1 lymph node (LYM) ESCC, PS 0-1, and 20-70 years old. Treatment consisted of docetaxel 70 mg/m^2, cisplatin 70 mg/m^2 on day 1 and fluorouracil 750 mg/m^2 on days 1 to 5, repeated every 3 weeks for three cycles, followed by cisplatin 70 mg/m^2 on days 64 and 92, and fluorouracil 700 mg/m^{2}on days 64 to 67 and 92 to 95 concurrently with radiotherapy (60Gy in 30 fractions, 5 days/week). **Results:** From August 2009 to November 2011, 33 patients were enrolled.There were 16 pts with T4M0 disease, 13 with nonT4M1 LYM, and 4 with T4M1 LYM.Most grade 3 or 4 toxicities were neutropenia (66%), leukopenia (39%), anorexia (18%), dysphasia (12%), nausea (9%), febrile neutropenia (6%), and hyponatremia (6%) during induction chemotherapy. Most grade 3 or 4 toxicities were leukopenia (27%), neutropenia (20%), dysphasia (17%), anorexia (13%), esophagitis (13%), nausea (10%), and febrile neutropenia (3%) during CRT. No treatment related death was observed. The completion rate of protocol treatment was 88% (29/33). The overall response rate after completion of induction chemotherapy was 61%. Eleven pts (38%) achieved CR after completion of protocol treatment. With a median follow-up period of 14 months, 1y-PFS and 1y-OS are 38.5 and 78.6 %, respectively. Of a total of 33 patients, eighteen patients (55%) received secondary treatment. **Conclusions:** Induction chemotherapy with DCF followed by CRT in unresectable locally advanced ESCC was well tolerated. Although these data are preliminay, this approach warrants further evaluation. Clinical trial information: UMIN000003370.

4075 General Poster Session (Board #20E), Sun, 8:00 AM-11:45 AM

Prognostic impact of human epidermal growth factor-2 (HER2) status on overall survival (OS) of advanced gastric cancer (AGC) patients (pts) treated with standard chemotherapy without trastuzumab as a first-line treatment: A Japanese multicenter collaborative retrospective study.

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Background: The prognostic impact of HER2 status on OS of AGC pts treated with standard chemotherapy without trastuzumab for first-line treatment remains controversial. This study investigated whether HER2 status is an independent prognostic factor for AGC pts. **Methods:** Formalin-fixed paraffin-embedded tumor samples from 293 eligible pts were examined for HER2 by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH). Eligible criteria included: 1) histologically confirmed gastric or gastroesophageal junction adenocarcinoma, 2) unresectable or recurrent cancer, 3) treated with S-1 plus cisplatin as first-line chemotherapy, 4) age: ≥20, 5) ECOG performance status score: 0-2 and 6) with archived tumor sample. HER2+ was defined as IHC 3+ or IHC 2+/FISH+. **Results:** Of 293 pts, 43 (15%) were HER2+. Baseline pt characteristics between HER2+ and HER2- pts were significantly different by histology (intestinal/diffuse, 65%/35% vs. 39%/61%; p=0.001), measurable disease by RECIST v1.0 (91% vs. 69%; p=0.003), No. of metastatic sites (≥2, 72% vs. 46%; p=0.003) and presence of liver metastasis (56% vs. 31%; p=0.003). After median follow-up time of 48.9 months with 270 (92%) death events, there was no significant difference in OS between HER2+ and HER2- pts (median, 11.7 vs. 13.7 months; hazard ratio [HR] 1.11, 95% CI 0.79–1.55; log rank p=0.550). After adjusting other prognostic factors with Cox hazard model, HER2+ was still not prognostic for OS (HR 0.890, 95% CI 0.627–1.262, p=0.513). **Conclusions:** HER2 status has no significant prognostic impact on OS of AGC pts treated with S-1 plus cisplatin without trastuzumab as a first-line treatment.

4076 General Poster Session (Board #20F), Sun, 8:00 AM-11:45 AM

Randomized phase II study comparing dose-escalated weekly paclitaxel versus standard dose weekly paclitaxel for patients with previously treated advanced gastric cancer.

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Background: Retrospective analyses of neutropenia during chemotherapy of weekly paclitaxel (wPTX) suggested better overall survival (OS) among patients with neutropenia. We conducted a randomized phase II trial comparing dose-escalated wPTX with dose adjustments determined by degree of neutropenia versus standard-dose wPTX for patients with previously treated advanced gastric cancer (AGC). **Methods:** Ninety-patients with AGC that progressed during one or more previous chemotherapy regimens were randomized to a standard dose of wPTX (80 mg/m^2, standard dose arm) or an escalated dose of wPTX (80 mg/m^2 on day 1, 100 mg/m^2 on day 8, and 120 mg/m^2 on day 15 unless severe toxicity nor neutropenia$<$1.5 x 10^9/L is observed, escalated dose arm) to assess superiority with a one-sided alpha of 0.3 and a power of 0.8. **Results:** The primary endpoint of median OS showed a trend towards longer survival in the dose-escalated arm (11.8 vs. 9.6 months; hazard ratio [HR], 0.75; 95% CI, 0.45-1.22; one-sided P=0.12). Median progression-free survival (PFS) was significantly longer in the dose-escalated arm (4.3 vs. 2.5 months, HR, 0.55; 95% CI, 0.34-0.90; P=0.017). Objective response rate was 30.3% with dose-escalation and 17.1% with standard dose (P=0.2). The disease control rate (DCR) was significantly higher with dose-escalation (78.8% vs. 48.6%, P=0.009). Subset-analysis according to stratification factors including ECOG PS, presence of measurable lesions and lines of previous chemotherapy indicated that OS benefit of the dose escalation is more prominent in PS 0-1 patients (N=81, median 13.6 vs. 9.8 months, HR 0.68, 95% CI 0.41-1.11) than PS2 patients with significant interaction (p=0.01) **Conclusions:** Dose escalated wPTX was associated with sufficiently longer OS in patients with pretreated AGC. In addition, significant longer PFS and higher DCR associated with dose-escalation and subset analysis according PS warrant further investigations in phase III trials, especially in patients with favorable PS patients. Clinical trial information: UMIN000004055.

4077 General Poster Session (Board #20G), Sun, 8:00 AM-11:45 AM

Promoter polymorphisms of the SWI/SNF chromatin remodeling complex molecule, BRM, and esophageal adenocarcinoma outcome.

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Background: Better understanding of the biology of esophageal cancer may help improve its treatment. The SWI/SNF chromatin remodeling complex is an important regulator of gene expression that has been linked to cancer development and outcome. Expression of Brahma (BRM), a critical catalytic subunit of SWI/SNF, is lost in a variety of solid tumors. Two novel BRM promoter polymorphisms (BRM -741 and BRM -1321) have been correlated with BRM loss and elevated cancer risk in upper aerodigestive cancers (Wang et al, Carcinogenesis, 2012) and more recently in lung cancer outcome (Cuffe et al, ESMO, 2012) by our research teams. Objectives: We evaluated BRM polymorphisms and their role in the survival of esophageal cancer patients. **Methods:** 223 histologically-confirmed esophageal adenocarcinoma patients of all stages were evaluated. The two BRM polymorphisms utilized Taqman genotyping. Cox proportional hazards models adjusted for clinical prognostic variables and determined the association of polymorphisms with overall survival (OS) and progression free survival (PFS). Adjusted hazard ratio (aHR) and 95% confidence intervals (CI) were calculated. **Results:** Among our patients, 85% were male; the mean age was 63 years. 37% had stage IV advanced tumors. The median PFS was 1.03 years, while median OS was 1.82 years. After adjustment for known prognostic clinical variables, carrying homozygous variants of both BRM polymorphisms (double homozygotes) was associated with a worse outcome: aHR 1.84 (1.06-2.34, $p=0.03$) for OS and aHR 1.93 (1.10-2.48, $p=0.02$) for PFS. The direction and magnitude of associations were similar in subsets of patients by age, gender, smoking status, use of platinum agents, and disease stage. Non-significant trends in the same direction but of aHR magnitudes 1.34-1.54 were seen in the patients who carried one homozygous variant or who were double heterozygotes. **Conclusions:** We report the initial association of BRM polymorphisms with survival in esophageal cancer. We plan to explore additional relationships and validate these findings in other datasets.

4078 General Poster Session (Board #20H), Sun, 8:00 AM-11:45 AM

A validated miRNA expression profile for response to neoadjuvant therapy in esophageal cancer.

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Background: For patients with esophageal adenocarcinoma (EAC) preoperative chemoradiation (trimodality therapy) is the preferred approach. We examined several patient cohorts to create and validate a miRNA signature predictive for response to this therapy in esophageal carcinoma. **Methods:** Pre-treatment tumor specimens from 10 patients with EAC treated with trimodality therapy were examined using a TaqMan Human MicroRNA Card Set (v3.0) for expression of 754 miRNAs, of which 306 were overexpressed. miRNA expression between patients with a pathologic complete response (pCR) and those with a non-pCR was then analyzed. 44 miRNAs differentially expressed between pCR and non-pCR patients were then examined in an additional 42 EAC patientsÕ tumors (model set) using the Fluodigm 48.48 Dynamic Array and were used to generate a miRNA expression profile (MEP) predicting for response in three groups: low, intermediate and high-risk. The MEP was then validated in an additional 72 EAC patients using the Illumina miRNA Expression Array. ROC curves were generated for clinical stage, MEP and a combination of both. **Results:** For the model set, pCR rates in low risk patients based on the MEP were 75%, 42.9% in intermediate risk and 12.5% in high-risk patients (p_{trend}=0.008). In the validation set the pCR rates were 66.7%, 36.5% and 15.7% for low, intermediate and high-risk patients respectively (p_{trend}=0.025). The AUC for the ROC using the MEP was 0.72 (p=7.8x10-12) in the model set, 0.69 (p=1x10-4) in the validation set and 0.7 for the two cohorts combined (p=1.4x10-18). When clinical stage was added to the predictive model, the ROC for each group was 0.79 (p=2.6x10-19), 0.75 (p=8.7x10-27) and 0.77 (p=2x10-41) respectively. **Conclusions:** The MEP represents the first validated miRNA signature for therapeutic response in esophageal carcinoma and improves significantly on clinical staging. Its use could select patients at high-risk for therapeutic resistance for trial-based therapy, as well as low-risk patients for whom resection may possibly be safely omitted.

4079 General Poster Session (Board #21A), Sun, 8:00 AM-11:45 AM

Interim safety analysis of a phase III trial with 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/oesophagogastric junction (OGJ) cancer: The AIO-sto-0210 FLOT4 study.

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Background: Perioperative ECF is a standard treatment for localized gastric/OGJ adenocarcinoma. However, 5-year survival rate remains below 40%. The FLOT regimen is an effective combination with pathologic response rates in the 15% range. This phase III study compares both regimens in resectable stages. **Methods:** Pts are stratified by different baseline criteria and randomized to either 3 + 3 perioperative cycles of ECF (epirubicin 50 mg/m^2, d1; cisplatin 60 mg/m^2, d1; 5-FU 200 mg/m^2, d1-d21, qd21) or 4 + 4 cycles of perioperative FLOT (docetaxel 50mg/m^2, d1; 5-FU 2600 mg/m^2, d1; leucovorin 200 mg/m^2, d1; oxaliplatin 85 mg/m^2, d1, qd14). 5-FU can be replaced by capecitabine in the ECF-arm (ECX). Central pathology is performed. This is a preplanned safety analysis after 300 patients. **Results**: The ongoing studyhas enrolled 380 of planned 590 pts, so far. 305 pts were included in this analysis. Median age is 62 yrs; 78% of pts are male. The primaries were gastric in 44.9%, OGJ in 50.4% and not evaluable/documented in 4.7% of pts. 281 pts were eligible for safety analyses. Median no. of preoperative cycles was 3 and 4 with ECF/ECX and FLOT, respectively, 35.9% vs. 44.6% of pts (ECF/ECX vs. FLOT) started postoperative chemotherapy (ct) and 22.5% vs 33.1% received all planned cycles. Grade 3/4 neutropenia was observed in 28.0% of ECF/ECX and 45.3% of FLOT pts (p=.0026). Thromboembolic events occurred in 14.1% vs. 5.8% in pts with ECF/ECX vs. FLOT (p=.027). Serious adverse events occurred in 52.1% vs. 47.5% of pts with ECF/ECX vs. FLOT (p=.48). Preoperative delay/interruptions of ct were observed in 71.1% vs. 56.8% of pts with ECF/ECX vs. FLOT (p=.013). Dose modifications of preoperative ct were performed in 27.5% vs. 20.1% of treatment cycles with ECF/ECX vs. FLOT, respectively. 197 pts have undergone surgery so far. Severe surgical morbidity was similar in both arms (ECF/ECX, 19.8%; FLOT, 16.8%). Surgical mortality was observed in 4 and 2 pts with ECF/ECX and FLOT. Toxic deaths were observed in 1 pt each. **Conclusions**: Perioperative FLOT is feasible and safe. Clinical trial information: NCT01216644.

4080 General Poster Session (Board #21B), Sun, 8:00 AM-11:45 AM

Safety, tolerability, and efficacy of the first-in-class antibody IMAB362 targeting claudin 18.2 in patients with metastatic gastroesophageal adenocarcinomas.

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Background: IMAB362 is a monoclonal antibody targeting isoform 2 of the tight junction component claudin 18 (CLDN18.2), a tumor-selective antigen frequently expressed in several types of epithelial adenocarcinomas. Preclinically, IMAB362 exerts its antitumor activity by ADCC, CDC, induction of apoptosis and inhibition of cell proliferation. **Methods:** Patients with treatment-refractory, metastatic gastroesophageal adenocarcinomas with CLDN18.2-positive tumors as determined by immunohistochemistry were enrolled in two clinical trials of IMAB362 monotherapy. A phase I inter-patient single dose escalation study (n=15, 5 dose groups from 33 mg/m² to 1000 mg/m² with 3 patients each, follow-up 4 weeks) was conducted followed by a phase II study (n=34, 300 mg/m^2 [n=4] and 600 mg/m^2[n=30]) administered every two weeks for 5 courses, imaging in week 11. Patients with disease control allowed to continue IMAB362 therapy until progression. Analysis of the phase II trial is ongoing. **Results:** In the phase I trial, all dose levels of IMAB362 were generally well tolerated. Nausea and vomiting were the most common adverse events (AEs). No dose limiting toxicity was observed at single doses up to 1,000 mg/m². Based on pharmacokinetic considerations and preclinical dose/response data, the recommended doses for the phase II multidose trial was 600 mg/m². In the phase II study, 34 patients were evaluable for safety. No grade 4 AEs occurred, grade 3 AEs were vomiting (n=8, 24%), nausea (n=4, 12%) and hypersensitivity (n=1, 3%). As of January 2013, 31 patients were evaluable for efficacy analysis. Four patients had achieved a confirmed partial response, and eight patients had disease stabilization (ORR=13%, DCR=39%). The longest observed response duration thus far was 40 weeks. **Conclusions:** IMAB362 antibody therapy of patients with advanced CLDN18.2-positive gastroesophageal adenocarcinomas is safe and well tolerated. Early evidence for antitumoral activity was observed in the phase II trial. Further clinical evaluation of IMAB362 in patients with CLDN18.2 tumors is warranted. Clinical trial information: NCT01197885.

4081 General Poster Session (Board #21C), Sun, 8:00 AM-11:45 AM

Final results of AGITG ATTAX3 study: Randomized phase II study of weekly docetaxel (T), cisplatin, and fluoropyrimidine (F) with or without panitumumab (P) in advanced esophagogastric (OG) cancer.

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Background: This randomized phase II study evaluated the efficacy and safety of P, a fully human mAb against the epidermal growth factor receptor combined with T-based chemotherapy in advanced OG cancer. **Methods:** Eligible pts had histologically confirmed metastatic OG cancer (adeno-carcinoma and squamous cell carcinoma) were ≥18 years of age, PS 0-2, with adequate renal, haematologic and liver function with measurable disease. All pts provided informed consent. Selection was not based on *kras* determination. Pts received T 30mg/m^2 d1,8, C 60mg/m^2 d1 and F; investigator choice of 5FU infusion 160mg/m^2/d or capecitabine 500mg/m^{2}bd continuous ±P 9 mg/kg d1 q3w. Treatment was administered for 8 cycles or until PD. The primary endpoint was response rate according to RECIST (1.1) assessed q6w. Planned enrolment target was 100 pts. Stratification variables included histology, PS and choice of F. **Results:** From April 2010 to November 2011, 77 pts were enrolled from 15 institutions. A safety alert from the REAL3 study (also involving P in OG cancer) prompted an unplanned review of data from ATTAX3 by the IDMC. The IDMC found no evidence of adverse outcomes associated with P, but as it did not appear that P would significantly improve efficacy, they recommended cessation of the study to new enrolment. Previously enrolled pts were treated and followed according to protocol. Median follow up is 24m. Treatment arms were well balanced; median age 59, 64y, male 77%, 87%, PS0-1 95%,90%, adenocarcinoma 90%,90%, capecitabine 67%, 66% for TCF/TCF-P, respectively. Common grade 3/4 toxicities include infection 18%,24%, febrile neutropenia 10%, 5%, anorexia 10%, 24%, nausea 18%,30%, stomatitis 3%,5%, diarrhoea 15%,24% , acneiform rash 0%, 8%, fatigue 18%, 30%, hypomagnesemia 10%, 16% for TCF/TCF-P. Efficacy outcomes are summarized in Table. **Conclusions:** The addition of P to T-based chemotherapy in advanced OG cancer did not improve efficacy and was associated with an increase in some toxicities. Clinical trial information: ACTRN12609000109202.

	TCF (n=39)	TCF +P (n=38)
Response rate % (95% CI)	49 (34-64)	58 (42-72)
Median PFS (m) (95% CI)	6.9 (5.7-8.5)	6.0 (4.4-7.3)
Median OS (m) (95% CI)	11.7 (7.8-15.9)	10.0 (8.3-12.0)

4082 General Poster Session (Board #21D), Sun, 8:00 AM-11:45 AM

Variable penetrance of CDH1 mutation diffuse gastric cancer: A genomic analysis.

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Background: CDH1 encodes E-cadherin; mutations (CDH1mut) increase the risk of diffuse gastric (DGC) and lobular breast cancers. Life-time risk of DGC is estimated at 80%. Current recommendations are prophylactic gastrectomy (PG) in CDH1mut carriers after age 20. Foci of DGC are found in some PG; others have none at PG, and some CDH1mut without PG never develop cancer. Identifying risk modifying alleles or other genomic events which increase the risk of DGC may improve understanding of DGC and may provide a biomarker for when to perform PG. **Methods:** For a Gastric Cancer Registry, we collected family pedigrees, germline DNA and FFPE tumor from CDH1mut DGC patients (pts) and their families. From 24 families, with 52 CDH1mut individuals, we identified 4 families in which a young CDH1mut pt developed advanced DGC while their CDH1mut parent and siblings had no clinical evidence of DGC. Several relatives had undergone PG with no DGC found. We hypothesize that there are risk modifying alleles and/or a "second hit" that causes variable penetrance and early onset of DGC in the young CDH1mut pts. Whole genome sequencing was performed on germ line DNA (Complete Genomics, Inc. Mountain View, CA); and whole exome sequencing on tumor specimens (MSKCC). **Results:** To date, 4 DGC pts and 8 relatives from 4 families have been studied. All 4 affected pts were women (ages 17, 25, 27, 42); their unaffected CDH1mut parents were 41, 51, 54, and 70 years old. The families are of Kenyan, Scandinavian, Italian, Eastern European, and Scottish origin. CDH1 mutations for the pts and their families were confirmed on WGS, and were as follows: 1451C>A(pro484his);c. 1792C>T (arg598ter);c. 1893dupA in exon 12;c. 1565+1G>A (IVS10+1G>A). Analysis of germline DNA for modifying alleles is being performed (Ingenuity Systems, Redwood, Ca.); whole exome sequencing of tumor to identify a possible ″second hit″ is underway. These data will be presented. **Conclusions:** Since at least some older pts with proven CDH-1mut do not develop DGC while their children do, CGH-1mut alone may not be sufficient to cause early onset DGC. We hope to identify the additional genomic events associated with early onset advanced DGC. Supported in part by grants from the Gerstner and DeGregorio Foundations.

4083 General Poster Session (Board #21E), Sun, 8:00 AM-11:45 AM

Pattern of local-regional relapse and survival after bimodality therapy for esophageal cancer: Implications for the surveillance strategy.

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Background: Evidence for definitive chemoradiotherapy (bimodality therapy [BMT]) has been established for patients with esophageal and gastroesophageal junction cancer (EGEJC) who do not qualify for surgery. Surveillance for these patients is often recommended but the literature lacks guidance for an evidence-based surveillance strategy after BMT. **Methods:** We analyzed 276 patients with EGEJC who underwent BMT and had pre- and postchemoradiation endoscopic biopsies and imaging studies available for review. Patients who underwent planned surgery or salvage surgery (SS) within 6 months from BMT were excluded. We reviewed the pattern of relapse over time. Local-regional disease (LRD) after BMT was classified as regional disease (RD) or luminal-only disease (LD). Overall survival (OS) probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test. **Results:** For 276 patients, the median follow-up time was 53.0 months (95% confidence interval [CI], 47.3-58.7). A total of 184 (66.7%) patients had a persistent disease or relapse after BMT: 120 distant metastases (43.5% of 276) and 64 LRD (23.2% of 276). Of 64 LRD, 58 (91%) were diagnosed within 2 years of BMT and 63 (98%) were diagnosed within 3 years (see Table). Twenty-three of 64 LRD patients underwent SS. For patients with SS, the median OS time from diagnosis of LRD was 58.0 months (95% CI, not reached), and that for patients without SS was 9.0 months (95% CI, 7.3-10.7); this difference was highly significant ($p < 0.001$). **Conclusions:** Our data suggest that 91% of LRD occurred within 2 years after BMT and the OS with SS for LRD was better than that without SS. These data can contribute to the development of an evidence-based surveillance strategy.

Duration-specific rate of relapse from BMT or persistent disease (months).

	Persistent disease at 1st surveillance after BMT	-12M***	13-24M	25-36M	37-48M	49M-
Luminal-only	15	25	12	4	0	1
*	5.4%	9.1%	4.3%	1.4%	0.0%	0.4%
**	23.4%	39.1%	18.8%	6.3%	0.0%	1.6%
Regional	5	1	0	1	0	0
*	1.8%	0.4%	0.0%	0.4%	0.0%	0.0%
**	7.8%	1.6%	0.0%	1.6%	0.0%	0.0%

* Total denominator: 276. ** Total local-regional disease after BMT: 64. *** Not including persistent disease at the 1st surveillance.

4084 General Poster Session (Board #21F), Sun, 8:00 AM-11:45 AM

Phase II study of mFOLFOX with bevacizumab (Bev) in metastatic gastroesophageal and gastric (GE) adenocarcinoma (AC).

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Background: The median survival for patients (pts) with metastatic GE AC in phase III studies is $<$12 mos. Bev has demonstrated promising activity in metastatic GE AC when used in combination with cisplatin-based regimens in studies with patients from the Americas. We conducted a prospective phase II trial to investigate the efficacy of Bev in combination with mFOLFOX6 in pts with metastatic GE AC. **Methods:** Pts with previously untreated metastatic GE AC (gastric, GE junction, distal esophagus) received mFOLFOX6 (LV 400 mg/m^2, 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 over 46 hr continuous infusion, Ox 85 mg/m^2) and Bev 10 mg/kg q 2 wks. Response by RECIST was evaluated by CT q 8 wks. Primary objective was time to progression (TTP); secondary objectives were safety, response rate (RR), and overall survival (OS). **Results:** 39 pts were enrolled between 09/08 and 06/12. Pt characteristics are as follows: median age, 59 yo (range 27-79); M/F, 31/8; ECOG PS 0/1, 11/28; gastric/distal E and GEJ, 13/26; metastatic sites: lymph nodes 23, liver 19, lung 9, peritoneum 9; $>$2 metastatic sites, 20; prior gastrectomy or esophagectomy, 7. Nine pts remain on study, and 15 pts are alive. Median # of cycles administered is 11 (range 4 - $>$31). RR is 56.4% (4 CR, 18 PR). Median TTP is 8.2 mos. Median OS is 15.2 mos. Three pts survived $>$24 mos. Grade 3/4 toxicities include neutropenia (13, 33.3%), neuropathy (8, 20.5%), DVT/PE (5, 12.8%), thrombocytopenia (3, 7.7%), anemia (1, 2.6%), hypertension (1, 2.6%), and proteinuria (1, 2.6%). We observed no GI perforations or grade 3/4 GI hemorrhagic events. **Conclusions:** FOLFOX6/Bev is well tolerated and associated with increased TTP and OS in pts with metastatic GE AC compared to historical data from similar populations treated without Bev. Our findings validate previous studies with Bev in combination with cisplatin-based regimens in pts from the Americas with metastatic GE AC. This study is supported by Genentech. Clinical trial information: NCT00673673.

4085 General Poster Session (Board #21G), Sun, 8:00 AM-11:45 AM

Customizing surveillance of patients with esophageal or esophagogastric junction adenocarcinoma (E-EGA) after trimodality therapy (TMT).

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Background: Follow-up strategy for E-EGA patients after TMT has varied and is debated often due to the lack of evidence. It is an expensive endeavor and the literature provides little guidance. **Methods:** Between 2000 and 2010, we identified 518 E-EGA patients who had TMT. We reviewed the timing/pattern of recurrence after TMT and grouped them as local-regional (LR) or metastatic (M). **Results:** The median follow-up time from date of surgery was 29.3 months (range, 0.8 to 149.2 months). 215 (41.5%) had a relapse (M=188 [87.5%] and LR=27 [12.5%]). Among LRs, regional node only in 16 (7.4%) and intra-luminal only occurred in 11 (5.1%). The frequency of relapses was highly associated with the surgical stage ($p<0.001$). >90% of all relapses occurred within 29.2 months of surgery. In addition, almost all intra-luminal only relapses occurred within 24 months (see Table). **Conclusions:** Our data suggest that it may be possible to customize surveillance of patients after TMT based on the surgical stage. Additionally, intra-luminal only relapse are rare and are unlikely after 24 months. Our data can contribute to the development of an evidence-based surveillance strategy.

Surgical stage	No. of recurrence/patient	Time to luminal only recurrence from surgery					
	0-12M	13-24M	25-36M	37-48M	49-60M	61M-	
0 / I	2 / 191 1.0%	0	1	0	0	0	1
II / III	9 / 327 2.8%	1	7	1	0	0	0

4086 General Poster Session (Board #21H), Sun, 8:00 AM-11:45 AM

FOLFIRI plus sunitinib versus FOLFIRI alone in advanced chemorefractory esophagogastric cancer patients: A randomized placebo-controlled multicentric AIO phase II trial.

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Background: Sunitinib is an receptor tyrosine kinase (RTK) inhibitor of VEGFR1-3, PDGFR-α-β, and other RTK. After we established Sunitinib (Sun) alone associated with limited response rate (RR) and good tolerability in refractory advanced esophagogastric cancer patients (Moehler et al. *EUR J Cancer*. 2011, 47: 1511), this double-blinded placebo-controlled phase II evaluated safety and efficacy of SUN as add-on in second-line or third-line FOLFIRI (ClinicalTrials.gov NCT01020630). **Methods:** Patients with failure of any prior docetaxel and/or platinum-based chemotherapy were randomized to receive 6-week cycles including FOLFIRI two weekly and SUN (25 mg) versus (vs) placebo (PLA) daily for 4 consecutive weeks followed by a 2-week rest. Primary endpoint was progression-free survival (PFS). **Results:** 91 randomized patients (ITT) had similar characteristics in both groups (SUN/PLA 45/46). Both groups had 2.7 treatment cycles. Objective RR was 20/29%, and tumor control rate was 58/56 % for SUN/PLA, respectively. Median PFS was similar for SUN vs. PLA with 3.6 vs. 3.3 months, respectively (HR 1.11; 95%CI 0.70-1.74, P = 0.66). Median overall survival (OS) was longer for SUN vs. PLA with 10.5 vs. 9.0 months, in ITT (HR 0.816; 95%CI 0.50 - 1.34, P = 0.42, one-sided 0.21) and in the per protocol population (HR 0.71; 95%CI 0.41 - 1.24, P = 0.23) respectively. No unexpected higher toxicities, SAE or SUSAR occurred with SUN. For SUN/PLA, all grade AEs (%) possibly related to study drug were nausea 49/47%, fatigue 36/29%, vomiting 27/29%, diarrhoea 36/38%, neutropenia 62/22%, stomatitis 27/20%, and palmar-plantar erythrodysaesthesia 13/3%, and Grade 3+ AEs (%) were neutropenia 56/20%, diarrhoea 2/13%, nausea 7/7%, fatigue 0/9% and pain 0/9%, respectively. Performed quality of life outcomes were mostly in favor of Sunitinib. **Conclusions:** In our phase II trial, Sunitinib added to FOLFIRI increased hematotoxicity and did not improve response rates or PFS in chemotherapy-resistant GC patients. Since the regimen was safe and patients had a trend to better OS, biomarker analyses will be performed to identify subgroups that benefit from add-on Sunitinib. Clinical trial information: NCT01020630.

4087 General Poster Session (Board #22A), Sun, 8:00 AM-11:45 AM

A phase II trial of induction epirubicin, oxaliplatin, and flourouracil, surgery and post-operative concurrent cisplatin and fluorouracil chemoradiotherapy (CRT) in patients (pts) with loco-regionally advanced (LRA) adenocarcinoma (ACA) of the esophagus (E) and gastroesophageal junction (GEJ).

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Background: In pts with LRA ACA of the E/GEJ, CRT and surgery results in excellent locoregional control. Distant failure remains common, however, suggesting potential benefit from additional chemotherapy. This single arm phase II study investigated the addition of induction chemotherapy to surgery and post-operative CRT. **Methods:** Pts with an ultrasound-based clinical stage of T3, N1 or M1a (AJCC 6th) ACA of the E/GEJ were eligible. Induction chemotherapy with epirubicin 50mg/m2 d1, oxaliplatin 130mg/m2 d1, and flourouracil 200mg/m2/day continuous infusion for 3 weeks, was given every 21 days for 3 courses and was followed by surgical resection. Adjuvant CRT consisted of 50-55Gy at 1.8-2.0 Gy/d and 2 courses of cisplatin (20mg/m2/d) and flourouracil (1000mg/m2/d) given as 96 hour infusions during weeks 1 and 4 of radiotherapy. **Results:** Between 2/08 and 1/12, 60 evaluable pts enrolled; 95% male, 97% white and 78% with GEJ tumors. Resection was accomplished in 54 pts (90%) and adjuvant CRT in 48 (80%). Toxicity included 1 death during induction (2%), and 2 post-operative deaths (4%). Unplanned hospitalization was required in 18% of pts during induction and 19% during adjuvant CRT. Induction chemotherapy produced a symptomatic response in 79% of pts, a clinical (ultrasound) response in 48% and a pathologic response in 41% (5% complete). With a median follow-up of 31 months, the Kaplan-Meier 3-year projected locoregional control (LRC) is 84%, distant metastatic control (DMC) 44%, relapse-free survival (RFS) 39%, and overall survival (OS) 42%. Symptomatic response to induction and the percentage of remaining viable tumor at surgery proved the strongest predictors of DMC, RFS, and OS. **Conclusions:** Induction chemotherapy, surgery and adjuvant CRT is feasible and produces outcomes similar to other multimodality treatment schedules in LRA E/GEJ ACA. Despite excellent LRC, projected DMC and OS remain poor. A symptomatic response to induction and less residual viable tumor at surgery are associated with improved outcomes. Clinical trial information: NCT00601705.

4088 General Poster Session (Board #22B), Sun, 8:00 AM-11:45 AM

A comparison of postoperative quality of life after open and laparoscopic gastrectomy for early gastric cancer: A multicenter, nonrandomized, controlled study (CCOG 0802).

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Background: The aim of this study was to compare the postoperative health-related quality of life (HRQoL) between open and laparoscopic distal gastrectomy. **Methods:** A multi-institutional non-randomized study was conducted, and early gastric cancer patients were prospectively enrolled and underwent distal gastrectomy either by the open or laparoscopic approach. HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Cancer (QLQ-C30) and the site-specific module for gastric cancer (QLQ-STO22). Questionnaires were completed at baseline and at 1, 3, 6 and 12 months postoperatively. Clinicopathological characteristics and short term outcome including postoperative morbidity and HRQoL were compared between the approaches. **Results:** A total of 159 patients with clinical T1 tumors were enrolled between September 2008 and January 2011. Those who were found upon pathologic examination to have ≥aStage II disease (n=14) were excluded, and the remaining 145 patients (open: n=72, laparoscopic: n=73) were analyzed. There were no significant differences between the two groups regarding age, gender, macroscopic type, depth of invasion, lymph node metastasis, and pathologic type. Laparoscopic approach was associated with longer operating time, smaller blood loss, and similar incidence of postoperative complications. At each time point, the questionnaires were sent to the data center from >90% of the patients. The worst scores for most of the items were observed at 1 month postoperatively and improved thereafter. The role, emotional, cognitive, and social functioning scores were superior in the laparoscopic group at 6 and 12 months postoperatively. Symptom scales including fatigue, pain, anxiety, eating restriction, and taste problem were better in the laparoscopic group before 6 months but not at 12 months. **Conclusions:** Patients treated by the laparoscopic approach benefitted from better HRQoL in terms of symptoms scores during the first 6 months, while the superiority in several functioning scores lasted for 12 months.

4089 General Poster Session (Board #22C), Sun, 8:00 AM-11:45 AM

PI3K pathway as a major determinant of resistance to HER2-targeted therapy in advanced gastric cancer.

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Background: Despite the improvement of survival with trastuzumab treatment, it is still unclear why majority of patients are initially nonresponsive or eventually become resistant to HER2-based therapy. To evaluate resistant mechanism and stimulate the development of rational drug, we investigated the role of phosphoinisitide 3-kinase (PI3K) pathway activation. **Methods:** With tumor tissues from HER2-overexpressing advanced gastric cancer, PIK3CA mutation status (by pyrosequencing of exon 9 and 20) and phosphatase and tensin homolog (PTEN) expression levels (using immunohistochemical analysis) were evaluated for the therapeutic response to HER2-based therapy. **Results:** Forty nine patients received trastuzuamb (n=39) or lapatinib (n=10) in combination with chemotherapy regimen. The age at diagnosis was 61 years and all the cases were HER2 positive and/or amplified. PTEN-loss was found in 67% (n=33) and all the patients showed PIK3CA wild-type tumors. Twenty nine patients (59%) responded to HER2-based therapy (complete and partial response), without significant difference between PTEN-loss and normal tumors (61% *vs* 62%). Among the patients with responsive disease, time to best response was not different but duration of response was shorter for the PTEN deficient patients (155 vs 244 days, P=0.016). In addition, PTEN-deficient patients have significantly shorter progression-free survival (median 160 vs 286 days, P=0.018), which implying the functional role of PTEN for the acquired resistance to HER2-based therapy. **Conclusions:** This data suggests PTEN as an important predictor for the early progression and acquired resistance to HER2-based therapy. Activated PI3K pathway may provide a biomarker to identify patients who may need additional or alternative therapies.

4090 General Poster Session (Board #22D), Sun, 8:00 AM-11:45 AM

A phase II clinical trial of ganetespib (STA-9090) in previously treated patients with advanced esophagogastric cancers.

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Background: Subsets of esophagogastric (EG) cancers harbor genetic abnormalities, including amplification of HER2 or MET, or mutations in PIK3CA, EGFR, or BRAF. These genes encode clients of the molecular chaperone heat-shock protein 90 (HSP90), and inhibition of HSP90 may promote the degradation of these oncogenic signaling proteins. Ganetespib is a novel triazolone heterocyclic inhibitor of HSP90 that is a biologically rational treatment strategy for advanced EG cancers. **Methods:** This was a multicenter, single-arm Phase 2 trial. Eligibility: Histologically confirmed advanced EG cancer; progression on $\leq$ 2 lines of systemic therapy; ECOG PS 0-1. Treatment: Ganetespib 200mg/m^{2}IV on Days 1, 8, and 15 of a 28-day cycle. Primary endpoint: overall response rate (ORR). **Results:** 26/28 patients enrolled received $\geq$ 1 dose of drug. The characteristics of the 26 patients were: male 77%, median age 64 years old; ECOG PS 0/1 42/58%; median number of prior therapies 2; esophageal/GEJ/gastric 27/42/31%; prior platinum 92%, prior fluoropyrimidine 88%, prior taxane 38%, prior trastuzumab 15%. Median follow-up was 83 days. The most common drug-related adverse events were: diarrhea (77%), fatigue (65%), elevated ALKP (42%), and elevated AST (38%). The most common Grade 3/4 AEs included: leucopenia (12%), fatigue (12%), diarrhea (8%), and elevated ALKP (8%). 14/26 required $\geq$ 1 dose modification. 22/26 patients completed at least 2 cycles of ganetespib and were evaluable for response. One complete response was seen, and this patient continues on treatment as of cycle 31 (27.5 mos). Molecular characterization of this patient's tumor revealed a KRAS mutation in codon 12. The ORR was 1/26 (4%). Two of six patients with HER2-positive disease achieved 12% and 19% tumor reduction from baseline, respectively. TTP was 48 days (1.6 mos) and OS was 83 days (2.8 mos). **Conclusions:** Ganetespib showed manageable toxicity. While the study was terminated early due to insufficient evidence of single agent activity, the durable CR and 2 minor responses suggest that there may be a subset of EG patients who could benefit from this drug. The molecular determinants of response, however, have yet to be fully characterized. Clinical trial information: CT01167114.

4091 General Poster Session (Board #22E), Sun, 8:00 AM-11:45 AM

Natural history of malignant bone disease in gastric cancer: Final results of a multicenter bone metastasis survey.

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Background: Bone metastasis represents an increasing clinical problem in advanced gastric cancer (GC) as disease-related survival improves. In literature few data on the natural history of bone disease in this malignancy are available. **Methods:** A retrospective, observational multicenter study aimed to define the natural history of GC patients with bone metastasis was conducted in 22 Italian hospital centres in which these patients received diagnosis and treatment of disease from 1998 to 2011. Data on clinicopathology, skeletal outcomes, skeletal-related events (SREs), and bone-directed therapies for 208 deceased GC patients with evidence of bone metastasis were statistically analyzed. **Results:** Median time to bone metastasis was 8 months (CI 95%, 6.125–9.875 months) considering all included patients. Median number of SREs/patient was one; less than half of the patients (31%) experienced at least one event and only 4 and 2% experienced at least two and three events, respectively. Median times to first and second SRE were 2 and 4 months, respectively. Median survival was 6 months after bone metastasis diagnosis and 3 months after first SRE. Median survival in patients who did not experience SREs was 5 months. Among patients who received zoledronic acid (ZOL) before the first SRE, median time to its appearance was significantly prolonged compared to control (7 months vs 4 months for control; *P:*0.0005). **Conclusions:** To our knowledge, this retrospective analysis is the largest multicenter study to demonstrate that bone metastases from GC are not so rare, are commonly aggressive and result in relatively early onset of SREs in the majority of patients. Furthermore, our large study, which included 90 patients treated with ZOL, showed, for the first time in literature, a significant extension of time to first SRE and increase in the median survival time after diagnosis of bone metastasis.

4092 General Poster Session (Board #22F), Sun, 8:00 AM-11:45 AM

Surgery-induced peritoneal metastasis and its intraoperative treatment.

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Background: A large number of advanced gastric cancer patients undergoing curative gastrectomy with D2 lymph node dissection (D2 gastrectomy) show peritoneal metastasis. The source of these metastatic cells and their treatment remain unclear. We examined the mechanism of surgery-induced peritoneal metastasis and determined the appropriate intraoperative treatment. **Methods:** (1) Curative gastrectomy was performed for 102 gastric cancer patients. Peritoneal lavage fluid was collected before and after gastrectomy. Cytology, RT-PCR, and cell culture were used to determine the presence of cancer cells. Proliferative potential of tumor cells was evaluated using Ki-67 staining. Tumorigenic capacity was assessed by cell injection into the peritoneal cavity of NOD/ShiJic-scid mice. (2) Fifty clinical T3(SE) or T4(SI) advanced gastric cancer patients undergoing curative D2 gastrectomy prospectively received intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) in a phase II trial. HIPEC comprised 50 mg CDDP, 10 mg MMC, and 1000 mg 5-FU in 5 L saline maintained at 42–43C° for 30 min. **Results:** (1) Of 102 peritoneal lavage fluid samples obtained before gastrectomy, 57 from both early and advanced cancer patients did not contain CEA or CK20 mRNA amplification products or cancer cells. Of these 57 samples, CEA or CK20 mRNA was detected in 35 and viable cancer cells were identified in 24 after gastrectomy. Viable cancer cells in all 24 cases showed Ki-67 positivity, indicating proliferative activity. Cultured viable cancer cells developed into peritoneal tumor nodules after spill over into the peritoneal cavity in NOD/ShiJic-scid mice. (2) Fifty patients were eligible for the phase II clinical trial. The overall 5-year survival rate for all patients was 92.4%. This rate in patients with pT2(ss) (n = 12), pT3(se) (n = 35), and pT4(si) (n = 3) disease was 90.0%, 92.3%, and 100%, respectively. Only 2 patients (4%) showed peritoneal relapse. **Conclusions:** Viable tumorigenic cancer cells spilled over the peritoneal cavity during curative gastrectomy. Intraoperative HIPEC following curative D2 gastrectomy effectively prevented peritoneal metastasis, thereby potentially improving the prognosis of patients with advanced gastric cancer.

4093 General Poster Session (Board #22G), Sun, 8:00 AM-11:45 AM

Who benefits from radiotherapy for gastric cancer? A meta-analysis.

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Background: Randomized trials have demonstrated significant survival benefits with the use of adjuvant (including neoadjuvant) chemotherapy or chemoradiotherapy for gastric cancer. The importance of adjuvant radiotherapy (RT) remains unclear. Here we perform an up-to-date meta-analysis of randomized trials testing the use of radiotherapy for resectable gastric cancer. **Methods:** We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized trials testing adjuvant RT for resectable gastric cancer. Hazard ratios describing the impact of adjuvant RT on overall survival (OS) and disease-free survival (DFS) were extracted directly from the original studies or calculated from survival curves. Pooled estimates were obtained using the inverse variance method. Subgroup analyses were performed to determine if the efficacy of RT varies with chemotherapy use, RT timing, geographic region, type of nodal dissection performed, and lymph node status. **Results:** Thirteen studies met all inclusion criteria and were used for this analysis. Adjuvant RT was associated with a significant improvement in both OS (HR=0.78, 95% CI: 0.70 to 0.86, $p<0.001$) and DFS (HR=0.71, 95% CI: 0.63 to 0.80, $p<0.001$). In the five studies that tested adjuvant chemoradiotherapy against adjuvant chemotherapy, similar effects were seen for OS (HR=0.83, 95% CI: 0.67 to 1.03, $p=0.087$) and DFS (HR=0.77, 95% CI: 0.91 to 0.65, $p=0.002$). Available data did not reveal any subgroup of patients that does not benefit from adjuvant RT. **Conclusions:** In randomized trials for resectable gastric cancer, adjuvant RT provides an approximately 20% improvement in both DFS and OS. Available data do not reveal a subgroup of patients that does not benefit from adjuvant RT. Further study is required to optimize the implementation of adjuvant RT for gastric cancer with regards to patient selection and integration with systemic therapy.

4094 General Poster Session (Board #22H), Sun, 8:00 AM-11:45 AM

Nomogram predicting long-term survival probability of thoracic esophageal squamous cell carcinoma after radical esophagectomy.

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Background: Nomograms have been widely and successfully used for numerous cancers to obtain reliable prognostic information for each individual patient.To date, however, no studies have conducted survival estimates using nomograms for esophageal squamous-cell carcinoma (ESCC) in Chinese population.The purpose of this study is to develop a nomogram to predict the long-term survival probabilities in patients diagnosed with ESCC after radical esophagectomy. **Methods:** This study involves a dataset containing 1923 patients who underwent radical esophagectomy for ESCC at Zhejiang Cancer Hospital in Hangzhou, China. Among them, 1,578 patients with no missing data were used to build a prognostic nomogram based on Cox proportional hazard regression model. A multivariate survival analysis using Cox regression model was applied to identify significant variables with P-values <0.05. On the basis of the predictive model with the identified variables, a nomogram was constructed for predicting five-year and ten-year overall survival probabilities. The prediction model was internally validated using bootstrap resampling, assessing its optimism-corrected discrimination and calibration. **Results:** The median of overall survival times of 1578 ESCC patients was 35.6 months, and the 5-year and 10-year survival rate was 32% and 20%, respectively. The multivariate Cox model identified alcohol, tumor length, surgical approach, number of surgical removed lymph node, ratio of metastatic lymph nodes, region of lymph nodes dissection, depth of invasion, differentiation of tumor, postoperative complications as covariates significantly associated with survival. Across the 100 bootstrap replicates, the median optimism-corrected summary C-index for predicting survival was 0.713 (SE=0.011). **Conclusions:** A nomogram predicting 5- and 10-year overall survival after radical esophagectomy for ESCC in Chinese population was constructed and validated based on nine significant variables. The nomogram can be applied in daily clinical practice for individualized survival prediction of ESCC patients after potentially curative esophagectomy.

4095 General Poster Session (Board #23A), Sun, 8:00 AM-11:45 AM

The association of objective response and overall survival in patients with inoperable or metastatic gastric and esophagogastric junction (EGJ) cancer: A pooled analysis of individual patient data from first-line clinical trials.

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Background: The aim of the study is to determine whether the achievement of an objective response to first-line chemotherapy is prognostic of patient's outcome in gastric/EGJ adenocarcinoma. **Methods:** Individual patient (pts) data from prospective first-line trials conducted by a single study group were used. Patients received platin/5-FU based chemotherapy with or without docetaxel. Responses were evaluated according to WHO criteria in all trials. Response data, patients' characteristics (age, sex, entity, histological type, primary location, ECOG PS, and type and number of metastatic sites), type of chemotherapy, and overall survival data were analyzed. **Results:** 612 pts were included. Median age was 66 yrs; 31.5% had ECOG status 0, 58.3% ECOG 1, and 9.8% ECOG 2 & 3. Gastric primaries were found in 44.4% and EGJ in 35.8% of pts (19.7% were overlapping/not evaluable). According to Lauren classification, 36.8% had intestinal, 32.4% diffuse, and 8.5% mixed types (22.4% were not classifiable). 64.5% had positive non-regional lymph nodes (LN) involvement, 14.1% LN involvement without other metastases, 33.3% had peritoneal carcinomatosis, 44.0% liver and 16.7% lung metastases. Response rates were complete (CR) in 3.1%, partial (PR) in 36.4%, stable disease (SD) in 34.5%, and progressive disease (PD) in 15.0% pts (10.9% were not evaluable). Overall response rate (OR; CR + PR) was 39.5%. Median overall survival times in pts with CR vs PR vs SD vs PD were 37.9 vs 14.7 vs 10.9 vs 5.2 months, respectively; $p=1.26 \times 10^{-33}$). OR (CR or PR) also strongly predicted OS (16.7 vs 8.1 months in pts with vs no OR, $p=1.08 \times 10^{-17}$). OR remained the strongest predictor of OS in the multivariate analysis ($p=6.55 \times 10^{-7}$) including all baseline criteria mentioned above followed by ECOG PS ($p=0.048$) and the presence of non-regional LN as the only site of metastasis ($p=0.034$). **Conclusions:** The achievement of an objective response is the strongest predictor of survival in pts with gastric and EGJ cancer and could serve as a surrogate marker if validated.

4096 General Poster Session (Board #23B), Sun, 8:00 AM-11:45 AM

Multicenter, phase II study of trastuzumab and paclitaxel to treat HER2-positive, metastatic gastric cancer patients naive to trastuzumab (JFMC45-1102).

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Background: The ToGA study indicated that first-line treatment using trastuzumab (T-mab) combined with capecitabine and cisplatin conferred a survival (OS) benefit to patients with HER2-positive metastatic gastric cancer (mGC). However, no reports have described the efficacy and safety of second-line treatment of HER2-positive mGC patients with T-mab who were naïve to the drug. **Methods:** JFMC45-1102 was a multicenter, Phase II study. Patients positive for HER2 (IHC3+ or IHC2+/FISH+) with gastric adenocarcinoma confirmed histologically; older than ≥ 20 y; who received one or more prior chemotherapies but no prior therapy with T-mab; and normal left ventricular ejection fraction (LVEF ≥ 50%) were eligible. Patients received paclitaxel (80 mg/m^{2}on days 1, 8, and, 15 q4w) plus T-mab (8 mg/kg initial dose, followed by 6 mg/kg q3w). Treatment continued until their disease progressed; there was unacceptable toxicity or patient's refused further treatment. The primary endpoint was overall response rate (ORR) evaluated according to RECIST ver. 1.0. Threshold and expected ORR were estimated at 15% and 30%, and secondary endpoints included progression free survival (PFS), time to treatment failure (TTF), overall survival (OS) and safety. **Results:** Fourty-six patients were enrolled between September 2011 and March 2012. Patients characteristics were: gender (M/F) 37/9; median age 69; ECOG PS0/1/2, 35/10/1; unresectable/recurrence 25/21; number of prior treatments (1/2), 41/5. The ORR was 37.2% (95% CI: 23.0-53.3%). The median PFS and TTF were 5.2 months (95% CI 3.9-6.6) and 5.2 months (95% CI 3.9-6.6), respectively. The protocol was discontinued for 27 patients (87.1%) for disease progression, and one patient each (3.2%) for severe adverse events, physician's recommendation, patient refusal, and treatment related death. **Conclusions:** Combination chemotherapy of paclitaxel plus T-mab showed promising activity and was tolerated well by patients naïve to T-mab who were positive for HER2 and treated previously for mGC. Clinical trial information: UMIN000006223.

4097 General Poster Session (Board #23C), Sun, 8:00 AM-11:45 AM

Nimotuzumab plus paclitaxel and cisplatin as first-line treatment for esophageal squamous cell cancer: A single center prospective clinical trial.

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Background: The aim of this present phase II study is to explore the safety and efficacy of paclitaxel (T), cisplatin (C), and nimotuzumab (N), a humanized anti-EGFR monoclonal antibody combination (TCN) as first-line treatment in advanced esophageal squamous cell cancer (ESCC). **Methods:** Patients with histologically confirmed advanced ESCC, measureable tumor, and no prior chemotherapy and radiotherapy except adjuvant treatment were enrolled. Patients were given cisplatin 60mg/m^2, paclitaxel 175mg/m^{2}per 21 days for at least 2 cycles. The nimotuzumab was given 200mg weekly. Radiotherapy was admitted for patients with unresectable local advanced disease after 4 cycle of TCN treatment. The primary endpoints were safety and objective response rate (ORR). The secondary endpoints were progression-free survival (PFS) and over-all survival (OS). The expression of EGFR and ERCC1 were also analyzed by histoimmunochemical staining. **Results:** Between Mar. 2011 and Dec. 2012, 55 patients with advanced ESCC were enrolled and 53 (96.4%) were eligible for evaluation. The ORR was 54.7% (29/53) and the DCR was 94.3% (50/53). The expression of EGFR and ERCC1 were detected in 46 and 31 patients respectively. The ORR had no relation to both the expression of EGFR (55.3% vs 62.5%, p=0.71) and ERCC1 (41.7% vs 58.3%, p=0.47). As a median follow-up of 15months, the median PFS was 10.5 months (95% CI 8.7 to 12.3 months).The TCN combination treatment was well tolerated and the most common adverse events were alopecia (86.8%), leukopenia (84.9%), anorexia (84.9%), vomiting (73.6%), fatigue (73.6%), pain (66.0%), and anaemia (39.6%). And 18 (34%) patients had Grade 3 to 4 leukopenia. The median OS have not yet been reached. **Conclusions:** In this study, the ORR, DCR and PFS are superior to previous published studies. The addition of anti-EGFR treatment of nimotuzumab to standard chemotherapy was well tolerated with no serious AEs. But the expression of EGFR by IHC could not predict the outcome of nimotuzumab treatment. A phase III study of TCN followed by radiotherapy in unresectable local advanced ESCC had been designed to explore the survival benefits. Clinical trial information: NCT01336049.

4098 General Poster Session (Board #23D), Sun, 8:00 AM-11:45 AM

NeoHx study: Perioperative treatment with trastuzumab in combination with capecitabine and oxaliplatin (XELOX-T) in patients with HER2 resectable stomach or esophagogastric junction (EGJ) adenocarcinoma—R0 resection, pCR, and toxicity analysis.

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Background: Perioperative chemotherapy has demonstrated better OS and DFS than surgery alone in resectable stomach or EGJ adenocarcinoma. Trastuzumab has improved OS when added to chemotherapy in pts with HER-2 + metastatic gastric cancer and is interesting to explore its role in the perioperative setting. **Methods:** A Spanish, multicenter, open-label phase II study evaluated the efficacy and toxicity profile of perioperative XELOX-T (capecitabine 1000 mg/m2/12h po days 1-14, oxaliplatin 130 mg/m2 day 1, trastuzumab 8 mg/kg→ mg/kg day 1, q3w ; 3 preoperative cycles and 3 postsurgery cycles followed by 12 cycles of trastuzumab monotherapy) in patients with T1-2N+M0 or T3-4NxM0 resectable stomach or EGJ adenocarcinoma, HER-2+ (IHQ3+ or IHQ2+/FISH+). The primary endpoint was 18 months DFS, secondary endpoint included pCR, R0 resection rate, ORR and toxicity of preoperative treatment (NCI CTC v3.0 criteria). **Results:** From June 2010 to March 2012, 36 pts were included: median age 65 (39-85); ECOG 0/1/2: 16/19/1 pts; localization: stomach 21 pts, EGJ 15 pts; histologic type: intestinal: 23 pts, diffuse: 4 pts, mixed: 1pt, not specified 8 pts; TNM: T 4: 7 pts; N+: 31 pts. Preoperative XELOX-T: Response: PR: 14 pts (39%), SD: 18 pts, PD: 0 pts, NE: 4 pts. G-3-4 toxicity (≥ 5% of pts): diarrhea 22% and asthenia 5%. Surgery was performed in 31 pts: R0: 28 pts (78%, 95% CI: 61-90%), R1: 1 pt, R2: 2 pts (1 had peritoneal carcinomatosis); pCR was observed in 7 pts (19 %; 95% CI: 8-36%) and 22 pts (61%) were pN0. Two pts died due to surgical complications,. We do not have mature data about postoperative XELOX-T yet. Follow-up is still too short for DFS and OS. **Conclusions:** This preliminary analysis suggests that perioperative XELOX+T in HER-2 positive resectable stomach or esophagogastric junction adenocarcinoma is feasible and has interesting activity. Clinical trial information: NCT01130337.

4099 General Poster Session (Board #23E), Sun, 8:00 AM-11:45 AM

Concurrent chemoradiotherapy with cetuximab plus twice-weekly paclitaxel and cisplatin followed by esophagectomy for locally advanced esophageal squamous cell carcinoma.

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Background: We investigated the efficacy and safety of adding cetuximab to twice-weekly paclitaxel/cisplatin-based concurrent chemoradiotherapy (CCRT), followed by surgery, for patients with locally advanced esophageal squamous cell carcinoma (ESCC). **Methods:** Patients with locally advanced ESCC (T3N0-1M0 or T1-3N1M0 or M1a by AJCC 2002) were treated with paclitaxel (35 mg/m^2 1 h D1, 4/wk), cisplatin (15 mg/m^2 1 h D2, 5/wk), cetuximab (400 mg/m^2 2 h D-5, then 250 mg/m^{2}1 h D3/wk) and radiotherapy (2 Gy D1-5/wk). The feasibility of esophagectomy was evaluated for all patients at the accumulated radiation dose of 40 Gy. If esophagectomy was not feasible, CCRT was continued to a radiation dose of 60-66 Gy. **Results:** 66 patients were enrolled between Oct 2008 and Jun 2010, and 61 (94%) of them had T3N1M0 or M1a tumors by endoscopic ultrasonographic staging. All patients received CCRT to 40 Gy. Forty-three patients underwent surgery, and 17 patients continued definitive CCRT to 60-66 Gy. Of the scheduled doses of paclitaxel, cisplatin, and cetuximab, 80%, 79%, and 99% were given, respectively. The most common grade 3/4 toxic effects were leukopenia (51%), neutropenia (15%), esophagitis (19%), and infection (12%). The pathological complete response rate was 24% (intent-to-treat, 16/66) (95% confidence interval: 13-35%) and 37% (who underwent resection, 16/43). At the median follow-up of 34.6 months, the median progression-free (PFS) and overall survivals were 21.6 and 33.9 months, respectively. No KRAS codon 12/13 mutations were identified in 47 tumor samples. The median PFS for patients with two, one, and no adverse tumor biomarkers (Tau+, ERCC1+, pEGFR-) (n = 40) was 12.3 months, 27.6 months, and greater than 33.6 months, respectively (p = .087). **Conclusions:** Adding cetuximab to twice-weekly paclitaxel/cisplatin-based CCRT prior to esophagectomy is an active and tolerable treatment for locally advanced ESCC. Clinical trial information: NCT01034189.

	All Grades	Grade 3	Grade 4
Thrombocytopenia	10 (17%)	2 (3%)	1 (2%)
Neutropenia	33 (56%)	8 (14%)	1 (2%)
Infection	8 (14%)	7 (12%)	0
Stomatitis	33 (56%)	1 (2%)	0
Esophagitis	43 (73%)	11 (19%)	0
Skin rash	57 (97%)	1 (2%)	0
Hypomagnesemia	14 (24%)	0	3 (5%)

4100 General Poster Session (Board #23F), Sun, 8:00 AM-11:45 AM

A comparison of immunohistochemistry (IHC) and dual-color silver in situ hybridization (SISH) with a novel method combining both gene and protein platforms on a unique slide for testing the HER2 in gastric carcinoma.

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Background: Amplification and/or protein overexpression of HER2 in gastric cancer is a prerequisite to establish an adequate treatment strategy. The European standard defined HER2 positivity by IHC as first evaluation assay followed by ISH in 2+ cases. Gastric tumors are heterogeneous and separate evaluations lead to uncertainties and in localizing distinct clones and are time consuming. The aim of this study was to evaluate the feasibility of gene-protein platform in comparison to single staining methods. **Methods:** IHC plus SISH and gene-protein platform (IHC/SISH, protein/gene) method for HER2 were performed in randomly collected 100 cases of gastric carcinoma. Results of IHC and SISH were compared with IHC/SISH staining. Rüschoff criteria were applied. Tumors were HER2 positive when expression 3+ or 2+ plus gene amplification (EU-Norm) was found. In Second definition (US-Norm), tumors showing HER2 expression 3+ or amplification were considered HER2 positive. **Results:** 96 of 100 samples were eligible. Amplification was observed in 14.6% and 15.6% by SISH and IHC/SISH. 71.9% by IHC vs. 75.0% by IHC/SISH had no expression (0) and 10.4% (IHC vs. IHC/SISH) had weak (1+) HER2 expression. Moderate expression (2+) and overexpression (3+) were observed in IHC 6.3%/11.5% and IHC/SISH 6.3%/8.3%, respectively. There were high concordances in IHC assessment of cases with score 0 (94.8%; κ=0.87) and 3+ (96.9%; κ=0.83) and moderate concordances in 1+/2+ cases (89.6%; κ= 0.44 vs. 93.8%; κ=0.47). Rate of HER2 positivity was similar in standard or novel method. In EU Definition 14.6% vs. 10.4% (p=0.52) were positive, respectively, with very good concordance (95.8%; κ=0.81).Concordance between HER2 positivity in standard or novel method was very good (99.0%; κ=0.96) in US definition with no significant differences (17.7% vs. 16.7%; p=1). **Conclusions:** Gene-protein platform has been tested for first time in gastric carcinoma. Results showed that this novel platform can be a feasible alternative to single methods. Discrepancies in cases with weak or moderate HER2 expression can be a result of observer variability.

4101 General Poster Session (Board #23G), Sun, 8:00 AM-11:45 AM

Preoperative chemotherapy plus bevacizumab with early salvage therapy based on FDG-PET response in locally advanced gastroesophageal junction and gastric adenocarcinoma.

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Background: Response on FDG-PET scan during preoperative chemotherapy has prognostic significance. We performed a phase II trial to examine the effectiveness of FDG-PET directed early switching to salvage chemotherapy measured by 2-year disease free survival (DFS). **Methods:** Pts with PET avid, endoscopic ultrasound and laparoscopically staged T3 or N+ resectable gastric or GEJ adenocarcinoma received induction epirubicin 50mg/m^2, cisplatin 60mg/m^2 Day 1, capecitabine 625mg/m^2 BID Days 1-21 (ECX) and bevacizumab 15mg/kg Day 1. PET scan was repeated at Week 3. PET responders (≥35% decline in SUV) continued with ECX for 2 more cycles. PET non-responders were switched to 2 cycles of salvage therapy: docetaxel 30mg/m^2 and irinotecan 50mg/m^2Days 1 and 8 q21 days and bevacizumab 15mg/kg Day 1. All pts went to surgery 4 weeks after Cycle 3. **Results:** Twenty of planned 60 pts were enrolled before the study closed for poor accrual. Eleven (55%) had a PET response after induction. Ten of 11 underwent R0 resection: 1/10 path complete response, 3/10 path partial response. Nine PET non-responders were switched to the salvage regimen. Seven of 9 non-responders had R0 resection, none achieved a pathological response. The median DFS for PET responders was 27.8 mos (95% CI 10.3-27.8) and DFS in salvage group has not been reached. There was no significant difference in DFS between the two groups (p= 0.4). Follow up for overall survival is ongoing. **Conclusions:** Response on PET scan during induction chemotherapy can identify early treatment failures. The results for therapy cross-over indicate a potentially improved DFS with salvage chemotherapy. Results from this trial are hypothesis generating and merit evaluation in a larger clinical trial. Updated survival data will be presented. Clinical trial information: NCT00737438.

4102 General Poster Session (Board #23H), Sun, 8:00 AM-11:45 AM

Early results of a randomized phase II, compass trial to compare regimen and duration of neoadjuvant chemotherapy for gastric cancer.

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Background: Prognosis for stage III gastric cancer was not satisfactory even by D2 gastrectomy and adjuvant chemotherapy. Neoadjuvant chemotherapy is another promising approach. This study investigated the outcomes of two and four courses of neoadjuvant S-1/cisplatin (SC) and paclitaxel/cisplatin (PC) using a two-by-two factorial design for locally advanced gastric cancer. **Methods:** Patients with stage II schirrhous/junctional tumors, stage III, or resectable stage IV, received S-1 (80 mg/m^2 for 21 days with 1 week rest)/cisplatin (60 mg/m^2 at day 8) or paclitaxel/cisplatin (80 mg/m^2 and 25 mg/m^2, respectively, on days 1, 8, and 15 with 1 week rest). The primary endpoint was 3-year OS. Key secondary endpoints included pathological/clinical response, R0 resection, and adverse events. Sample size was set at 60 to 80 to achieve 10% improvement of 3-year OS by four courses or by PC with approximately 80% probability of the correct selection. **Results:** Between Oct 2009 and July 2011, 83 patients were assigned to arm A (2 courses of SC, n=21), arm B (4 courses of SC, n=20), arm C (2 courses of PC, n=21), and arm D (4 courses of PC, n=21). Clinical response (arm A/B/C/D) was 29%/40%/33%/24%. R0 resection (arm A/B/C/D) was 76%/75%/57%/76%. Pathological response (arm A/B/C/D), defined as tumor regression more than two third in the primary tumor, was 43%/40%/29%/38%. Pathological complete response (arm A/B/C/D) was 0%/10%/0%/10%. Major grade 3/4 toxicities (arm A/B/C/D) were anemia (14%/15%/0%/28.6%), neutropenia (10%/15%/14%/33%), nausea (0%/10%/5%/5%), and appetite loss (5%/10%/0%/5%). Pathological complete response by per-protocol analysis (arm B/D) was 17% and 12%. Treatment discontinuation (number of patients, arm A/B/C/D) was disease progression (1/3/0/1), toxicities (1/4/0/3), and others (0/1/0/0). No surgical mortality was observed. Grade 3 morbidity classified by Clavien-Dindo was leakage in 5% (arm A), pancreatic fistula in 5% (arm C), and postoperative hemorrhage in 5% (arm B). **Conclusions:** Pathological complete response could be induced by four courses of neoadjuvant chemotherapy without a marked increase of toxicities, regardless of a SC or PC regimen. Clinical trial information: UMIN000002595.

4103 General Poster Session (Board #24A), Sun, 8:00 AM-11:45 AM

Effect of the revised AJCC staging (7th edition) on prognostic stratification in patients with surgically resected esophageal squamous cell carcinoma.

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Background: Historically, the AJCC esophageal staging system separated patients into prognostic groups based on tumor, node, and metastasis (TNM) classifications. In 2010, the 7th edition (AJCC 7) significantly modified esophageal squamous cell cancer (ESCC) staging by separating ESCC from adenocarcinoma, incorporating tumor grade and location for node negative cancers, and stratifying by the number of involved regional nodes for node positive cancers. Our study aim was to determine whether AJCC 7 stage groupings provide improved survival prognostication compared to 6th edition (AJCC 6). **Methods:** We abstracted pathology and survival for 150 consecutive ESCC patients who underwent esophagectomy (1994-2012); 44 patients received induction therapy. AJCC 6 and AJCC 7 stages were assigned and overall survival analyzed from esophagectomy to death or most recent alive contact and censored at 60 months. Discriminatory ability and homogeneity within subgroups was assessed with Kaplan-Meier curves and monotonicity comparisons were evaluated with linear trend chi-squared tests. Overall survival was compared using Cox regression and Akaike Information Criterion (AIC) used to assess model fit. **Results:** Compared to AJCC 6, AJCC 7 upstaged 32 patients from IIa to IIb and 1 patient from IIb to IIIa and downstaged 3 patients from stage IIa to Ib. AJCC 7 subclassified 42 AJCC 6 stage III patients (17 IIIa, 10 IIIb and 15 IIIC). Median overall survival was 19 months. Kaplan-Meier log-rank statistic indicated stronger differentiation in AJCC 7 (19.8 vs 29.7). Cox regression likelihood (19.5 vs 26.1), AIC (618.1 vs 611.6), and linear trend chi-squared at 24- (17.5 vs 24.3) and 60-months (13.3 vs 17.3), were all superior for AJCC 7 stage groupings (AJCC 6 vs AJCC 7, respectively). **Conclusions:** AJCC 7 stage groupings demonstrate superior homogeneity, discriminatory ability and monotonicity compared to AJCC 6. Incorporating the extent of nodal disease, tumor location and tumor grade into the revised AJCC 7 stage classification improves prognostic stratification of surgically resected ESCC patients, including patients who received induction therapy.

4104 General Poster Session (Board #24B), Sun, 8:00 AM-11:45 AM

Determination of the optimal cutoff percentage of residual tumors to define the pathologic response rate (pathRR) of gastric cancer (GC) treated with preoperative therapy (JCOG1004-A).

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Background: PathRR is a common endpoint used to assess the efficacy of preoperative therapy for GC. PathRR is estimated based on the percentage of the residual tumor area in the preexisting tumor bed. Various cut-off definitions that have used for past studies (e.g. 10%, 33%, 40%, 50%, 67%) often impair the comparability of pathRRs between studies. **Methods:** Individual patient data from four JCOG trials evaluating preoperative chemotherapy were used (JCOG0001, irinotecan+cisplatin, n=55; JCOG0002, S-1, n=55; JCOG0210, S-1+cisplatin, n=50; JCOG0405, S-1+cisplatin, n=53). Pathological specimens were evaluated from 173 out of 188 patients (92%) who underwent surgery. Residual and preexisting tumor areas were traced on a virtual microscopic slide by one pathologist and another confirmed these areas. The hazard ratio (HR) in overall survival was calculated for each cut-off percentage by stratified Cox regression analysis including the study as a stratification factor, and concordance probability estimates (CPE) were also calculated. **Results:** The numbers of patients with 0-10%/11-33%/34-50%/51-66%/67-100% residual tumors were 43/33/27/23/47, respectively. Overall, HR was the largest in the 10% cut-off and CPE was the largest in 33%. When patients with R1/R2 resections were excluded, both HR and CPE were the largest in the 10% cut-off. In subgroup analyses, almost all cut-offs predicted survival well regardless of the histologic type (intestinal/diffuse), and no cut-off predicted survival for type 4 (linitis plastica type) tumors. **Conclusions:** PathRR is not recommended for clinical trials including type 4 tumors. The 10% cut-off is recommended for non-type 4 tumors, though 33% is also applicable.

	Cut-off percentage	HR	P value	CPE
Overall (n=173)	10% 33%	1.91 1.70	0.010 0.009	0.559 0.565
	50%	1.55	0.027	0.552
	67%	1.71	0.011	0.552
Only R0 resection (n=134)	10% 33%	1.87 1.54	0.036 0.079	0.561 0.553
	50%	1.24	0.397	0.524
	67%	1.38	0.233	0.528
Non-Type 4 (n=105)	10% 33%	2.59 2.40	0.004 0.003	0.591 0.602
	50%	1.91	0.012	0.576
	67%	2.16	0.004	0.592
Type 4 (n=68)	10% 33%	1.25 1.10	0.579 0.762	0.518 0.512
	50%	1.08	0.799	0.510
	67%	1.62	0.165	0.550

4105 General Poster Session (Board #24C), Sun, 8:00 AM-11:45 AM

Result of clinical study on feasibility of laparoscopy-assisted D2 distal gastrectomy to treat advanced gastric cancer (COACT_1001).

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Background: Benefit of quality of life made laparoscopic gastric cancer surgery attractive, but there are still concerns about laparoscopic lymph node dissection. The aim of this study was to evaluate a feasibility of laparoscopy-assisted distal gastrectomy (LADG) with D2 lymph node dissection compared with open distal gastrectomy (ODG) for advanced gastric cancer (AGC). **Methods:** Patients with cT2-T4a and cN0-2 (AJCC 7^{th} staging system) distal gastric cancer were randomly assigned to LADG or ODG. The primary endpoint was the non-compliance rate of the lymph node dissection defined as rate of cases where there was more than one missing lymph node station according to the guidelines of the Japanese Research Society for Gastric Cancer lymph node grouping. Secondary endpoints were perioperative complications, changes of inflammatory and immunological parameters, postoperative hospital stay, and 3 year disease free survival. This trial was registered at ClinicalTrials.gov as NCT01088204. **Results:** Between Jun 2010 and Oct 2011,204 patients were randomly allocated and underwent either LADG (n=105) or ODG (n=99). 8 patients were excluded in the intention to treatment analysis because of protocol violation and patient's withdrawal of permission, and finally 100 patients in LADG and 95 patients in ODG were analyzed. There were no significant differences of overall non-compliance rate of lymph node dissection between LADG and ODG groups; they were respectively 47.0% and 43.2%. (p=0.648). In the subgroup analysis according to the stratified risk groups, non-compliance rate in LADG was significantly higher than ODG (52.0% vs. 25.0%, p=0.043) for clinical stage III but it was not significantly different for stage II (46.2% vs. 48.9%, p=0.788). Intraoperative event rate was not significantly different between groups (LADG;6.0% and ODG;4.2%, p =0.748). Complications rate in early postoperative period up to 1 month was also not different between groups (LADG;17.0 %, ODG;18.8%, p=0.749). **Conclusions:** LADG was feasible in AGC compared with ODG, especially in clinical stage II in terms of non-compliance rate of D2 lymph node dissection and perioperative complications. Clinical trial information: NCT01088204.

4106 General Poster Session (Board #24D), Sun, 8:00 AM-11:45 AM

Comprehensive genetic mutation analysis of human gastric adenocarcinomas.

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Background: Gastric cancer is the one of the major cause of cancer-related death, especially in Asia. Gastric adenocarcinoma, the most common type of gastric cancer, is heterogeneous and its incidence and cause varies widely with geographical regions, gender, ethnicity, and diet. Since unique mutations have been observed in individual human cancer sample, identification and characterization of the molecular alterations underlying individual gastric adenocarcinoma is a critical step for developing more effective, personalized therapies. Until recently, identifying genetic mutations in an individual basis by DNA sequencing remains a daunting task. The recent advance of new next-generation DNA sequencing technologies, such as the semiconductor-based Ion Torrent sequencing platform, makes DNA sequencing cheaper, faster and more reliable. **Methods:** In this study, we aim to identify genetic mutations in the genes, which are targeted by drugs in the clinical use or under development, in individual human adenocarcinoma sample by using Ion Torrent sequencing. We sequenced 739 loci from 46 cancer-related genes in 242 human gastric adenocarcinoma samples using the Ion Torrent Ampliseq Cancer Panel. **Results:** The sequencing analysis revealed frequent mutations in *MLH1* (8.3%), *MET* (11.2%), *KIT* (21.5%), and *PIK3CA* (40.5%) genes in the human gastric adenocarcinomic samples. Many mutations that are not previously reported in gastric adenocarcinomas were also identified. Moreover, distinctive patterns and the combination of mutations in various sets of genes, including *HER2, EGFR, MET, FGFR, PI3K/MTOR*, *MLH1, MET, KIT, PIK3CA,* and *P53,* were also identified in these gastric adenocarcinoma samples. **Conclusions:** Thus, this study indicates the necessity of sequencing individual human adenocarcinoma in order to match the use of personalized single targeted drugs or two or more targeted drugs in combination against individual adenocarcinoma-specific mutations.

4107 General Poster Session (Board #24E), Sun, 8:00 AM-11:45 AM

Evaluation of serum HER2 extracellular domain in in metastatic gastric or gastro-esophageal junction cancer: Correlation with HER2 status by immunohistochemistry and fluorescence in situ hybridization and clinicopathologic parameters.

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Background: To explore the association between serum human epidermal growth factor receptor-2 (HER2) extracellular domain (ECD) and tissue HER2 status, their relationship with clinicopathological parameters and impact on overall survival (OS) in metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma. **Methods:** A total of 219 histologically confirmed inoperable locally advanced, recurrent, or metastatic gastric or GEJ adenocarcinoma were included. Serum HER2 ECD was measured by chemiluminescent assay. Tissue HER2 status was accessed by fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) assay. **Results:** The median serum ECD level was 9.3 ng/ml (range 3.0 to >350). Tissue HER2 status was positive (IHC3+ or 2+ with FISH amplification) in 37 patients (16.9%) and negative in 182 patients (83.1%). Statistically significant associations were found between serum HER2 ECD level and HER2 status assessed by IHC and FISH. The ROC-analysis suggested the cutoff of 16.35 ng/ml (24 of 219 patients had HER2 ECD >16.35 ng/ml) could produce a sensitivity of 51.4% and a specificity of 97.3% to predict tissue HER2 status. If the cutoff value was increaseed to 22 ng/ml, then all 12 patients with serum HER2 ECD >22 ng/ml were HER 2 positive in primary tumor, corresponding to a specificity of 100% and a sensitivity of 32.4%. High serum HER2 ECD levels were strongly associated with liver metastasis ($P < 0.001$), the intestinal histologic type (Lauren's classification) ($P = 0.003$), large number of metastais (>2) ($P = 0.012$) and increased LDH level ($P < 0.001$) . High serum HER2 ECD levels were more common in GEJ adenocarcinoma although the difference had no stastical significance. HER2 ECD levels did not show a significant impact on OS. **Conclusions:** A significant association was observed between serum HER2 ECD levels and tissue HER2 status in metastasis gastric or GEJ adenocarcinoma. The high specificity of serum HER2 ECD assay to predict tissue HER2 status suggests its potential use as a surrogate marker of the HER2 status in gastric cancer.

4108 General Poster Session (Board #24F), Sun, 8:00 AM-11:45 AM

Concordance of HER2 and its related molecules between primary and paired liver metastatic sites in gastric cancer.

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Background: Trastuzumab is the 1st molecular targeting drug in HER2-positive advanced gastric cancer that has been shown to confer overall survival benefit adding to chemotherapy. In breast cancer it has been already used long time, it is known that there are the discordance of its target; HER2 between primary and metastatic site. Although molecular targeting drugs as Trastuzumab are expected to control the metastatic disease, molecular status is usually evaluated in the primary site because metastatic sites are difficult to biopsy. In this study we attempted to compare HER2 and its related molecular status, which have interaction each together, between primary and paired liver metastatic sites in gastric cancer. **Methods:** Total 58 consecutive cases with gastric cancer who underwent surgical resection of primary site and synchronous or metachronous liver metastasis were examined. HER2, EGFR, c-MET and IGF-1R status were evaluated by immunohistochemistry(IHC) in primary and paired liver metastasis. HER2 expression by IHC using HercepTest (DAKO) were assessed according to Gastric Cancer Scoring System. On the other molecular expression by IHC, positive expression was defined as 25% or more staining with intensity 2 or 3+. We analyzed the concordance of their expression in both sites. **Results:** The patient cohort consists predominantly of male (78%), with Lauren's diffuse (37%) and intestinal tumors (62%). Fifty three percent of cases were synchronous liver metastasis. The positive rate of primary and paired liver metastatic sites were 10.3%, 8.6% in HER2, 1.7%, 5.1% in EGFR, 44.8%, 31.0% in c-MET and 31.0%, 29.3% in IGF-1R. The concordance between primary and paired liver metastatic sites were 91.3%, 93.1%, 75.8%, and 70.6%, respectively. **Conclusions:** Our data suggested that in HER2 and EGFR the concordance between primary and metastatic site were high, other hands the concordance of c-MET and IGF-1R were relatively low. It might be necessary to rebiopsy to estimate the expression of c-MET and IGF-1R in gastric cancer.

4109 General Poster Session (Board #24G), Sun, 8:00 AM-11:45 AM

The Chinese subgroup from a randomized phase III study of lapatinib in combination with weekly paclitaxel versus weekly paclitaxel alone as second-line treatment of HER2-amplified advanced gastric cancer (AGC) in Asian countries.

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Background: TyTAN is a randomized phase III study to evaluate lapatinib (L) plus paclitaxel (P) in pretreated HER2 amplified (HER2+) advanced gastric cancer (AGC). The disease characteristics and GC treatment pattern differed in Japan and in China, so a subgroup analysis was done for subjects recruited in mainland China. **Methods:** AGC subjects with prior 5-FU and/or cisplatin and HER2 amplification by fluorescence in situ hybridization (FISH) in tumor tissue were randomized 1:1 to L (1500mg QD) and P (80mg/m^2, Day 1, 8, 15 q4w) or P alone (80mg/m^2, Day 1, 8, 15 q4w). 1st endpoint was overall survival (OS). 2nd endpoints included progression free survival (PFS), overall response rate (ORR) and safety. A total of 95 subjects recruited from mainland China. **Results:** TyTAN was not significant in OS (HR0.84), but 2 months OS improvement was observed in L+P arm. The results from Chinese subgroup are shown in the Table. The most common adverse events in Chinese subjects were similar as in whole population (neutropenia, diarrhea, rash, leukopenia, anemia, fatigue). Compare to the overall results, less Chinese subjects reported nausea and vomiting. **Conclusions:** This analysis showed that there were clear regional differences as observed between subjects in China and Japan. The addition of L to P was associated with a clinically meaningful benefit in subjects recruited from mainland China. These data warrants further prospective evaluations on the impact of regional differences in the outcome of HER+ GC in East Asian patients. Clinical trial information: NCT00486954.

	Overall (n=261)	Mainland Chinese (n=95)
Disease		
Type of gastric cancer Diffuse/intestinal/mixed (%)	34/43/23	51/13/37
PS 0/1 (%)	41/59	21/79
Gastrectomy pylorus removed (%)	49	37
HER2 FISH+ and IHC +++ (%)	53	65
Treatment		
Median treatment duration (weeks)	16.6	18
Post-study chemotherapy (treatment vs control arm; %)	58 vs 64	42 vs 42
Efficacy		
OS (HR; 95%CI); median	0.84 (0.64-1.11) 11.0 vs 8.9 months	0.62 (0.39-0.98) 9.7 vs 7.6 months
PFS (HR; 95%CI); median	0.85(0.63-1.13) 5.4 vs 4.4 months	0.52(0.32-0.86) 7.2 vs 4.7 months
ORR (treatment vs control)	27% vs 9%	42% vs 8%

4110 General Poster Session (Board #24H), Sun, 8:00 AM-11:45 AM

Prognostic outcome of gastric cancer patients with cancer stem cell SNPs in Asian versus western countries.

Melissa Janae Labonte, Takeru Wakatsuki, Wu Zhang, Dongyun Yang, Mizutomo Azuma, Armin Gerger, Michael Stotz, Yan Ning, Nico Benjamin Volz, Sebastian Stintzing, Joseph Ethan Li, Rita Elie El-Khoueiry, Peter M. D. Wilson, Wasaburo Koizumi, Masahiko Watanabe, Martin K. H. Maus, Afsaneh Barzi, Syma Iqbal, Anthony B. El-Khoueiry, Heinz-Josef Lenz; Azusa Pacific University, Azusa, CA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Department of Gastroenterology, Kitasato University East Hospital, Sagamihara, Japan; Division of Oncology, Medical University of Graz, Graz, Austria; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Department of Gastroenterology, Kitasato University Schoool of Medicine, Sagamihara, Japan; Department of Surgery, Kitasato University School of Medicine, Kanagawa, Japan; Department of General, Visceral, and Tumor Surgery, University of Cologne, Cologne, Germany

Background: The clinical significance of cancer stem cells (CSC) has been well established; however, its prognostic role remains controversial. CD44 is recognized as a CSC marker in gastric cancer (GC) and, recently, the clinical impact of CD166 in GC was reported. Our group previously reported SNPs of CD44 and CD166 are associated with outcome in US patients (pts) with adjuvant GC and colorectal cancer, respectively. Since GC has regional differences in epidemiology and clinicopathology, we hypothesized that ethnicity and regional differences in GC could influence the prognostic role of CD44 and CD166. **Methods:** A total of 369 pts with histopathologically-confirmed localized (stage Ib to IV; AJCC-6th) GC were enrolled from Japan (n=169), the US (n=137), and Austria (n=63) between 2002 and 2010. CD44 rs187116 G>A and CD166 rs1157 G>A were analyzed. Genomic DNA was extracted from blood or tissue, and all samples were analyzed by PCR-based direct DNA-sequencing. **Results:** Pts homozygous for A/A CD44rs187116 (n=20) showed a median OS of 2.0 yrs vs not reached for patients harboring at least one-G allele (n=144) (HR: 2.87 [95%CI: 1.61-5.13], $p<0.001$) in Japanese cohort, while pts homozygous A/A (n=30) showed a median OS of 7.3 yrs vs 4.1 yrs for pts harboring at least one-G allele (n=94) (HR: 2.0 [95%CI: 0.90-4.55], $p=0.079$) in the US cohort. There were no significant differences in Austrian cohort alone or in combination with US cohort. In CD166 rs1157, pts harboring at least one-A allele (n=27) showed a median OS of 3.9 yrs vs not reached for pts homozygous G/G (n=142) (HR: 1.81 [95%CI: 1.05-3.12], $p=0.033$) in Japanese cohort., Although there were no significant differences in the US or Austrian cohort when analyzed separately, combining cohorts demonstrated that pts homozygous A/A (n=12) showed a median OS of not reached yrs vs 4.7 yrs for pts harboring at least one-G allele (n=179) (HR: 5.00 [95%CI: 0.70-35.95], $p=0.073$). **Conclusions:** SNP profiles in CSC markers predicted opposite prognostic outcomes in patients with GC among Asian and Western countries. This is the first report suggesting that the prognostic role of CSC markers in GC may differ based on ethnic groups or etiology differences.

4111 General Poster Session (Board #25A), Sun, 8:00 AM-11:45 AM

Association of transcription factor 7-like 2 (TCF7L2) polymorphisms with worse survival in three independent cohorts from the United States, Austria, and Japan in patients with gastric cancer.

Rita Elie El-Khoueiry, Takeru Wakatsuki, Yan Ning, Wu Zhang, Dongyun Yang, Mizutomo Azuma, Armin Gerger, Michael Stotz, Melissa Janae Labonte, Peter M. D. Wilson, Nico Benjamin Volz, Sebastian Stintzing, Martin K. H. Maus, Yu Sunakawa, Wasaburo Koizumi, Masahiko Watanabe, Joseph Ethan Li, Afsaneh Barzi, Anthony B. El-Khoueiry, Heinz-Josef Lenz; University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; Department of Gastroenterology, Kitasato University East Hospital, Sagamihara, Japan; Division of Oncology, Medical University of Graz, Graz, Austria; Azusa Pacific University, Azusa, CA; USC Norris Comprehensive Cancer Center, Los Angeles, CA; Department of General, Visceral, and Tumor Surgery, University of Cologne, Cologne, Germany; Saitama Medical University International Medical Center, Saitama, Japan; Department of Gastroenterology, Kitasato University Schoool of Medicine, Sagamihara, Japan; Department of Surgery, Kitasato University School of Medicine, Kanagawa, Japan

Background: The Wnt/β-catenin signaling pathwaycontrols cell proliferation and differentiation. Disruption of this pathway has been shown in the majority of colorectal (CRC) and gastric cancer (GC). The TCF7L2 complex plays a critical role in this pathway. Interaction of TCF7L2 and β-catenin results in translocation to the nucleus and leads to up-regulation of target genes, including *c-myc* and *cyclin D1*. Previous reports have shown that TCF7L2 polymorphism rs7903146 C/T is associated with CRC risk and outcome; however, the prognostic role of this polymorphism in GC is unknown. Therefore, we tested the hypothesis of whether this polymorphism could predict outcome in GC in three independent cohorts. **Methods:** A total of 369 patients (pts) with histopathologically-confirmed localized GC were enrolled from Japan (n=169), the US (n=137), and Austria (n=63) between 2002 and 2010. **Results:** In the US cohort, pts with at least one-T allele ((T/T or C/T; n=46) showed a median TTR of 1.7 yrs vs. 4.4 yrs compared to pts homozygous C/C (n=76) (HR: 2.09 95%CI: 1.21- 3.59, $p=0.0053$). A similar trend was shown in the Austrian cohort, where pts harboring at least one-T allele (n=25) showed a median DFS of 2.08 yrs vs. 5.42 yrs for pts homozygous C/C (n=38) (HR: 1.79 [95%CI: 0.90-3.55], $p=0.092$). Moreover, in the Japanese cohort, pts homozygous for T/T demonstrated (n=2) a median DFS of 0.15 yrs vs. 4.82 yrs for pts harboring at least one-C allele (n=165) (HR: 10.5 [95%CI: 2.46-45.5], $p=0.001$). These results were confirmed in the OS in the US and Japanese cohorts. Pts at least one-T allele (n=46) showed a median OS of 3.3 yrs vs. 5.5 yrs for pts homozygous C/C (n=76) (HR: 2.41 95%CI: 1.28-4.53, $p=0.0043$) in the US cohort, while pts homozygous T/T showed (n=2) a median OS of 0.22 yrs vs 5.76 yrs for pts harboring at least one-C allele (n=165) (HR: 15.2 [95%CI: 3.50-66.7], $p<0.001$). **Conclusions:** TCF7L2 polymorphism was associated with worse prognosis in recurrence in pts with GC in three independently global cohorts. This polymorphism may be negative prognostic factor in GC regardless of ethnicity and etiology, suggesting the importance role of Wnt/β-Catenin signaling in GC.

4112 General Poster Session (Board #25B), Sun, 8:00 AM-11:45 AM

Efficacy and safety of dose-dense modified TCF regimen (TCF-dd) in metastatic or locally advanced gastroesophageal cancer (GEC).

Laura Toppo, Gianluca Tomasello, Wanda Liguigli, Margherita Ratti, Rossana Poli, Federica Negri, Alessandra Curti, Marco Vismarra, Mariangela Maltese, Roberto Delfrate, Maddalena Donini, Chiara Colombi, Matteo Brighenti, Stefano Panni, Bruno Perrucci, Silvia Lazzarelli, Rodolfo Passalacqua; Istituti Ospitalieri di Cremona, Cremona, Italy; Casa di Cura-Figlie di San Camillo, Cremona, Italy

Background: TCF is a standard first line option for GEC. The Norton-Simon hypothesis suggests that chemotherapy efficacy can be enhanced by decreasing intervals between cycles. We previously reported on the high activity of TCF-dd in GEC (Tomasello 2010). The aim of this study is to investigate the efficacy and safety of this intensified dose-dense regimen in a single-center large cohort of patients (pts). **Methods:** 150 pts with measurable or evaluable GEC, PS 0-2, with adequate organ function, treated in our center from 2004 to 2012 received TCF-dd: Docetaxel (60-85 mg/m2 d 1), Cisplatin (50-75 mg/m2 d 1), l-Folinic Acid (100 mg/m2 d 1-2), 5-FU (400 mg/m2 bolus d 1-2, and 600 mg/m2 as a 22 h continuous infusion d 1-2), plus Pegfilgrastim 6 mg d 3, every 14 days. Pts aged $\geq$ 65 years received the same schedule with a dose reduction by 30%. Analysis was based on the intention to treat population. **Results:** At a median follow-up of 44 months, 128 pts were evaluable for response, all for survival. Median age 65 (range 31-81), M:F 112:38. 17 pts (11%) with locally advanced inoperable GEC, 133 pts (89%) with metastatic GEC. Metastatic sites: liver 40%, peritoneum 31%, bone 14%, lung 12%. A median of 4 cycles (range 1-7) per patient was administered. 33% required a dose reduction. 33% were treated without any delay. 10 CR, 74 PR, 24 SD and 20 PD were observed, for an ORR of 66% (95% CI 57-74). Median OS was 13 months (95% CI 9.7-14.2). Most frequent grade 3/4 toxicities: neutropenia (34%), asthenia (28%), thrombocytopenia (17%), hypokalemia (16%), diarrhea (11%), febrile neutropenia (10%), anemia (9%), and stomatitis (4%). 11 pts (7%) [7 metastatic, 4 locally advanced] became operable after TCF-dd and underwent surgery. We identified 12 metastatic pts (8%) with overall survival $>$ 3 years and 7 (5%) still maintaining a long lasting CR at the time of the current analysis. **Conclusions:** TCF-dd in GEC is very active and may be an option for conversion therapy. Toxicity can be relevant and requires a careful monitoring.

4113 General Poster Session (Board #25C), Sun, 8:00 AM-11:45 AM

Association of YAP1 activation with poor patient prognosis and effect on chemoresistance in gastric cancer.

Sung Sook Lee, Sang Cheul Oh, Woojin Jeong, Sang Ho Lee, Sang-Bae Kim, Yun-Yong Park, Bo Hwa Sohn, Jae-Ho Cheong, Jae Yong Cho, Jae Yun Lim, Eun Sung Park, You-Jin Jang, Young-Jae Mok, WonKyung Jung, Baek-Hui Kim, Keun-Wook Lee, Patrick Tan, Sung Hoon Noh, Jaffer A. Ajani, Ju-Seog Lee; Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; Korea University Guro Hospital, Seoul, South Korea; Department of Life Science, Division of Life and Pharmaceutical Sciences, Center for Cell Signaling and Drug Discovery Research,E-wha Womans University, Seoul, South Korea; Departments of Surgery, Kosin University College of Medicine, Busan, South Korea; Departments of Systems Biology, Houston, TX; Department of Surgery, Yonsei University College of Medicine, Seoul, South Korea; Gangnam Severance Hospital, Seoul, South Korea; Department of Medical Oncology, Gangnam Severance Hospital, Seoul, South Korea; Institute for Medical Convergence, Yonsei University College of Medicine, Seoul, South Korea; Department of Pathology, Korea University Medical Center, Korea University College of Medicine, Seoul, South Korea; Department of Surgery, Korea University Medical Center, Korea University College of Medicine, Seoul, South Korea; Department of Internal Medicine Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea; Duke-National University of Singapore Graduate Medical School, Singapore, Singapore; Department of Surgery, Yonsei University Health System, Seoul, South Korea; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Clinical heterogeneity in gastric cancer is likely due to biological differences among patients. Molecular subtypes and their associated biomarkers need to be established to improve treatment of this disease. We aimed to uncover subgroups of gastric cancer that have distinct biological characteristics associated with clinical outcome and to identify potential best treatments or therapeutic targets for each subgroup. **Methods:** We analyzed gene expression profiling data from gastric cancer cell lines and 267 patients with gastric cancer to uncover tumor subtypes and identify a gene expression signature associated with prognosis and response to adjuvant chemotherapy. The association of the signature with prognosis was validated in an independent cohort of 200 patients, and its association with response to adjuvant therapy was validated by cell culture experiments. **Results:** We identified an expression signature of 88 genes that specifically reflected activation of the oncogene YAP1. Compared with patients without this signature, patients with the YAP1 signature had significantly poorer prognosis. In multivariate analysis, the signature was the strongest indicator of overall survival among all demographic and clinical variables examined together (hazard ratio, 2.1; 95% confidence interval, 1.3-3.3;P = .002). Activation of YAP1 was significantly associated with resistance to adjuvant chemotherapy. We also demonstrated that the Notch pathway is a potential therapeutic target for overcoming chemoresistance mediated by YAP1. **Conclusions:** Activation of the oncogene YAP1 is significantly associated with poorer survival of patients with gastric cancer and induces chemoresistance to this disease. Therefore, YAP1 may be highly attractive therapeutic target for patients with gastric cancer resistant to standard chemotherapy.

4114 General Poster Session (Board #26A), Sun, 8:00 AM-11:45 AM

A phase II study of perioperative S-1 combined with weekly docetaxel in patients with locally advanced gastric cancer: Clinical and pharmacogenetic results.

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Background: We conducted a phase II study to evaluate the efficacy and safety of perioperative S-1 + docetaxel (DS) in locally advanced gastric cancer (LAGC), and to investigate the association between *CYP2A6* genotypes and treatment outcomes. **Methods:** Eligibility criteria included 18-70 yrs, PS 0-1, measurable lesion(s), and LAGC (clinical stage III-IV (M0) by Japanese staging system). Pts were given each 3 cycles of pre- and post-operative chemotherapy (S-1 40 mg/m^2 bid on D1-14, docetaxel 35 mg/m^{2}iv on D1, 8 q 3 wks), and underwent surgery (≥D2). **Results:** From Oct 2006 to June 2008, 44 pts entered into the study, and 43 pts were eligible. Median age=53 yrs (range, 33-69); PS 0/1=2/41; M/F=29/14; and stage IIIA/IIIB/IV (M0)=20/18/5. All 43 eligible pts completed preoperative DS and 40 pts (93%) completed postoperative DS. The most common G3/4 toxicities during pre- and post-operative DS were neutropenia (28% vs. 65%), stomatitis (19% vs. 5%), and abdominal pain (5% vs. 18%). The clinical response rate was 74.4% (95% CI, 61.4-87.4%) with 1 CR (2.3%) and 31 (72.1%) PRs. R0 resection rate was 97.7%, major pathologic response rate was 48.8% with 1 CR, and pathologic stage was 0/1/2/3/4 (%) = 2.3/44.2/20.9/20.9/11.6. With a median follow-up of 66.6 months, 3-yr PFS and 5-yr OS was 62.8% and 69.6%, respectively. Survival differed according to clinical response, clinical downstaging, and *CYP2A6* genotypes (Table). Pts with two *CYP2A6* variant alleles (*V/V*) had higher C_{max} (27.7±4.6 vs. 20.3±1.2; p=0.045) and AUC_{inf} (220.4±43.1 vs. 172.5±12.5; p=0.187) of tegafur, and lower C_{max} (1.4±0.2 vs. 1.8±0.1; p=0.178) and AUC_{inf} (8.4±1.2 vs. 9.7±0.5; p=0.308) of 5-FU than those with no or one variant allele (*W/W* or *W/V*). **Conclusions:** DS is active with a manageable toxicity profile in the perioperative setting in pts with LAGC. *CYP2A6* genotype may be predictive of efficacy (S-1 and docetaxel was provided by JEIL Pharm. Co., Ltd. and sanofi-aventis Korea Co., Ltd., respectively). Clinical trial information: NCT00587145.

	3-yr PFS (%)	P	5-yr OS (%)	P
Clinical response		<0.0001		<0.0001
CR/PR	78.1		81.1	
SD	22.2		44.4	
PD	0		0	
Clinical downstaging		0.01		0.055
Yes	87.5		83.0	
No	48.1		60.0	
***CYP2A6* genotypes**		0.102		0.032
W/W* or *W/V	67.6		75.6	
V/V	33.3		33.3	

4115 General Poster Session (Board #26B), Sun, 8:00 AM-11:45 AM

Vascular endothelial growth factor expression in hepatitis C virus (HCV)-related advanced hepatocellular carcinoma (HCC) compared with hepatitis B virus (HBV)-related advanced HCC.

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Background: HCC with different etiologic factors may result in activation of different signaling pathways. This study aimed to clarify if HBV-related HCC (HBV-HCC) and HCV-related HCC (HCV-HCC) may have difference in the expression of key molecules that are relevant to contemporary molecular targeted therapy. **Methods:** We enrolled patients diagnosed with advanced HCC from 2001 to 2011 who had tumor tissues obtained upon the diagnosis of advanced HCC at our center. Tumor slides were immunohistochemically stained for phosphorylated extracellular signal-regulated kinases (p-ERK), Raf kinase inhibitory protein (RKIP), and vascular endothelial growth factor (VEGF). The expressions of p-ERK and RKIP were evaluated according to percentages of positive-staining cells and graded as: 0: 0; 1+: 1-10%; 2+: 11-50%; 3+: $>$ 50%. Grades 0 and 1 were considered negative, and grades 2 and 3 positive. VEGF staining was evaluated as strong or weak according to staining intensity. The staining results of VEGF were further recorded as H scores, defined as intensity (0, 1, 2, or 3) $\times$ percentages of positive staining. **Results:** In total, 131 patients were enrolled in this study; 94 (72%) patients had HBV-HCC, and 37 (28%) patients had HCV-HCC. HBV-HCC and HCV-HCC had similar expression of p-ERK (positive: 45% vs. 51%, $p = 0.491$) and RKIP (positive: 83% vs. 84%, $p = 0.912$). HCV-HCC was more likely to have strong VEGF staining than HBV-HCC (95% vs. 72%, $p = 0.005$) and higher H scores for VEGF staining (289.5 vs. 248.8, $p < 0.001$). In multivariate analysis adjusting for age, sex, macrovascular invasion, extrahepatic metastasis, and α-fetoprotein level, HCV-HCC remained an independent factor associated with strong VEGF staining. VEGF staining intensity was not associated with age, sex, macrovascular invasion, extrahepatic metastasis, and α-fetoprotein level. **Conclusions:** HCV-HCC has stronger VEGF expression than HBV-HCC. (This study was supported by the grant of NSC101-2314-B-002-141, 100CAP1020-2, and NTUH.101-N1965.)

4116 General Poster Session (Board #26C), Sun, 8:00 AM-11:45 AM

Hepatic arterial infusion for unresectable intrahepatic cholangiocarcinoma: An update on survival from two prospective clinical trials.

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Background: Patients with unresectable intrahepatic cholangiocarcinoma (IHC) experience poor survival. This study summarizes the long-term outcome of two previously reported clinical trials using hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone (Dex) (with or without bevacizumab (Bev)) in advanced IHC. **Methods:** Prospectively collected clinicopathologic and survival data were retrospectively reviewed. Disease response was based on RECIST. All patients underwent pre-treatment dynamic contrast enhanced MRI (DCE-MRI), and tumor perfusion data were correlated with outcome. **Results:** Forty-four patients were analyzed (FUDR=26, FUDR/Bev=18). At a median follow-up of 30 months, 41 patients had died of disease and 3 were alive. Partial response was observed in 48% of patients, and another 50% had stable disease. Three patients underwent resection after HAI and 84% received additional HAI after removal from the study. Median survival was similar in both trials (FUDR=29 months vs. FUDR/Bev=28.5 months p=0.96). Ten patients (23%) survived ≥3 years including 5 (11%) ≥ 5 years. Tumor perfusion, as measured on pre-treatment DCE-MRI (area under the gadolinium concentration curve (AUC180)), was significantly higher in ≥3-year survivors, and was the only factor that distinguished this group from <3-year survivors (mean AUC180 48.9mM.s vs 32.3mM.s, respectively; p=0.003). Time to liver progression was longer in ≥3-year survivors (19.8 months vs 11.2 months, respectively; p=0.02). **Conclusions:** HAI chemotherapy can result in prolonged survival in unresectable IHC. Pre-treatment DCE-MRI may predict response and survival.

Factors	≥3Y survivors (n=10)	<3Y survivors (n=34)	P
Mean age (yr)	55.4±10	60±13.9	0.28
Male gender	20%	32%	0.69
Mean tumor size (cm)	9.2±2.9	9.4±3.5	0.67
Single tumor	70%	73%	1
Previous chemotherapy	10%	15%	1
Mean AUC180 (mM.s)	48.9±13.3	32.3±13.7	0.003
Partial response (RECIST)	70%	41%	0.1
Relative dose intensity (6mo)	0.63±0.25	0.56±0.2	0.48
Grade 3/4 toxicity	10%	26%	0.26
Stable liver disease (mo)	19.8±11	11.2±6.6	0.02

4117 General Poster Session (Board #27A), Sun, 8:00 AM-11:45 AM

A multicenter phase II study of sorafenib, capecitabine, and oxaliplatin (SECOX) in patients with advanced hepatocellular carcinoma: Final results of Hong Kong-Singapore Hepatocellular Carcinoma Research Collaborative Group study.

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Background: This is a single arm, multi-center, phase II study to assess the efficacy and tolerability of sorafenib, oxaliplatin and capecitabine combination for the treatment of advanced hepatocellular carcinoma (HCC) patients. **Methods:** Eligible patients received SECOX regime—sorafenib 400 mg bid (Day one-fourteen), oxaliplatin 85 mg/m^2 (Day one) and capecitabine 1700 mg/m^2(Day one-seven) every two weeks. Response assessment was based on RECIST 1.0 criteria. The primary endpoint was time-to-progression (TTP) and the secondary endpoints were tumor response rate (RR), progression-free survival (PFS), overall survival (OS) and tolerability. **Results:** A total of 51 patients were enrolled in the trial.The median age was 58 years (range, 28-81) and 84% of patients were chronic hepatitis B carriers. Ninety percent of recruited patients belonged to BCLC stage C disease and 41 (80%) patients had extra-hepatic metastasis. The best RR was 16% and they were all partial response. Another 62% of patients achieved stable disease for at least eight weeks. The median TTP was 5.29 months (95% CI 3.81-5.88 months), PFS 5.26 months (95% CI 3.75-5.88 months) and OS was 11.73 months (95% CI 8.87- 15.38 months). Diarrhea (75%), Hand-foot-skin reaction (73%) and transient liver function derangement were the most commonly encountered adverse events, with the majority of patients having grade one or two. No treatment-related death was reported. **Conclusions:** The SECOX regime indicates preliminary promising activity and safety in Asian population with advanced HCC. Our data support a randomized trial comparing SECOX versus sorafenib alone for treatment of advanced HCC. Clinical trial information: NCT00752063.

4118 General Poster Session (Board #27B), Sun, 8:00 AM-11:45 AM

Randomized dose comparison phase II study of the oral transforming growth factor-beta (TGF-ß) receptor I kinase inhibitor LY2157299 monohydrate (LY) in patients with advanced hepatocellular carcinoma (HCC).

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Background: TGF-ß signaling is associated with HCC progression in moderate to poorly differentiated tumors overexpressing alpha-fetoprotein (AFP) levels. We report here the safety and antitumor activity of LY in HCC patients with elevated AFP in this ongoing study. **Methods:** Patients with advanced HCC who progressed on sorafenib (SF) or are ineligible to receive SF, advanced Child-Pugh A/B7 HCC, AFP ≥1.5x ULN, ECOG PS ≤1, measurable disease (RECIST 1.1), and ≤1 prior systemic regimen were eligible. LY was administered as intermittent dosing of 14 days on/14 days off (28 days =1 cycle). Patients were randomized to either 160 mg/day (Arm A) or 300 mg/day (Arm B) LY. Primary endpoints were time-to-progression (TTP) and biomarker changes (serum AFP, TGF-ß and E-cadherin) for each dose. Secondary endpoints included toxicity (CTCAE, V 4.0) and pharmacokinetics (PK). **Results:** 106 patients were enrolled (Arm A=37; B=69), including 92% non-Asians. Baseline characteristics were (Arm A/B): median age 61/66 years; PS=0 60/51%; Child-Pugh A 97/86%; etiology: hepatitis C 30/33%, hepatitis B 24/25%, alcohol 22/22%. Overall, 78/83% of patients had received prior SF; 64/58% of patients had AFP ≥400 ng/mL. Median TTP was 12.0 weeks (90% CI: 7.1, 12.6) in the overall population (Arm A, 12.6 weeks; Arm B, 10.9 weeks). In SF-naïve patients, TTP was 18.3 weeks (90% CI: 6.3-non-estimable). TTP was higher in the non-alcohol compared to alcohol-only etiology group (median 12.1 vs. 6.1 weeks). Median baseline serum TGF-ß1 was 3.4 ng/mL (range: 1.4-3.7) and E-cadherin was 6.1 mg/mL (range: 1.9-17.3). AFP decline of >25% occurred in 21/106 patients (20%). Four patients discontinued treatment due to a drug-related AE. Most common grade 3/4 related AEs in patients were: neutropenia (n=3), GI bleeding (n=2), fatigue (n=2), and anemia (n=2). Preliminary PK analysis (51 patients) demonstrated moderate interpatient exposure variability (42%). **Conclusions:** Based on the manageable toxicity profile, the evidence for biomarker/TTP responses, and an analysis of the aggregate PK/PD data, the 300 mg/day dose was chosen for future studies in HCC. Clinical trial information: NCT01246986.

4119 General Poster Session (Board #27C), Sun, 8:00 AM-11:45 AM

Prognostic delineation of papillary cholangiocarcinoma based on the invasive proportion.

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Background: Intraductal papillary neoplasm of the bile duct (IPNB) is a presumed precursor lesion in biliary carcinogenesis, clinicopathologically overlapping with papillary cholangiocarcinoma (PCC); however, as IPNB has no standardized definition, this relationship remains equivocal. Here, we aimed to develop a new PCC prognostic model, focusing on the invasive proportion. **Methods:** Among 605 patients with surgically resected cholangiocarcinoma in Nagoya University Hospital between 2000 and 2011, 173 (29%) had intraductal exophytic papillary lesions. These were divided into four subsets based on the invasive component: non-invasive (PCC-1, n = 13), ≤10% (PCC-2, n = 30), 11-50% (PCC-3, n = 55), and >50% (PCC-4, n = 75). **Results:** Invasion beyond the ductal wall was observed in 83% of PCCs and 99% of non-papillary cholangiocarcinomas (NPCC, n = 432; $P < 0.001$). Regional lymph node metastases were more frequent in NPCC (48%) than PCC (32%; $P < 0.001$). Five-year survival was better for PCC (52%) than NPCC (37%; $P < 0.001$), indicating the papillary component to be a significant independent prognosticator. PCC-4 and NPCC had similar clinicopathological features and overlapping survival curves: 32% and 37% at 5 years ($P = 0.877$), both lower than those of PCC-1, PCC-2, and PCC-3 (respectively, 91%, 71%, and 60% at 5 years; $P < 0.01$ in all combinations). Multivariate analysis in PCC showed >50% invasive component, nodal metastasis, and positive surgical margin as independent predictors. **Conclusions:** The presence of an intraductal papillary component was an important determinant of better survival in cholangiocarcinoma. PCC exhibited a more aggressive histologic character and worse survival with progression of the invasive component. PCC with >50% invasive component was morphologically and prognostically similar to NPCC. Therefore, we propose that IPNB should be nosologically applied only for PCC cases with ≤50% invasive component.

4120 General Poster Session (Board #28A), Sun, 8:00 AM-11:45 AM

Cisplatin and gemcitabine for advanced biliary tract cancer: A meta-analysis of two randomized trials.

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Background: Two recent randomised studies (ABC-02 [UK] and BT22 [Japan]) have demonstrated the superiority of cisplatin and gemcitabine (CisGem) chemotherapy over gemcitabine (Gem) alone for patients with pathologically-proven advanced biliary tract cancer (BTC: cholangiocarcinoma, gallbladder and ampullary cancers). **Methods:** We performed a meta-analysis of individual patient-level data of these studies to establish the effect of CisGem vs. Gem on progression-free survival (PFS), overall survival (OS) and performed exploratory sub-group analyses. **Results:** A total of 493 patients, median age 64 years (range 23-84 years) with approximately equal sex distribution, were randomised (ABC-02 study n=410; BT22 study n=83) to receive either CisGem (n=245) or Gem (n=248). CisGem demonstrates a significant improvement in PFS (hazard ratio (HR)=0.64 (95%-CI: 0.53-0.76), $p<0.001$) and OS (HR=0.65 (95%-CI: 0.54-0.78), $p<0.001$) over Gem. This effect is most marked in patients with good performance status (PS 0-1): HR for PFS is 0.61 (95%-CI: 0.51-0.74), $p<0.001$ and HR for OS is 0.64 (95%-CI: 0.53-0.77), $p<0.001$. CisGem resulted in improved PFS and OS for intra- and extra-hepatic cholangiocarcinomas and gallbladder cancer. The treatment effect between UK and Japanese patients was consistent with respect to OS (HR=0.65, 95%-CI 0.53–0.79 and 0.65, 95%-CI 0.42–1.03, respectively); with similar median survival in the combination arms (median 11.7 and 11.1 months, respectively). Subgroups least likely to benefit included patients with ampullary tumours and poor performance score (PS2). **Conclusions:** CisGem is the standard of care for the first-line treatment of good-PS patients with advanced BTC regardless of ethnicity. Future studies should aim to enhance the effectiveness of this regimen in the first-line setting and establish the role of subsequent (second-line) therapy. Clinical trial information: ABC-02: NCT00262769, BT22; NCT00380588.

4121 General Poster Session (Board #28B), Sun, 8:00 AM-11:45 AM

Phase I study of PF-03446962 (anti-ALK-1 mAb) in hepatocellular carcinoma (HCC).

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Background: PF-03446962, a fully human IgG2 mAb against ALK-1 (Activin-Receptor Like Kinase-1, a specific TGF-β receptor) with anti-angiogenesis activity, showed a favourable safety profile and early signs of efficacy in a dose escalation study in patients (pts) with solid tumors. While the interplay between ALK-1 and VEGF-A is not fully elucidated, the clinical benefit observed in VEGF-TKI pre-treated pts supports ALK-1 acting as an escape mechanism after failure of VEGF blockade. Herein we report preliminary efficacy, safety and PK results from an expansion cohort in HCC pts who progressed after receiving at minimum sorafenib. **Methods:** Child-Pugh A HCC pts progressed on/intolerant to sorafenib. Tumor specimens (diagnostic and pre-PF-03446962) collected for IHC assessment of CD31, TGF-β, ALK-1 and cMET. Pts treated with 7 mg/kg PF-03446962 on Day 1, 29 and then q2 wks. Efficacy endpoints: Objective Tumor Response (OR) by RECIST, Disease Control Rate (DCR) at 12 wks, and Time To Progression (TTP). Secondary objectives: safety, PK and PD. **Results:** 24 pts with advanced HCC pre-treated at minimum with sorafenib (12/24 with $\geq$ 2 prior therapies) have been enrolled; 19 males and 5 females (median age: 64 y). Pts' characteristics were: ECOG PS = 0 in 10 and = 1 in 14 pts; Child-Pugh = A5 in 16 and = A6 in 8 pts. The PK profiles from the HCC cohort were consistent with those of the dose escalation cohorts. Safety profile was manageable and mainly characterized by Gr 1-2 events. Gr 3-4 events were represented by thrombocytopenia (12.5%) and lipase increase, AST increase and abdominal pain (4.2% each). Telangiectasia, an anti-ALK-1 mediated toxicity, was also observed (8.3%, Gr 1). There were 3 treatment-related serious AEs (one tumor necrosis and two abdominal pain). No CRs or PRs were reported; DCR was 29.2% and mTTP was 3.0 months. In 7 pts, PF-03446962 was associated with stable disease for $\geq$ 12 weeks, suggesting that anti-ALK-1 treatment may be an effective strategy in the post-VEGFi setting. Correlation data of target tumor protein expression with efficacy will be presented at the Conference. **Conclusions:** PF-03446962 is a first in class mAb anti ALK-1. Preliminary clinical activity observed in this HCC expansion cohort warrants further investigations. Clinical trial information: NCT00557856.

4122^ General Poster Session (Board #28C), Sun, 8:00 AM-11:45 AM

Phase II trial of Pexa-Vec (pexastimogene devacirepvec; JX-594), an oncolytic and immunotherapeutic vaccinia virus, followed by sorafenib in patients with advanced hepatocellular carcinoma (HCC).

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Background: Pexa-Vec is a vaccinia virus engineered to express granulocyte-macrophage colony stimulating factor (GM-CSF), thereby stimulating direct oncolysis, tumor vascular disruption and anti-tumor immunity (*Nat Rev Cancer* 2009). Pexa-Vec was shown to replicate in metastatic tumors following intratumoral (IT) or intravenous (IV) administration (*Lancet Oncol* 2008; *Nature* 2011). Preclinical and clinical data suggest that Pexa-Vec-induced acute vascular disruption sensitizes tumors to anti-angiogenic effects of sorafenib (*Mol Ther* 2011). **Methods:** Treatment-refractory HCC patients received Pexa-Vec for 3 weeks (Day 1 IV, Day 8 IT and Day 22 IT) followed by sorafenib at Day 25. The primary objective of the study was to determine the safety of Pexa-Vec followed by sorafenib. Secondary objectives include disease control rate based on mRECIST and Choi (hypodensity) response criteria after Pexa-Vec only (Day 25) and after sorafenib initiation (Week 6 and 12). Optional assessments included response by positron-emission tomography (PET). Data summarized prior to database lock. **Results:** Enrollment is completed: 25 patients of which 20 were refractory to sorafenib. The treatment regimen was well-tolerated. Transient flu-like symptoms, including fever (n=23; 92%), chills (n=19; 76%), headache and nausea (n=10; 40%), abdominal pain and lymphopenia (n=10; 40%) were the most common adverse events following Pexa-Vec. Sorafenib toxicities were consistent with the expected profile. After Pexa-Vec alone the Choi tumor response rate was 47%. Following subsequent sorafenib therapy, 75% had Choi responses, including 81% of sorafenib-failure patients. The mRECIST disease control rate was 62% with Pexa-Vec alone and 59% following initiation of sorafenib. Two of 4 patients evaluable for PET response exhibited decreased PET signal after Pexa-Vec. **Conclusions:** Pexa-Vec was well-tolerated and associated with Choi tumor responses and disease control in patients with advanced HCC. Subsequent sorafenib was well-tolerated and associated with Choi responses. Further trials of Pexa-Vec in HCC patients are warranted. Clinical trial information: NCT01171651.

4123 General Poster Session (Board #29A), Sun, 8:00 AM-11:45 AM

Correlation between VEGF and VEGF-R polymorphisms, toxicity, and clinical outcome in HCC patients receiving sorafenib.

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Background: The introduction of sorafenib for the treatment of advanced HCC radically changed patients' clinical outcome. However response to treatment as well as toxicity are still largely unpredictable in the single patient. We previously reported that VEGF and VEGFR polymorphisms may have a predictive and prognostic role in this setting, but little is known about the possible correlation with toxicity. The aim of our study was to evaluate whether VEGF and VEGFR genotyping was able to correlate with toxicity in HCC patients receiving sorafenib. **Methods:** 73 histological samples of HCC patients receiving sorafenib were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Patients time to progression (TTP), overall survival (OS) and toxicities were analysed. **Results:** VEGF-A rs833061 T>C, rs699947 C>A and rs2010963 C>G polymorphisms were statistically significant associated with any grade global (respectively: $p=0.031$; $p=0.018$; $p=0.003$) and cutaneous toxicities (respectively: $p=0.043$; $p=0.019$; $p=0.025$). Furthermore patients with any grade global and cutaneous toxicities showed a better progression free survival and overall survival (global toxicity PFS: 7.0 vs 5.0 months, $p=0.016$; OS: 26.8 vs 13.0 months, $p=0.023$) (cutaneous toxicity PFS: 7.6 vs 5.1 months, $p=0.033$; OS: 22.7 vs 13.3 months, $p=0.014$) **Conclusions:** In our analysis patients with polymorphism T at rs833061, C at rs699947 and C at rs2010963 showed a higher rate of toxicities and, accordingly to our previous report, this correlates with a better PFS and OS. Analysis of VEGF and its receptor genes polymorphisms represents a clinical tool to identify patients with favourable response to sorafenib presumably related to a more efficient control of tumour growth. The occurrence of toxicity could be an interesting clinical surrogate during sorafenib treatment and may help clinicians in a more cautious and aware management of HCC patients.

4124 General Poster Session (Board #29B), Sun, 8:00 AM-11:45 AM

Prospective phase II trial of sorafenib combined with doxorubicin eluting bead-transarterial chemoembolization for patients with unresectable hepatocellular carcinoma: Efficacy analysis.

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Background: This study reports the final analysis (n=50) of a prospective phase II study evaluating the efficacy of the combination of sorafenib and doxorubicin eluting bead transarterial chemoembolization (DEB-TACE) in patients with unresectable hepatocellular carcinoma (HCC). **Methods:** Protocol consisted of 6-week cycles with sorafenib at 800 mg/day beginning 1 week prior to DEB-TACE; up to 4 DEB-TACE treatments within 6 months. Tumor response was assessed by RECIST and EASL criteria using MRI at baseline and at 1 month follow-up. Time to untreatable progression (TTUP) was defined as the interval from initiation of sorafenib therapy until inability of patient to further receive intra-arterial therapy. Overall survival (OS) and TTUP were calculated with the Kaplan-Meier method; outcomes were stratified by BCLC A/B and C and compared with the log-rank test. **Results:** DEB-TACE + sorafenib successfully performed in 50 patients: mean 62yrs (range, 31-88 yrs), Child-Pugh A/B (92%/8%), BCLC A/B/C (10%/28%/62%), ECOG 0/1 (52%/48%), HCV/HBV (44%/8%), mean tumor burden 20%, mean tumor size 7.2cm (range, 1–17.6), and mean tumor enhancement 78%. Patients were enrolled for a median of 3 (range, 1-22) cycles including a median of 1 (range, 0-6) DEB-TACE procedure. Median dose regimen was 400mgQD and the median dose taken while on study was 318 mg/day (range, 100-800). 1 month follow-up showed a mean tumor enhancement reduction of 48.2% (n=46, p<0.001) and an average reduction in lesion diameter of 8.5%(n=48, p=0.02). The Disease Control Rate was 98% using the EASL amendment and RECIST. Median TTUP was 11.9 mths (95% CI, 1.8-22 mths) with a significant difference between BCLC A/B (median 22.9 mths) and BCLC C (median 6.2mths) patients (log-rank, p=0.01). Median OS was 24.5 mths (95% CI, 14.3-35 mths) with a significant difference between BCLC C (median 17.1 mths) and BCLC A/B (median 33.7 mths) patients (log-rank, p=0.001). **Conclusions:** The results of this phase II study suggest a potential benefit to the combination of sorafenib and DEB-TACE. Single arm and non-randomization are limitations of the study. Clinical trial information: NCT00844883.

4125 General Poster Session (Board #29C), Sun, 8:00 AM-11:45 AM

Circulating oncometabolite 2-hydroxyglutarate (2HG) as a potential surrogate biomarker in patients with *isocitrate dehydrogenase* mutant (*IDH*m) intrahepatic cholangiocarcinoma (ICC).

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Background: Mutations in the genes encoding for IDH1 and IDH2 occur in ~20% of ICC patients (pts), and they lead to the production of the oncometabolite 2HG. We examined whether serum 2HG levels in *IDH*m ICC pts may 1) serve as a surrogate biomarker for *IDH* status, 2) correlate with tumor burden, and 3) correlate with circulating proangiogenic biomarkers. **Methods:** Blood samples from 33 ICC pts [11 *IDH*m, 22 *IDH* wild-type (*IDH*wt)] of different AJCC stages from MGH and 39 surgically resected ICC patients (7 *IDH*m, 32 *IDH*wt) from HKU were analyzed for serum 2HG concentration by reverse-phase liquid chromatography coupled to mass spectrometry. Eight circulating proangiogenic biomarkers were measured in plasma using multiplex ELISA. **Results:** In the MGH cohort, median serum 2HG levels were significantly elevated in *IDH*m (478 ng/ml [interquartile range 174–643]) versus *IDH*wt ICC pts (118ng/ml [68–160])($p<0.001$). Similarly, in the HKU cohort, the pre-resection median serum 2HG levels were significantly elevated in *IDH*m (343ng/ml [192–596]) versus *IDH*wt ICC pts (56ng/ml [42–81]) ($p<0.0001$). The area under ROC curve for prediction of an IDH mutation using 2HG was 93%; with a threshold of 2HG≥170ng/ml, the sensitivity was 83% and specificity was 90%. *IDH2* mutations were more frequent in the HKU cohort (3/7, 43%) compared with the MGH cohort (0/11, 0%) ($p<0.05$), but 2HG levels did not differ among the specific *IDH1* or *IDH2* allelic variants. 2HG levels correlated directly with tumor burden (Spearman's rho=0.89; $p<0.05$) in the HKU cohort. Median plasma levels of PlGF—a growth factor from the VEGF-family—were higher in *IDH*m (35pg/ml [33–40]) versus *IDH*wt ICC pts (median 26pg/ml [24–34]) from the HKU cohort ($p<0.05$). No other associations were seen between proangiogenic biomarkers and IDH status. **Conclusions:** *IDH*m ICC pts had significantly higher serum 2HG levels compared to *IDH*wt ICC pts. High serum 2HG correlated with increased tumor burden. Pre-resection circulating PlGF levels were higher in *IDH*m ICC versus *IDH*wt pts. These data support further exploration of circulating 2HG as potential surrogate and response biomarker in *IDH*m ICC.

4126 General Poster Session (Board #29D), Sun, 8:00 AM-11:45 AM

Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of Its Treatment with Sorafenib [Sor]) in >3000 Sor-treated patients (pts): Clinical findings in pts with liver dysfunction.

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Background: GIDEON is a prospective, non-interventional study. Completion of GIDEON creates a large, global database of >3000 Sor-treated unresectable HCC (uHCC) pts, allowing for evaluation of a broad pt population, including Child-Pugh (CP) B pts with more advanced liver dysfunction. **Methods:** Baseline characteristics were collected in pts for whom a decision to treat with Sor had been made in clinical practice. Adverse events (AEs), dosing, and outcomes data were collected during follow-up. **Results:** 3,202 pts were evaluable for safety. Overall, the incidence of AEs and drug-related (DR) AEs was similar across CP subgroups, although serious AEs (SAEs) were more common in CP-B than CP-A pts. The rate of DR AEs (event per patient-year) was also comparable between CP-A and CP-B pts. The average daily Sor dose was slightly higher in CP-B than CP-A pts; duration of treatment was longer in CP-A (Table). In the intent-to-treat population (n=3,213), median overall survival (OS) (months [95% CI]) was longer in CP-A (13.6 [12.8-14.7]) than CP-B pts (5.2 [4.6-6.3]); time to progression was similar: CP-A (4.7 [4.3-5.2]); CP-B (4.4 [3.5-5.5]). Median OS was shorter in pts with a higher CP-B score: 7 (6.2 [4.9-8.7]); 8 (4.8 [4.1-6.9]); 9 (3.7 [3.0-5.1]). **Conclusions:** Sor safety and dosing during treatment are generally consistent across pts irrespective of liver function. As anticipated, CP status is a strong prognostic factor for OS in uHCC pts.

	Total N=3202[a] (100)		CP-A n=1968 (61.5)		CP-B n=666 (20.8)	
	All	DR	All	DR	All	DR
AEs, %[b]						
All grades	85.3	66.0	84.0	68.5	88.6	64.4
Grade 3/4	31.7	23.5	32.4	25.6	31.5	21.9
SAEs	43.3	9.3	36.0	8.8	60.4	14.1
AE rate (event per patient-year)[b,c]						
Any AE	1.61	1.24	1.44	1.17	2.14	1.55
Diarrhea	0.58	0.51	0.54	0.48	0.71	0.62
Hand-foot skin reaction	0.51	0.50	0.55	0.54	0.42	0.41
Fatigue	0.45	0.29	0.38	0.27	0.62	0.34
Discontinuation due to AEs, %[b]	31.4		28.9		40.1	
Daily dose, median, mg[d]	688.0		677.0		741.5	
Treatment duration, median, weeks[d]	15.0		17.6		9.9	

[a]Includes CP-C, 74 pts; not evaluable, 493 pts; [b]Treatment-emergent; [c]Calculated based on 365.25 days per year; [d]Pts with dosing data.

4127 General Poster Session (Board #29E), Sun, 8:00 AM-11:45 AM

Gemcitabine and oxaliplatin (GEMOX) alone or with cetuximab in first-line treatment of advanced biliary cancers (ABC): Exploratory analyses according to tumor KRAS/BRAF mutations and EGFR expression in a randomized phase II trial (BINGO).

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Background: Gemcitabine-platinum regimens are the standard of care for ABC. Whether GEMOX-cetuximab may be beneficial in ABC patients (pts) was tested in BINGO, an international, open-label, randomized phase II study (ASCO 2012). With a 4-month progression-free survival (PFS) rate of 63% [CI: 52-74], the primary endpoint was met (target, ≥60%; GEMOX, 54% [43-65]). However, median PFS (6.1 vs. 5.5 months) and overall survival (OS) (11.0 vs. 12.4 months) were similar in both arms. Available data on KRAS/BRAF mutation rates in ABC pts are sparse. **Methods:** Planned exploratory endpoints included tumor KRAS/BRAF mutational status (high-resolution melting and DNA sequencing) and EGFR expression score (immunohistochemistry [IHC]), and their impact on patient outcome according to treatment arm. **Results:** Tumor samples were collected for 91 (61%) consenting pts among the 150 randomized pts, and were suitable for DNA analysis and IHC in 75 (50%) and 77(51%) pts, respectively. Tumor KRAS and BRAF mutations (MT) were found in 14 (19%) and 4 (5%) pts, respectively. High EGFR score (≥ 200) was observed in 18 (23%) pts. 4-month PFS rates did not differ according to tumor KRAS MT (wild-type [WT] vs. MT: 62% vs. 57%, p=0.72), BRAF MT (61% vs. 75%, p=1.00) or EGFR score (≥ vs. <200: 56% vs. 63%, p=0.42) overall, or according to treatment arm (table). PFS and OS (log rank test) also did not significantly differ according to these biomarkers, overall or between treatment arms. **Conclusions:** Tumor KRAS/BRAF mutations and EGFR overexpression were found in 24% and 23% of pts respectively. With the limit of statistical power in these exploratory analyses, they had no statistically significant prognostic or predictive impact. Clinical trial information: 2007-001200-20.

	4-month PFS (%)		Odds ratio [95% confidence interval]
GEMOX	GEMOX + cetuximab		
KRAS WT (n=61)	58	65	1.32 [0.46-3.79]*
KRAS MT (n=14)	50	63	1.67 [0.20-14.27]*
KRAS/BRAF WT (n=57)	59	63	1.17 [0.39-3.49]*
KRAS or BRAF MT (n=18)	50	70	2.33 [0.34-16.18]*
EGFR score < 200 (n=59)	64	68	1.19 [0.39-3.61]*
EGFR score ≥ 200 (n=18)	50	58	1.40 [0.20-10.03]*

* Interaction test, not significant.

4128 General Poster Session (Board #29F), Sun, 8:00 AM-11:45 AM

Impact of gender on survival of patients (pts) with hepatocellular carcinoma (HCC): A SEER analysis.

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Background: The incidence of HCC is significantly higher in males (M) than females (F). Preclinical models suggest a role for estrogen in attenuating progression of HCC by various mechanisms such Il-6 suppression or estrogen receptor α-mediated inhibition of NF-κB activity. We investigated the impact of age and gender on survival in patients with HCC using the SEER data. **Methods:** We identified all patients diagnosed with HCC (ICD-O-3 Site code C22.0 and Histology Code 8170-8175) from 1988 to 2009 from the SEER registry. Pts with information on gender, age, ethnic background, and staging were included in the analysis. Exclusion criteria included fibrolamellar histology, diagnosis at autopsy or by death certificate, and absence of survival data. Hazard ratios (HR) for survival were derived using Cox regression model adjusted for race, year of diagnosis, marital status, treatment, birthplace, differentiation and tumor size. **Results:** A total of 38,250 pts were identified; 76% males; 50% White, 12% African American, 21% Asian, 16% Hispanic, and 1% Native American. 45% had liver limited disease (44%M, 50%F), 37% had macrovascular invasion (37%M, 35%F), 18% had metastatic disease (19%M, 15%F). Treatment information was available for pts diagnosed after 1998 (n=32,938): 11% received liver directed therapy, 11% had surgical resection, and 7% underwent liver transplantation. Median age at diagnosis was 61 years for M versus 68 years for F. HR for OS of F versus M was 0.83 (95%CI:0.78-0.89) for pts $<$ 55 years old. In contrast, the OS HR of F versus M was 0.95 (95%CI:0.92-0.98) for pts $\geq$ 55 years old and 0.98 (95%CI: 0.94-1.01) for pts $\geq$ 65 years old. The F vs. M ($<$55 yrs old) HR for OS by stage of disease was: liver limited disease: HR 0.90, CI: 0.81-1.01; macrovascular invasion: HR 0.81, CI: 0.73-0.89; metastatic disease, HR 0.80, CI: 0.70-0.92. **Conclusions:** Females under the age of 55 appear to have superior survival compared to males with HCC based on a SEER data analysis. This finding is in line with preclinical reports of estrogen attenuation of HCC development and progression.

4129 General Poster Session (Board #29G), Sun, 8:00 AM-11:45 AM

Postoperative nomogram for predicting survival after resection for intrahepatic cholangiocarcinoma.

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Background: Conventional staging systems have limited value for survival estimation in individual patients because of the multiple predictors of outcome. Nomograms may overcome these limitations. Thus we developed and internally validated a postoperative nomogram to predict survival after resection of intrahepatic cholangiocarcinoma (IHC) and compared its predictions to those obtained using the 7th Ed. AJCC/UICC stage groupings. **Methods:** Prospective clinicopathologic data from 574 patients who underwent hepatic resection at 12 tertiary hepatobiliary centres (1995-2011) were used. After inputting missing values with regression imputation, the nomogram was developed from a Cox regression model with overall survival (OS) as the primary end-point. Calibration and internal validation were performed calculating the agreement between observed and predicted outcomes in terms of percentage of predicted errors (PE). Discrimination was quantified with the concordance index (CI). Both CI and PE were then corrected for over-optimism using bootstrapping with 100-fold cross-validation sampling. Credibility intervals around 3- and 5-year predicted survival were estimated from an empirical Bayesian model. **Results:** At last follow-up (median duration 27.6 months) 243 patients had died. Three and five-years OS were 52% and 39%. The predictive accuracy of the nomogram (CI: 66.5), which includes 7 variables (tumour size and number, lymph-node metastases, vascular invasion, perineural invasion, CA19.9 level, and radicality of resection), was good and superior to that of the current AJCC/UICC staging system (CI: 58.4). Percentage of PE for the AJCC/UICC staging system were 24%, while the studied model offered a PE slightly under 20%. Heterogeneity was observed in the distribution of nomogram-predicted survival probabilities within stage groups. **Conclusions:** The nomogram developed in this study overcomes some of the prognostic limitations associated with simple models by including all prognostic variables excluded from the AJCC/UICC staging system and may serve as an instrument for future refinements in determining individual patient prognosis necessary for accurate patients stratification.

4130 General Poster Session (Board #29H), Sun, 8:00 AM-11:45 AM

Neutrophil/lymphocyte ratio (NLR) as a prognostic factor in biliary tract cancer (BTC).

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Background: BTCs include intrahepatic (IHC), hilar, distal bile duct (DBD), and gallbladder carcinoma (GBC). Risk factors include conditions associated with chronic inflammation. NLR, an inflammatory marker, is prognostic in several cancers but has not been reviewed in large BTC series, hilar or GBC. **Methods:** Baseline demographics and NLR at diagnosis were evaluated in 864 patients (pts) with BTC from 01/87 - 12/12 treated at Princess Margaret Cancer Center. Their prognostic significance for overall survival (OS) was determined using a Cox proportional hazards model. **Results:** High NLR ≥3.0 was associated with poor survival using univariable analysis as was stage/site of primary ($P<0.05$), age >65yrs, lymphocytes ≤1.6 ($P<0.01$), neutrophils ≥5.0, platelets ≥280, hemoglobin (Hb) < 110 g/L ($P<0.001$). Median OS in pts with NLR<3.0 was 21.6 mo, 12.0 mo with NLR ≥3.0 ($P<0.001$). NLR retained its significance as a prognostic marker on multivariable analysis (Table), along with GBC ($P<0.05$), age>65yrs, DBD primary ($P<0.01$), stage and Hb <110g/L ($P<0.001$). NLR was prognostic for OS on multivariable analysis for hilar: overall (Table) and advanced grp (n=102) (HR 1.68, 95%CI 1.07-2.64, $P<0.05$) and in advanced DBD (n=102) (HR 1.63, 95%CI 1.03-2.57,$P<0.05$). On subgrp analysis, NLR was prognostic for OS in advanced BTC (ABTC) (n=538) ($P<0.01$) but not in surgical grp. NLR did not predict RECIST response to first line palliative chemotherapy in ABTC. **Conclusions:** Baseline NLR is prognostic in BTC, specifically ABTC and hilar subgrp, suggesting the importance of systemic inflammation influencing outcome in pts with ABTC, thus providing a simple inexpensive prognostic biomarker while also possibly identifying pts that may benefit from antiinflammatory mediation. NLR was not predictive for response in BTC.

Location	N	Variable	OS univariable analysis HR (95% CI, p value)	OS multivariable analysis HR (95% CI, p value)
GBC	304	NLR≥3.0	1.80 (1.39-2.34, <0.001)	0.87 (0.58-1.30, 0.21)
DBD	220	NLR≥3.0	1.21 (0.90-1.62, 0.21)	1.55 (1.12-2.13, 0.18)
Hilar	161	NLR≥3.0	1.53 (1.06-2.20, <0.05)	1.64 (1.12-2.41, <0.05)
IHC	179	NLR≥3.0	2.20 (1.49-3.26, <0.001)	1.38 (0.91-2.08, 0.13)
Overall	864	NLR≥3.0	1.60 (1.37-1.87, <0.001)	1.46 (1.25-1.72, <0.001)

4131 General Poster Session (Board #30A), Sun, 8:00 AM-11:45 AM

Use of the mitotic kinase aurora-A activation to predict outcome for primary duodenal adenocarcinoma.

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Background: We and others had proved that hypoxia-inducible factor-1α (HIF-1α) and transcriptionally upregulated Aurora-A were required for disease progression in several tumors. **Methods:** We addressed the clinicopathologic value of HIF-1α and Aurora-a in primary duodenal adenocarcinoma (PDA). Aurora-a and HIF-1α expression were semi-quantitative evaluated by immunohistochemistry in 140 PDA. Among which, 76 patients from one institute acted as training set, and 64 cases from another two institutes were used as testing set to validate the prognostic effect of Aurora-a and HIF-1α. **Results:** We found that Aurora-a was high or sufficient expressed in tumor zone, whereas low-expressed in the normal adjacent epithelia. Moreover, Aurora-a high expression, classified by training set ROC analysis-generated cutoff score, predicted an inferior overall survival both in testing set and training set. Multivariate Cox regression confirmed that Aurora-a was indeed an independent prognostic factor (Table). Contrary to previous studies, we did not detect any correlation between Aurora-a and HIF-1α in PDA. Additionally, survival analysis showed that HIF-1α level was not correlated with patient outcome ($p = 0.466$). **Conclusions:** Activation of Aurora-A, an independent negative prognostic biomarker, might be used to identify particular patients for more selective therapy.

Variable	Testing set			Training set		
	HR	95% CI	P value	HR	95% CI	P value
Tumor stage (T3+T4 vs. T1+T2)	2.591	0.854-7.856	0.093	2.620	0.882-7.781	0.083
Node stage (N0+N1 vs. N2+N3)	3.062	0.783-11.975	0.108	7.189	1.144-45.163	0.035
TNM stage (III+IV vs. I+II)	2.046	0.999-4.192	0.050	2.146	1.022-4.507	0.044
CEA level (high vs. normal)	2.063	0.962-4.423	0.063	1.221	0.581-2.566	0.599
Bilirubin level (normal vs. high)	1.205	0.555-2.618	0.638	1.741	0.637-4.760	0.280
Tumor size (≤2.5cm vs. >2.5cm)	0.660	0.330-1.321	0.241	.861	0.449-1.653	0.654
Differentiation (moderate +high vs. poor)	0.426	0.199-0.911	0.028	.380	0.174-.830	0.015
Aurora-A level (high vs. low)	2.111	1.041-4.281	0.038	2.861	1.326-6.172	0.007
Hypoxia (vs. normoxia)	1.003	0.510-1.974	0.992	1.325	0.701-2.503	0.387

4132 General Poster Session (Board #30B), Sun, 8:00 AM-11:45 AM

Cost-effectiveness and optimal diagnostic sequence of CT, MRI, and PET-CT in the management of colorectal liver metastases.

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Background: CT, PET-CT and MRI play a role in the decision making process in managing colorectal liver metastases (CRLM). This study aimed to determine the optimal sequence of these investigations in order to reduce the rate of futile laparotomy and improve cost effectiveness of treatment. **Methods:** All patients referred to our specialist multidisciplinary team (sMDT) with CRLM were reviewed to investigate specific reason(s) for not offering potentially curative surgery. Clinical parameters were recorded for analysis. Three hypothetical scenarios were derived for cost-effectiveness analyses: 1) "up-front" with all imaging prior to sMDT, 2) "sequential", with individual imaging following each sMDT, and 3) "hybrid" with PET-CT and MRI after review of the initial CT scan. **Results:** 644 consecutive patients were reviewed. Following assessment of initial CT, 165 patients (26%) were referred for palliative chemotherapy. After further evaluation by PET +/- MRI, 307 patients proceeded for potentially curative resection. Of those excluded from surgery, 48% were following PET-CT. Median overall survival (OS) for the resection and palliative groups were 46 and 14 months respectively ($p<0.001$). Futile laparotomy rate was 5.5%.The optimum strategy of lowest average time to decision, and lowest average cost is the hybrid model. Cost-utility analyses demonstrated a saving of approx. £319 (USD$ 515) per patient compared to the other 2 models. **Conclusions:** Decision making regarding further imaging after initial CT scan for CRLM should be performed at the sMDT to minimise delays and maximise efficiency of resources allocation. Triple assessment with CT, PET and MRI and sMDT decision process may reduce risk of futile laparotomy. A hybrid model using PET and MRI following a sMDT discussion of the initial CT provides the most cost effective algorithm for the management of CRLM.

4133 General Poster Session (Board #30C), Sun, 8:00 AM-11:45 AM

Diagnostic utility and prognostic performance of a 92-gene cancer classifier to molecularly profile periampullary adenocarcinomas (PAA).

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Background: Due to the small anatomic size, multiplicity of epitheliums, and suboptimal diagnostics determining the site of origin of PAA is a challenge. We investigated the ability of a 92-gene RT-PCR assay (CancerTYPE ID) to categorize PAA and to prognostically stratify ampullary adenocarcinomas. **Methods:** 171 PAA patients who underwent pancreaticoduodenectomies were included; samples were histopathologically verified for tumor subtype determination: pancreatic (PAN), extrahepatic biliary (EB), ampullary (AMP), or duodenal (DOUD). Blinded FFPE tumor sections underwent molecular testing. Analytical sets were an initial 45 PAA set evaluating concordance to histopathological tumor types and prognostic performance, and a second set of 126 AMP and DOUD adenocarcinoma for validation of prognostic performance. **Results:** Of the initial 45 patient cohort, molecular classification of 43 (96%) evaluable samples (13 AMP, 10 PAN, 10 EB, 10 DOUD) showed 91% concordance: AMP [5 intestinal (int), 7 pancreaticobiliary (pb)], PAN [10 pb], DOUD [3 int, 7 gastroesophageal (ge)], EB [7 pb]. The 92-gene assay was prognostic with a median OS of 70 m for ge/int cases vs. 32 m for pb cases, P=0.05. Discordant classifications were ge for 1 AMP and 2 EB samples, and ovary for 1 EB case. Previous unsupervised RNA hierarchical clustering (Overman GI ASCO 2011 a161) of all 13 AMP cases had identified two prognostic groups (a good-prognosis int-like and a poor-prognosis pb-like), which were identical to the 92-gene classification for 12 of the 13 cases. **Conclusions:** In the initial cohort of 45 patients, the 92-gene assay demonstrated diagnostic utility for molecular site-of-origin classification of PAA; evaluation of the remaining 126 ampullary and duodenal cases will be presented. Results support exploration of this approach for the management of metastatic PAA (in which pathologic review of a primary resection specimen is not an option). Molecular classification of ampullary adenocarcinomas into intestinal and pancreaticobiliary subgroups is prognostically relevant; these and the gastric-like molecular profile of duodenal adenocarcinomas may have therapeutic implications.

4134 General Poster Session (Board #30D), Sun, 8:00 AM-11:45 AM

Impact of multidisciplinary therapy on high-grade appendiceal adenocarcinoma (AA).

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Background: AA is a rare malignancy ranging from well-differentiated to poorly differentiated carcinoma, including those with signet ring cells. Optimal therapy for low grade peritoneal disease is cytoreductive surgery (CRS) combined with heated intraperitoneal chemotherapy (HIPEC). However, some patients (pts) are suboptimal for CRS/HIPEC, and are considered for systemic chemotherapy (SC) alone, or SC + CRS. In light of our previously reported overall survival (OS) benefits for the role of SC in metastatic AA, here we explore the impact of surgical intervention on OS in these pts. Our aim was to clarify the OS benefit of multidisciplinary therapy (SC + CRS + HIPEC) in those pts with aggressive tumor biology. **Methods:** A retrospective chart review of AA pts registered in our tumor registry between Jan. 2005 to Dec. 2009 was undertaken to identify patients with AA who received SC. Electronic medical records (EMR) were reviewed for CRS, HIPEC, histology, SC, and OS. The K-M method and Log-Rank test were used for statistical analysis. **Results:** Of 143 AA pts, 52 (36%) pts were high grade with 33 (23%) having signet ring cells. After a median follow-up of 35M, high grade tumors were noted to have worse OS overall (24M vs 56M, $p<.001$). When comparing treatment received, and adjusting for tumor biology, those pts with high grade disease again fared worse, and experienced comparatively worse OS. However, those treated with SC + CRS + HIPEC experienced the longest median survival. **Conclusions:** Pts with peritoneal disease from high grade AA who completed SC with CRS + HIPEC experienced prolonged OS compared to those treated by SC +/- CRS. Our data suggest that SC + palliative CRS offers minimal benefit for high grade disease. Selection bias influences these results heavily; as those who do well proceed to complete all components of therapy. A treatment plan that includes SC + CRS + HIPEC can result in durable survival, and is a strategy that warrants further study emphasizing the importance of multidisciplinary management.

Group	N	Therapy	Median OS (95% CI)	P value
High grade	52	SC alone	21M (16.7 – 25.3)	0.025
		SC + CRS	29M (22.8 – 35.2)	
		SC + CRS + HIPEC	46M (33.2 – 58.8)	
Other	91	SC alone	39M (33.2 – 44.8)	
		SC + CRS	56M (45.4 – 66.6)	
		SC + CRS + HIPEC	83M (50.3 – 115.7)	

4135 General Poster Session (Board #30E), Sun, 8:00 AM-11:45 AM

Molecular characterization of nonpancreatic neuroendocrine neoplasms (NENS): First description of mutations in the tumor suppressor gene (TSG) *SMARCB1* in NENS of colorectal origin using next-generation sequencing (NGS).

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Background: The knowledge of molecular aberrations that characterize the different types of NENS is still limited. Recent exome sequencing data has allowed the definition of the genetic basis of pancreatic NENS. We aimed to define the tumor genomic profiling in non-pancreatic NENS using NGS. **Methods:** FFPE samples from NENS of different non-pancreatic origins were analyzed. A single pathologist evaluated them for tumor content (cutoff >30% tumor cells) and lymphocyte infiltration. DNA was obtained and quality assessed by a qPCR-based method. We performed amplicon-seq using 476 primer pairs targeting hotspot mutation loci in oncogenes as well as TSG. An initial amplification step was performed, amplicon sizes ranging 80-120 bp. After that, 100 ng of dsDNA were used for standard indexed TruSeq Genomic sample preparation. Samples were pooled in two groups and sequenced in a MiSeq instrument (Illumina) in a 2X100 run. Reads were aligned (BWA), variants called (GATK) and annotated. Final individual manual check of mutations was performed. NENS types were classified following the 2010 WHO classification. **Results:** We analyzed 38 NENS samples of different origins and grades: 7 G3 colon, 8 G1/2 colon, 8 G1/2 ileum, 8 G1/2 gastric, and 7 G1/2 lung. We identified 24 mutations in several genes and different distribution regarding tumor origin was observed. G3 colon NENS presented mutations in *KRAS* (43%), *APC* (28%), and *VHL* (14%). Ileum NENS showed mutations in *TP53* (50%), *VHL* (37%), *FGFR3* (12%) and *APC* (12%). In G1/2 NENS of colon origin, mutations in *SMARCB1* (37%), *KRAS* (12%) and *NF2* (12%) were identified. Less frequent mutations were present in gastric and lung samples (*KRAS*, *TP53* and *FGFR3* in 12% each). **Conclusions:** A tumor origin specific mutation pattern has been observed for NENS. To our knowledge this is the first time to describe mutations in *SMARCB1* TSG in this setting. Further investigation is warranted to define the role of SMARCB1 in the pathogenesis of NENS.

4136^ General Poster Session (Board #30F), Sun, 8:00 AM-11:45 AM

Everolimus in combination with octreotide LAR as the first-line treatment for advanced neuroendocrine tumors: A phase II trial of the I.T.M.O. (Italian Trials in Medical Oncology) group.

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Background: Everolimus has shown antitumor activity in patients (pts) with advanced pancreatic neuroendocrine tumors (NETs). We aimed to assess efficacy and safety of everolimus in combination with octreotide long-acting repeatable (LAR) in patients with well differentiated NETs of gastroenteropancreatic and of lung origin. **Methods:** We performed a phase II, multicenter trial using a Simon two-stage minmax design. Pts with advanced well differentiated, previously untreated NETs of the gastroenteropancreatic tract and of the lung received octreotide LAR 30 mg every 28 days in conjunction with everolimus 10 mg per day continuously. The primary endpoint was objective response rate (ORR). **Results:** A total of 50 pts (58% males) were enrolled. The median age was 60.5 years (range 25-76). Primary tumor site was pancreas in 14 (28%), unknown in 14 (28%), lung in 11 (22%), ileum in 9 (18%) and jejunum and duodenum in 2 (4%) of pts. 13 (26%) pts had carcinoid syndrome. The ORR, calculated on the ITT population, was 20.0% (95% CI 8.9-31.1): 2 patients (4%) had a complete response (CR), 8 (16%) a partial response (PR). Thirty-six patients (72%) achieved stable disease (SD). All CR and all PR as well as 91.7% of SD had a duration $\geq$ 6 months. Clinical benefit (CR+PR+SD) was 92%. At a median follow-up of 277 days, the median time to progression (TTP) was 16.3 months (95% CI 10.7-20.1). Overall survival could not be assessed. Treatment-related adverse events (AEs) were mostly of grade 1 or 2; the only grade 4 AE was mucositis in 1 patient, while grade 3 AEs included skin rash in 1 case, stomatitis in 4 cases (8%) and diarrhea in 11 cases (22%). **Conclusions:** Everolimus in combination with octreotide LAR has shown to be active and well tolerated in advanced NETs and, in this study, not only in primary pancreatic tumors. Compared to other clinical trials with everolimus in NETs, the observed ORR in this study was higher. Aknowledgements: The Authors thank the Italian Trials in Medical Oncology (I.T.M.O.) group and Novartis Pharma for the support provided. Clinical trial information: 2008-007153-13.

4137 General Poster Session (Board #30G), Sun, 8:00 AM-11:45 AM

A multitranscript blood neuroendocrine tumor molecular signature to identify treatment efficacy and disease progress.

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Background: Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NENs) or NETs (also called "carcinoids") are problematic since they present with advanced disease and have limited treatment options. Imaging has proved to be insensitive in identifying treatment effect. Similarly, the currently used biomarker, a neurosectory peptide, Chromogranin A (CgA) is of limited value as a predictor of treatment efficacy. We have developed a multi-transcript ($n=51$ genes) molecular signature for PCR-based blood analysis which exhibits a high sensitivity (85-98%), specificity (93-97%), positive predictive value (95-96%) and negative predictive value (87-98%) for the identification of GEP-NENs. This test significantly outperforms ($p<0005$) plasma CgA (measured by ELISA). **Methods:** The candidate gene signature was examined by a 2-step PCR method in a training set of 130 blood samples (GEP-NENs: $n=63$, treatment-naïve (n=28)) and validated in an independent set ([$n=182$, GEP-NENs: $n=133$, including complete remission ($n=4$), clinically stable disease ($n=82$) and non-responders/clinically progressive disease ($n=47$). **Results:** The PCR score was significantly elevated ($p<0.0001$) in the treatment-naïve group compared to treated GEP-NENs, while levels were significantly reduced ($p<0.004$) in 11 matched samples (pre- and post-treatment – surgical removal ($n=10$), RFA ($n=1$)). In the independent set, the scores for complete remission were not different to controls (0.5 ± 0.25 vs. 0.4 ± 0.16), while scores for stable disease (0.63 ± 0.12) were significantly lower than for non-responders (5.85 ± 0.34, $p<0.002$). Stable disease could be differentiated from clinically progressive disease since the latter exhibited a high score (85% vs. 10%, $p<0.0001$). The performance metrics for differentiation were: sensitivity (91%), specificity (91%), PPV (86%), NPV (95%). **Conclusions:** This study demonstrated that the multi-transcript molecular signature is both sensitive and specific for the detection of neuroendocrine tumor disease and is capable of differentiating clinically stable from progressive disease. It therefore has potential utility as a measure for monitoring treatment efficacy for GEP-NENs.

4138 General Poster Session (Board #30H), Sun, 8:00 AM-11:45 AM

Open-label, phase IIIb, multicenter, expanded access study of everolimus in patients with advanced neuroendocrine tumors (NET).

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Background: Everolimus (EVE) antitumor efficacy in patients (pts) with advanced NET was demonstrated in 2 double-blind, placebo (P)–controlled, phase III trials (RADIANT-2 and RADIANT-3). Median PFS in pancreatic (pNET) pts was 11.0 months (EVE) vs. 4.6 months (P) (HR 0.35, 95% CI 0.27-0.45, $P < 0.001$) in RADIANT-3. Median EVE exposure in RADIANT-3 was 38 wks. EVE was approved for advanced pNET in the US and Europe in 2011. An expanded access protocol was launched to gather additional safety data and provide access to EVE for pts with advanced NET while awaiting regulatory approval. **Methods:** Pts aged ≥18 years with biopsy-proven NET; WHO performance status 0-2; and adequate bone, hepatic, and renal function were enrolled. Main exclusion criteria were poorly differentiated NET and cytotoxic therapy within 4 wks of enrollment. EVE (10 mg/d) was administered until disease progression, unacceptable toxicity, discontinuation, death, commercial availability of EVE, or until May 30, 2012. Pts were enrolled from April 21, 2011 to April 20, 2012. Primary objective was grade 3/4 and serious adverse events (AEs). Secondary objectives included investigator-assessed best overall response rate and PFS. **Results:** The full analysis set included 246 pts (pNET, n=126; non-pNET, n=120); the safety set included 240 pts (pNET, n=123; non-pNET, n=117). Median age was 61 and 66 years; 54% and 49% were male. Main primary tumor sites in non-pNET pts included small intestine (40%) and lung (22%). Median duration of EVE exposure was 12.1 wks and 24 wks in pNET and non-pNET. At data cutoff, there were 21 and 32 PFS events; 105 and 88 pts were censored. Grade 3/4 AEs were reported in 42.3% and 69.2% of pNET and non-pNET; those reported in ≥10% of pts in pNET and non-pNET included hyperglycemia (12.2% and 5.1%), diarrhea (10.6% and 31.6%), stomatitis (9.8% and 11.1%), nausea (8.1% and 10.3%), and anemia (5.7% and 11.1%). Median investigator-assessed PFS was 7.6 (95% CI 5.52-7.62) months and 10.8 (8.77-Not Estimable) months in pNET and non-pNET. **Conclusions:** EVE was well tolerated in pts with advanced NET. AEs were similar to those previously reported. Protocol-specified early termination of pts limits the interpretation of PFS medians. Clinical trial information: EudraCT Number: 2010-023032-17.

4139 General Poster Session (Board #31A), Sun, 8:00 AM-11:45 AM

Study on activation of the IGF-1R mTOR pathway in neuroendocrine tumours (NETs).

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Background: NETs are a heterogeneous group of rare neoplasms. Preclinical studies have shown that IGFR overestimulation can lead to constitutional activation of mTOR pathway. The main objective of this study is to describe the activation status of IGF1R-mTOR pathway by immunohistochemistry in a series of NETs and to assess the association with IGF1R expression. **Methods:** We studied 69 paraffin tumour blocks: 28 pancreatic NETs (pNETs) (2 gastrinomas, 1 glucagonoma, 4 insulinomas and 21 non-functioning (nf) pNETs), 32 GI NETs (4 stomach, 8 colorectum, 18 ileum and 2 dudodenum) and 9 NETs from other origins (2 anterior mediastinum, 2 ovary, 3 bile duct and 2 kidney). The expression of IGF1R, phosphorylated (p) mTOR and (p)S6 has been determined by immunohistochemistry using anti-IGF1Rβ (sc-713), anti-Phospho-mTOR (S2448) (49F9, Cell Signaling) and anti-Phospho-S6 Ribosomal Protein (S235/336)(91B2, Cell Signaling). **Results:** Expression of IGF1R has been observed in 46 of 69 (66%) samples with the highest expression in 2/4 (50%) insulinomas, 5/21 nf pNETs (23%) and 3/18 ileum (17%). We have observed activation of the mTOR pathway by immunodetection of (p)mTOR in 14 of 69 samples (20%): 2/21 nf pNETs (9.5%), 1/8 colorectum (12.5%), 8/18 ileum (44%), 1/2 anterior mediastinum, 1/2 ovary, 1/3 biliar tract. We haven't detected any (p)S6 activation in these samples. Consistent IGF1R-mTOR pathway activation was detected in 11/14 (78%) samples with mTOR positivity that also showed expression of IGF1R. The most relevant finding is that all of the 8 samples from ileum with activation of mTOR showed some degree of expression of IGF1R. **Conclusions:** 2/3 of NETs show varying levels of expression of IGF1R, but only 16% demonstrate activation of the IGF1R-mTOR pathway. While the positivity of (p)mTOR in pNETs is lower than expected, we have identified a subgroup of ileal NETs with consistent activation of both IGF1R and (p)mTOR which could help stratify patients in clinical trials involving modulation of this pathway. In contrast, none of the 69 samples studied was positive for (p)S6 which suggests this marker is not valid to be used in the clinic. Further validation studies are required to help clinical stratification for therapies against IGF1R mTOR pathways.

4140 General Poster Session (Board #31B), Sun, 8:00 AM-11:45 AM

sVEGFR2 and circulating tumor cells to predict for the efficacy of pazopanib in neuroendocrine tumors (NETs): PAZONET subgroup analysis.

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Background: The PAZONET trial (Grande et al, ESMO 2012) performed by the GETNE group analyzed the efficacy and safety of the use of pazopanib (800 mg/qd) in patients (pts) with progressive metastatic NETs that had been previously treated with other novel targeted agents. Here we report on the relationship between clinical outcome and circulating and tumor-related biomarkers. **Methods:** Kaplan-Meier analysis was used to correlate progression-free survival (PFS) with: blood circulating markers at baseline and after 12 weeks of treatment (VEGF-A and sVEGFR2 circulating plasma, Circulating Tumor Cells (CTC) and Circulating Endothelial Cells (CEC)), tumor functional status, Ki67, concomitant somatostatin analogues (SSA), chromogranin A (CgA) and primary tumor location. **Results:** 44 pts were enrolled, 42 were evaluable for response. sVEGFR2 decreased after 12 weeks of treatment (median decrease 20%, $p<0.0001$) and the duration of treatment with pazopanib was associated with a decrease in sVEGFR2 ($p=0.0046$). Pts with a decrease in sVEGFR2 of $>20\%$ and $<=20\%$ had a median progression-free survival (mPFS) of 12.6 and 9.1 months (mo) respectively ($p=0.067$). Pts with and without CTC at baseline had a mPFS of 5.8 and 9.1 mo respectively ($p=0.12$). VEGFA and CEC were not found to predict PFS. mPFS in the intention to treat population was 10.0 mo (95% CI 4.3-15.6). Significant differences in mPFS were found in concomitant SSA treatment (11.9 mo [10.6-13.2]) vs. pazopanib alone (4.8 mo [3.0-6.6]) ($p=0.007$); decrease of CgA (3.4 mo [0.0-6.8]) vs no decrease (11.2 mo [8.4-14.1]) ($p=0.024$) and pancreatic (12.8 mo [11.0-14.6]) vs gastrointestinal (10.0 mo [4.9-15.1]) vs other primary tumors (3.4 mo [0.0-7.0]). No differences in mPFS were seen in functioning (10.0 mo) and non-functioning tumors (9.3 mo) and Ki67 status ($< 2\%$ 10.0 mo, 3-10% 10.8 mo or $>10\%$ 4.1 mo). **Conclusions:** sVEGFR2 and baseline CTC are promising predictive biomarkers for pazopanib in NETs. The updated results confirm the efficacy of pazopanib as a sequencing treatment of pts with progressive NETs, particularly in those with pancreatic primary tumors. The combination of pazopanib and SSA seems to be synergistic. Clinical trial information: NCT01280201.

4141 General Poster Session (Board #31C), Sun, 8:00 AM-11:45 AM

Gene expression profiling (GEP) to predict the primary site of metastatic neuroendocrine tumors (NETs) presenting with an unknown primary.

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Background: NETs often present as liver metastasis with an unknown primary. Accurate subtyping of NETs has important clinical implications for staging and site-specific targeted therapy. Traditionally, the work-up to identify a primary NET as being lung, pancreatic or gut-based can be challenging and time-consuming. **Methods:** GEP was performed on formalin-fixed, paraffin-embedded tumor samples using a 92-gene RT-PCR assay (CancerTYPE ID, bioTheranostics Inc.) as part of the clinical work-up for patients diagnosed with NETs and unknown primaries. **Results:** Results were categorized by level of agreement (Table). Of the 39 patients tested with the assay, 82% presented with liver metastasis. Assay results from those patients with adequate work-up were concordant with clinical data in 77% (23/30) of cases. Surgery was performed in 12 of these cases and 100% accuracy of the molecular assay was confirmed, resulting in 75% of primary tumors being found in the gut and 25% in the pancreas or duodenum. Assay predictions were clinically plausible but inconsistent in 13% (4/30) of cases and were discordant with histology, IHC, imaging/radiological findings, and clinical impression in 10% of the cases. **Conclusions:** The 92-gene assay accurately predicted tumor subtype in patients presenting with NETs and an unknown primary. These findings have clinical utility for appropriate treatment selection, particularly where targeted therapies are available (everolimus, sunitinib). We believe the 92-gene assay can be useful in clinical management, and that our approach will lead to effective diagnosis and treatment algorithms to streamline extensive pre-operative work-up.

Level of agreement	Criteria	92-gene assay results (N=39)
1	GEP result concordant with surgical results	12
1a	GEP result concordant with histology, IHC, imaging/radiological findings, and clinical impression	11
2	GEP result provided additional information that was inconsistent with histology, IHC, imaging/radiological findings, and clinical impression	4
3	GEP result discordant with histology, IHC, imaging/radiological findings, and clinical impression	3
	Insufficient information on additional work-up	9

4142 General Poster Session (Board #31D), Sun, 8:00 AM-11:45 AM

Dosing patterns for octreotide LAR in neuroendocrine tumor (NET) patients: NCCN NET outcomes database.

Jonathan R. Strosberg, Sarah Bobiak, Carrie C. Zornosa, Michael A. Choti, Emily K. Bergsland, Al Bowen Benson, Mark Bloomston, Matthew Kulke, Manisha H. Shah, James C. Yao; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; National Comprehensive Cancer Network, Fort Washington, PA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; Dana-Farber Cancer Institute, Boston, MA; The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Among patients (pts) with neuroendocrine histology, 10 mg – 30 mg of octreotide-LAR administered intramuscularly every 4 weeks is FDA-approved for the long term treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors and pancreatic VIPomas. In clinical practice, higher doses and/or more frequent administration is often prescribed for pts who experience refractory symptoms (e.g., flushing and/or diarrhea) on the maximal labeled dose. **Methods:** National Comprehensive Cancer Network (NCCN) created a comprehensive longitudinal database to characterize pts treated for NETs. This database was queried to identify pts presenting to 7 NCCN institutions, from 2004 to 2010, with a confirmed carcinoid or pancreatic NET (pNET) diagnosis who received octreotide LAR. The primary aim of this analysis was to describe octreotide LAR dosing patterns when beyond label recommendations, clinical characteristics, reasons for dose increase, and maximal dose. **Results:** Among 1,886 pts in the database, 271 carcinoid and pNET pts received octreotide LAR. 40% of carcinoid pts (n=82) and 23% of pNET pts (n=15) received octreotide LAR above-label dosing, defined by dose and/or frequency greater than 30 mg every 4 weeks. The primary tumor sites among carcinoid pts receiving above label dosing were small bowel (n=40), colorectal (n=4), and unknown (n=34). Reasons for above label dosing among carcinoid pts included uncontrolled symptoms (n=53, 65%), tumor progression (n=21, 25%), high urine 5-HIAA (n=1, 1%) and unknown (n=7, 9%). The most common dose/frequency combinations for carcinoid pts were 40 mg every 4 weeks (32 pts, 39%), 40 mg every 3 weeks (15 pts, 18%), and 30 mg every 2 weeks (14 pts 17%). Among pNET pts, reasons for change included uncontrolled symptoms (n=5, 33%), tumor progression (n=9, 60%), and unknown (n=1, 7%). The most common maximal dose/frequency combinations among pNET pts were 40mg every 4 weeks (n=5, 33%), 30mg every 2 weeks (n=4, 27%), and 60 mg every 4 weeks (n=4, 27). **Conclusions:** Above label dosing of octreotide LAR is common in NCCN institutions. The primary indication is refractory carcinoid syndrome. Prospective studies are planned to validate this strategy.

4143 General Poster Session (Board #31E), Sun, 8:00 AM-11:45 AM

Treatment of liver metastases in patients with neuroendocrine tumors: A National Comprehensive Cancer Network analysis.

Michael A. Choti, Sarah Bobiak, Mark Bloomston, Carrie C. Zornosa, Emily K. Bergsland, Jonathan R. Strosberg, Al Bowen Benson, Matthew Kulke, Manisha H. Shah, Eric K. Nakakura, James C. Yao; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; National Comprehensive Cancer Network, Fort Washington, PA; The Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; University of California, San Francisco Comprehensive Cancer Center, San Francisco, CA; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH; UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The choice of therapy in patients with hepatic metastases from neuroendocrine tumors is controversial. The purpose of this study was to describe the utilization of liver resection and other locoregional therapies in the management of NET hepatic metastases in NCCN centers. **Methods:** The National Comprehensive Cancer Network (NCCN) Neuroendocrine Tumor Database tracks longitudinal care for patients treated at seven specialty cancer centers in the U.S. from 2004 to 2010. Patient and tumor characteristics, as well as the use of liver-directed therapy (LDT) in patients with neuroendocrine liver metastases (NELM) were evaluated. **Results:** Among 907 patients presenting with metastatic disease, 606 patients presenting with newly diagnosed disease or previously diagnosed disease with first distant recurrence of NELM were evaluated. LDT was used during some component of the patient care in only 43% of patients with NELM, the remainder received only systemic or no therapy. LDT varied by extent of disease ($p=0.002$) with a higher proportion of patients with liver-only disease receiving LDT (45%) compared to those with liver and extrahepatic disease (26%). There was a significant difference in LDT by functional tumor status ($X^2=6.84$, $p=0.03$) and primary site of disease ($X^2=14.95$, $p=0.001$) where a higher proportion of patients with hormonally functional tumors received LDT when compared to non-functional tumors (48% vs 42%) as well as those with primary small bowel carcinoid vs pancreatic NET (56% vs 39%). Among those treated with LDT, 39% underwent surgical resection, 57% intra-arterial therapy (IAT), and 4% ablation alone. Major hepatectomy was performed in 21%, multiple resections in 13%, and resection combined with ablation in 24% of patients receiving surgical therapy. Among the 147 patients treated with IAT, 52% received standard chemoembolization, 23% bland embolization, and 18% yttrium-90 therapy. **Conclusions:** Even at specialty centers less than half of patients received LDT, among which one-fifth had a hepatic resection. Future studies on this cohort will measure outcomes based on type of LDT.

TPS4144 **General Poster Session (Board #31F), Sun, 8:00 AM-11:45 AM**

Randomized phase II study of gemcitabine (G), cisplatin (C) with or without veliparib (V) (arms A, B) and a phase II single-arm study of single-agent veliparib (arm C) in patients with *BRCA or PALB2*-mutated pancreas adenocarcinoma (PC).

Eileen Mary O'Reilly, Maeve Aine Lowery, Kenneth H. Yu, Marinela Capanu, Zsofia Kinga Stadler, Andrew S. Epstein, Talia Golan, Amiel Segal, Michal Segal, Erin E. Salo-Mullen, Laura H. Tang, Ellen Hollywood, Mary Ellen Moynahan, Kinh G Do, Malcolm J. Moore, Hedy Lee Kindler, Robert J. Mayer, Alice P. Chen, David Paul Kelsen; Memorial Sloan-Kettering Cancer Center, New York, NY; Sheba Medical Center, Tel HaShomer, Israel; Shaare Zedek Medical Center, Jerusalem, Israel; Clinical Genetics Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; Princess Margaret Cancer Center, University Health Network, Division of Medical Oncology & Hematology, Department of Medicine, University of Toronto, Toronto, ON, Canada; The University of Chicago Medical Center, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; National Cancer Institute, Bethesda, MD

Background: Germline mutations in *BRCA1*, *2* predispose to PC (Lal, G. Cancer Res, 2000). 5-8% PC have *BRCA 1,2* mutations; higher in Ashkenazi Jewish (10-15%). Pre-clinical data demonstrates that platinums and poly-ADP ribose polymerase inhibitors (PARPi) have activity in *BRCA*-mutated PC models. Early clinical data supporting (Lowery, M. Oncol, 2011). We are evaluating the role of platinum agents and PARPi, veliparib (ABT-888), in *BRCA* or *PALB2*-mutated PC. **Methods:** Arm A, B: Includes non-randomized phase to optimize V dose combined with G, C (Arm A). Subsequently randomized phase II study will evaluate G, C +/- V. Primary endpoint: RECIST 1.1 response rate (RR) G, C, V (Arm A) and G, C (Arm B). Secondary endpoints: Progression-free survival, safety, disease-control rate, overall survival and correlatives involving pre, post biopsies to evaluate mechanisms of sensitivity, resistance to platinums, PARPi. Arm C: Evaluates single-agent V in previously-treated PC. Primary and secondary endpoints similar. Eligibility: *BRCA*, *PALB2*-mutated, measurable, stage III/IV PC; Untreated (Arm A, B), $\leq$ 2 lines therapy (Arm C); ECOG 0-1 (Arm A, B), ECOG 0-2 (Arm C). Treatment Plan: Arm A, B: V PO BID d1-12 (Arm A), q 3 weeks, G 600mg/m^2 IV, C 25mg/m^{2}IV, both d3, 10, q 3 weeks (Arm A, B). Arm C: V 400mg PO BID d1-28 q 4 weeks. Biostatistics: Arms A, B: Simon's 2-stage minimax design per arm. Unacceptable RR 10%, promising 30%, type I, II errors 10%. N= 16 stage I, +N= 9 (stage II). If $\geq$ 5/25, then promising. If both arms promising, option to add N= 10, allows distinction between RR 20% and 40%, 83% power. Arm C: Simon's 2-stage, single-arm, uninteresting RR 10%, promising if $\geq$ 28%. N= 15 stage I, +N= 18 (stage II). Promising RR $\geq$ 6/33. Total N 47- 95. Contingency for slow accrual. Progress to Date: Accrual: Arm A (non-randomized): 13 screened, N= 5 enrolled. Arm C: 9 screened, N= 4 enrolled. Israeli, Canadian, other U.S. sites opening 2013. Funding and acknowledgements: National Cancer Institute, Lustgarten Foundation. NCT01585805. Clinical trial information: NCT01585805.

TPS4145 General Poster Session (Board #31G), Sun, 8:00 AM-11:45 AM

SWOG S1115: Randomized phase II clinical trial of selumetinib (AZD6244; ARRY 142886) hydrogen sulfate (NSC-748727) and MK-2206 (NSC-749607) versus mFOLFOX in patients withmetastatic pancreatic cancer after prior chemotherapy.

Vincent M. Chung, Shannon McDonough, Philip Agop Philip, Dana Backlund Cardin, Andrew M. Lowy, Jacqueline K. Benedetti, Charles Davic Blanke; City of Hope, Duarte, CA; SWOG Statistical Center, Seattle, WA; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Vanderbilt-Ingram Cancer Center, Nashville, TN; University of California, San Diego Moores Cancer Center, La Jolla, CA; Southwest Oncology Group Statistical Center, Seattle, WA; Oregon Health & Science University, Portland, OR

Background: Pancreatic cancer remains a deadly disease and despite advances in chemotherapy treatment, survival for most patients is still less than one year. Over 80% of pancreatic cancers are *KRAS* mutant which activates the PI3K/AKT pathway and signals downstream to mTOR leading to cell growth, proliferation and survival. Recent data has shown that blocking both the PI3K/AKT and MEK pathways simultaneously is effective in *KRAS*mutant tumors. Our trial is a novel, molecular targeted treatment approach for patients with metastatic pancreatic cancer that has the potential to establish a new treatment paradigm. **Methods:** S1115 was activated in SWOG in August 2012 and is currently IRB approved at 130 institutions within SWOG and the Clinical Trials Support Unit (CTSU). Patients (performance status 0 or 1) with metastatic pancreatic cancer failing standard gemcitabine chemotherapy are randomized to MK-2206 135 mg orally weekly plus selumetinib 100 mg orally daily or mFOLFOX IV every 2 weeks. Eligibility criteria allow metastatic patients who have progressed within 6 months of receiving adjuvant gemcitabine. Patients receiving prior 5-fluorouracil (excluding radiation-sensitizing doses), capecitabine, oxaliplatin, MEK or PI3K/AKT inhibitors are not eligible. Stratification factors include duration of prior systemic therapy and presence of liver metastases. The primary endpoint of this study is overall survival (OS) in patients treated with the combination of MK-2206 and selumetinib compared with those treated with mFOLFOX. Based on previous studies, median OS in the control group is approximately 6 months. Assuming a one-sided type 1 error of 10%, 80% power, approximately 2 years of accrual and 1.5 years of follow-up, 120 eligible patients will be accrued to detect an improvement in median survival from 6 to 9 months (corresponding to a 1.5 hazard ratio). Prospective tumoral tissue collection will be undertaken. ClinicalTrials.gov Identifier: NCT01658943. Support: NCI grants CA32102 & CA38926 Clinical trial information: NCT01658943.

TPS4146 General Poster Session (Board #31H), Sun, 8:00 AM-11:45 AM

Pilot, proof-of-concept studies for determining the feasibility of the use of FLT-PET in patients with pancreatic adenocarcinoma.

Angela Lamarca, Prakash Manoharan, Marie-Claude Asselin, Ioannis Trigonis, Pamela Hindmarsh, Sarah Wood, Ray McMahon, Madhu Rao, Richard Hubner, Tamal Mahbubunnabi, Derek O'Reilly, Rahul Deshpande, Juan W. Valle, Azeem Saleem; Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; University of Manchester Wolfson Molecular Imaging Centre (WMIC), Manchester, United Kingdom; Wolfson Molecular Imaging Centre, University of Manchester, Manchester, United Kingdom; Central Manchester-Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; Department of Hepatobiliary Surgery, North Manchester General Hospital, Manchester, United Kingdom; Department of Medical Oncology, Christie NHS Foundation Trust, Manchester, United Kingdom; North Manchester General Hospital,The Pennine Acute Hospital NHS Trust, Manchester, United Kingdom; University of Manchester, Manchester Academic Health Science Centre; Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; Imanova Centre for Imaging Sciences, London, United Kingdom

Background: Pancreatic cancer (PC) has one of the lowest 5-year survival rates. Gemcitabine (G)-based chemotherapy is standard-of-care first-line systemic therapy. Fluorine-18 radiolabelled 3-deoxy-3-fluorothymidine (FLT), a thymidine analogue, is a substrate for thymidine kinase 1 (TK1), which is highly expressed in proliferating cells in late G1/S phase. FLT uptake (imaged and quantified by positron emission tomography (PET)) correlates with pathology-based proliferation markers and with decreases with therapy in a number of cancers. G, a nucleoside analogue, decreases proliferation by inhibiting DNA synthesis, primarily acting on S and G1/S phase thus decreasing tumour FLT uptake. Human equilibrative nucleoside transporter (hENT1) transports G and FLT into cells, making hENT1 activity a key determinant of both FLT uptake and G efficacy. **Methods:** Two parallel proof-of-concept studies are designed to explore the feasibility of assessing proliferation, nucleoside transport, magnitude of treatment-related FLT uptake changes and understanding the pathophysiological basis of FLT-PET imaging in patients (pts) with (1) localized or (2) advanced PC. Up to 24 PC pts with ECOG PS 0-2, able to undergo imaging and with at least one potentially evaluable lesion larger than 2cm on CT/MRI are eligible. Pts with localized disease (study 1) will have dynamic FLT-PET pre-operatively preceded by a radiolabelled H_2O PET scan to assess tumour perfusion. These pts will also undergo 2-deoxy-2-fluoro-D-glucose (FDG)-PET and diffusion-weighted MR scans. For pts with metastatic disease (study 2), dynamic FLT-PET will be performed before and after G-based chemotherapy. FLT uptake expressed as a standardized uptake value (SUV), will be determined. Tumour pathological markers from the surgical samples and imaging parameters will be correlated; hENT1 status will be assessed (by immunohistochemistry) after surgery (study 1) and before treatment (study 2). Reproducibility FLT-PET studies will be performed in a cohort of subjects to assess the variability in uptake quantification.

TPS4147 General Poster Session (Board #32A), Sun, 8:00 AM-11:45 AM

Phase II clinical trial of biomarker-directed therapy for localized pancreatic cancer.

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Background: Several candidate biomarkers exist for the common chemotherapeutic agents used to treat pancreatic cancer (PC) (Table). The predictive value of these markers in the treatment of PC has not been established. This is the first prospective clinical trial utilizing biomarker-directed therapy for localized pancreatic cancer. **Methods:** Patients with localized pancreatic cancer undergo endoscopic ultrasound-guided fine needle aspiration (FNA) for confirmation of diagnosis and immunohistochemical profiling . Six biomarkers (STREET profile) were selected based on their relevance to accepted pancreatic chemotherapy regimens (table). The treatment algorithm selected for each individual patient is based on the clinical stage of resectability (resectable/borderline resectable) and the STREET profile results. Neoadjuvant therapy is followed by restaging (CT and serum Ca19-9) and in the absence of disease progression, patients undergo surgery. Post-surgical (adjuvant) therapy is determined by the STREET profile of the resected specimen. The primary endpoint is an increase in the rate of surgical resection 20% compared with historical controls treated with best available neoadjuvant therapy which was not biomarker-directed. Secondary endpoints include assessment of overall and progression-free survival, comparative STREET profiling of pre- and post-treatment specimens, and changes in radiographic response. Eligbility Criteria: Patients with resectable or borderline resectable pancreatic cancer undergo endoscopic ultrasound-guided fine needle aspiration (FNA) for confirmation of diagnosis and immunohistochemical profiling. Enrollment: 26 of planned 100 patients have been enrolled. Clinical trial information: NCT01726582.

STREET panel	Function	Expression	Favored agent
SPARC	Cellular matrix protein	High SPARC	Nab-paclitaxel
TOPO1	DNA relaxation	High TOPO	Irinotecan
RRM1	Nucleotide synthesis	Low RRM1	Gemcitabine
ENT1	Membrane transporter	High ENT1	Gemcitabine
ERCC1	Nucleotide excision repair complex	Low ERCC1	Platinum analog
TYMS	Nucleotide synthesis	Low TYMS	5-FU

TPS4148 General Poster Session (Board #32B), Sun, 8:00 AM-11:45 AM

Efficacy and safety of gemcitabine in combination with TH-302 compared with gemcitabine in combination with placebo in previously untreated patients with metastatic or locally advanced unresectable pancreatic adenocarcinoma: The MAESTRO trial.

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Background: Tumors often consist of highly hypoxic subregions that are resistant to chemotherapy and radiotherapy. The investigational hypoxia-targeted drug TH-302 is reduced at its nitroimidazole group, and under hypoxic conditions releases the DNA alkylator bromo-isophosphoramide mustard (Br-IPM). A randomized Phase IIb trial of TH-302 in pts with metastatic or locally advanced unresectable pancreatic adenocarcinoma (PDAC) confirmed a significant PFS improvement ($p=0.008$) in pts treated with TH-302 at 340 mg/m^2+ gemcitabine compared with gemcitabine alone (Borad et al, ESMO 2012). Skin and mucosal toxicities, mainly Grade 1/2, and myelosuppression (thrombocytopenia, neutropenia and anemia) were the most common AEs related to TH-302 and did not lead to increases in treatment discontinuation. Grade 3/4 myelosuppression was more frequent in the TH-302 + gemcitabine arm. AEs leading to treatment discontinuation as well as non-hematological serious AEs were balanced across arms. **Methods:** This is a Phase III, randomized, double-blind, placebo-controlled trial (NCT01746979) of gemcitabine + TH-302 compared with gemcitabine + placebo in pts with locally advanced unresectable or metastatic PDAC. The study is designed to detect a 25% risk reduction of death with 90% power and two-sided alpha of 5%. A total of 660 pts are planned to be randomized 1:1. Key eligibility criteria include histologically or cytologically confirmed disease, no prior chemotherapy or systemic therapy (except as specified in the protocol), ECOG performance status 0 – 1, and bilirubin $\leq$ 1.5x upper limit of normal. Randomized pts receive TH-302 + gemcitabine or gemcitabine + placebo in 4-week cycles until progressive disease, intolerable toxicity, or pt withdrawal. The primary objective is to evaluate OS. Secondary objectives include PFS, objective response, and disease control; safety and tolerability; pt-reported QoL and pain; CA 19-9 levels and PK of TH-302; exploratory pharmacogenomic markers and potential predictive biomarkers. Enrollment to the study is ongoing. Clinical trial information: NCT01746979.

TPS4149 **General Poster Session (Board #32C), Sun, 8:00 AM-11:45 AM**

A phase II randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of simtuzumab (GS-6624) combined with gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma.

Al Bowen Benson, Zung Thai, Michael J. Hawkins, Douglas Werner, Hua Dong, Claudia Lee, Johanna C. Bendell; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Gilead Sciences, Inc., Foster City, CA; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN

Background: Lysyl oxidase-like molecule 2 (LOXL2) is an extracellular matrix enzyme that catalyzes the covalent cross-linking of collagen and is widely expressed across desmoplastic tumors. Simtuzumab (GS-6624) is a humanized antibody that specifically inhibits LOXL2 enzymatic activity. Inhibiting LOXL2 is expected to block formation of desmoplasia, which is thought to play an important role in tumor progression and metastasis. **Methods:** The primary objective and of the study is to compare the additive efficacy of simtuzumab vs. placebo in combination with gemcitabine as measured by improvement in progression free survival (PFS). The secondary objective is to compare the additive efficacy of simtuzumab vs. placebo as measured by overall survival (OS) and objective response rate. Study Design: The study is a randomized, double-blind, placebo controlled Phase 2 trial in subjects with metastatic pancreatic adenocarcinoma. A total of 234 subjects will be randomized to 200 mg simtuzumab, 700 mg simtuzumab, or placebo at a 1:1:1 ratio (78 subjects per treatment group) in combination with gemcitabine in cycles of 28 days. In each cycle, subjects will receive IV GS-6624 or placebo infused on Days 1 and 15, and IV gemcitabine (1000 mg/m2) on Days 1, 8, and 15. CT or MRI scans will be performed every 8 weeks to evaluate response to treatment. Subjects will continue courses of treatment every 28 days in the absence of disease progression or unacceptable toxicity. As of January 30, 2013, 162 subjects have been randomized. Clinical trial information: NCT01472198.

TPS4150 General Poster Session (Board #32D), Sun, 8:00 AM-11:45 AM

Pertuzumab (P) with trastuzumab (T) and chemotherapy (CTX) in patients (pts) with HER2-positive metastatic gastric or gastroesophageal junction (GEJ) cancer: An international phase III study (JACOB).

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Background: Human epidermal growth factor receptor 2 (HER2) is overexpressed in ~20% of gastric cancers. Specific targeting of HER2 by T in combination with CTX has demonstrated significantly improved overall survival (OS) vs CTX in pts with advanced gastric or GEJ cancer (Bang Lancet 2010). In HER2-positive 1L metastatic breast cancer the combination of T plus docetaxel with a second HER2-targeted antibody, P, demonstrated significant improvement of progression-free survival (PFS) and OS vs placebo+T+docetaxel (Baselga NEJM 2012; Swain SABCS 2012). Based on these positive findings with HER2-targeted therapies in gastric and breast cancer, JACOB, a double-blind, placebo-controlled, randomized Phase III study, is designed to evaluate efficacy and safety of P+T+CTX in pts with HER2-positive 1L metastatic gastric or GEJ cancer. **Methods:** Pts will be randomized 1:1 to receive P+T+cisplatin+fluoropyrimidine or the same regimen replacing P with placebo, q3w (P: 840 mg; T: 8 mg/kg first dose, then 6 mg/kg; cisplatin: 80 mg/m^2; 5-fluorouracil: 800 mg/m^2/24 h given continuously for 120 h or capecitabine: 1000 mg/m^2 bid for 14 days). P/placebo+T will be given until progressive disease (PD) or unacceptable toxicity. On or before Cycle 6, CTX should only be discontinued for PD or unacceptable toxicity. Continuation of CTX after Cycle 6 is at the discretion of pt and physician. Randomization will be stratified by region (Japan vs North America/Western Europe/Australia vs Asia [excluding Japan] vs South America/Eastern Europe), prior gastrectomy, and HER2-positivity (IHC 3+ vs IHC 2+ and ISH+). Primary endpoint: OS; secondary endpoints include PFS, objective response rate, duration of response, clinical benefit rate, safety, pharmacokinetics of P, and patient-reported outcomes. Tumor and blood samples for biomarker evaluation will be collected. The study is estimated to have 80% power to detect a significant improvement in OS at a two-sided α-level of 5% (HR=0.777), with ~502 deaths required for the primary analysis. Target enrollment is 780 pts from ~200 sites and 35 countries; FPI is planned for April 2013. NCT01774786 Clinical trial information: NCT01774786.

TPS4151 General Poster Session (Board #32E), Sun, 8:00 AM-11:45 AM

Sequential ipilimumab (Ipi) versus best supportive care (BSC) following first-line chemotherapy (Ctx) in patients (pts) with unresectable locally advanced or metastatic gastric or gastro-esophageal junction (GEJ) cancer: A randomized, open-label, two-arm, phase II trial (CA184-162) of immunotherapy as a maintenance concept.

Markus Hermann Moehler, Yeul Hong Kim, Iain B. Tan, Agnes Balogh, Teresa Kong Sanchez, Yung-Jue Bang; Department of Internal Medicine, Johannes Gutenberg Universität Mainz, Mainz, Germany; Division of Oncology and Hematology, Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea; Department of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore; Bristol-Myers Squibb, Braine-l'Alleud, Belgium; Bristol-Myers Squibb, Singapore, Singapore; Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea

Background: First-line systemic CTX is standard-of-care for advanced gastric cancer. However, most pts relapse or have severe adverse events (AEs), creating a need for new therapies with better benefit/risk and toxicity profiles. Endogenous immune activity against tumor cells has been demonstrated in the human gastric cancer tumor microenvironment, supporting a role for immunotherapy. As a new maintenance concept, sequential administration of immunotherapy may prolong clinical benefit of first-line CTX before disease progression (PD). Ipi, a fully human monoclonal antibody which binds CTLA-4, augments the antitumor immune response. Ipi improved overall survival (OS) in patients with advanced melanoma with AEs managed using product-specific treatment guidelines.This global (32 sites among 10 countries), multicenter, randomized, open-label, phase II trial (ClinicalTrials.gov identifier NCT01585987) will compare the efficacy of Ipi and BSC after first-line CTX. **Methods:** Pts with good performance status (0 or 1) and histologically confirmed, unresectable locally advanced or metastatic gastric or GEJ cancer without PD after first-line CTX with a fluoropyrimidine (F) and platinum (P) doublet will be eligible. Pts with radiological evidence of brain metastases, autoimmune/immune-mediated disease, inadequate hematologic, renal, and hepatic function, or are HER2+ will be ineligible. Pts will be randomized to Ipi (4 doses [10 mg/kg, IV Q3W], followed by Q12W) until confirmed immune-related PD or unacceptable toxicity, or to BSC (continuing F used in lead-in CTX or no active systemic therapy). The primary objective is to compare immune-related progression-free survival (PFS): immune-related response criteria were derived from World Health Organization (WHO) criteria to better capture Ipi response patterns. Secondary objectives are to compare PFS per mWHO criteria and OS, and estimate immune-related best overall response rate. The study is planned to randomize 114 pts. Clinical trial information: NCT01585987.

TPS4152 General Poster Session (Board #32F), Sun, 8:00 AM-11:45 AM

Next study (JCOG1109): A three-arm randomized phase III study comparing preoperative CDDP+5-FU(CF) versus docetaxel+CF versus CF-radiation followed by esophagectomy with D2-3 lymphadenectomy for locally advanced esophageal squamous cell cancer.

Ken Kato, Hiroyasu Igaki, Yoshinori Ito, Junki Mizusawa, Yasuhiro Tsubosa, Satoru Nakagawa, Hiroyuki Daiko, Shuichi Hironaka, Harushi Udagawa, Kazuhiko Hayashi, Isao Nozaki, Masahiko Yano, Yusuke Kimura, Hisayuki Matsushita, Tetsuya Abe, Hiroshi Okabe, Kenichi Nakamura, Haruhiko Fukuda, Motohiro Hirao, Yuko Kitagawa; Gastrointestinal Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan; Esophageal Surgery Division, National Cancer Center Hospital, Tokyo, Japan; Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; Japan Clinical Oncology Group Data Center, National Cancer Center, Tokyo, Japan; Department of Esophageal Surgery, Shizuoka Cancer Center, Shizuoka, Japan; Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan; Esophageal Surgery Division, National Cancer Center Hospital East, Kashiwa, Japan; Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan; Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan; Department of Chemotherapy and Palliative Care, Tokyo Women's Medical University, Tokyo, Japan; Department of Surgery, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; Department of Surgery, Iwate Medical University School of Medicine, Morioka, Japan; Department of Surgery, Tochigi Cancer Center, Tochigi, Japan; Department of Gastrointestinal Surgery, Aichi Cancer Center Hospital, Nagoya, Japan; Kyoto University Surgical Oncology Group, Kyoto, Japan; JCOG Data Center, National Cancer Center, Tokyo, Japan; Department of Surgery, National Hospital Organization Osaka National Hospital, Osaka, Japan; Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: Based on the results of JCOG9907, preoperative cisplatin plus 5- fluorouracil (CF) followed by esophagectomy with D2-3 lymphadenectomy has become standard care for advanced esophageal cancer in Japan, while the standard therapy in Western countries is preoperative chemoradiotherapy. A new clinical question has thus arisen of whether CF plus docetaxel (DCF) or CF plus radiotherapy (CF-RT) shows a survival benefit over preoperative CF even with intensive surgery. **Methods:** Eligibility criteria include histologically proven thoracic esophageal squamous cell carcinoma with stage IB/II/III (excluding T4) based on the 7th UICC-TNM, age 20 to 75, and performance status 0 to 1. No prior chemotherapy, radiotherapy, or hormonal therapy is allowed. Adequate organ function and written informed consent are required. Patients are randomized into any of the following three arms by a minimization method balancing the arms in terms of institution and tumor depth (T1–2 versus T3). Patients in arm A (CF) receive two courses of cisplatin at 80 mg/m^2 on day 1 and fluorouracil at 800 mg/m^2 on days 1–5, repeated every three weeks. Patients in arm B (DCF) receive three courses of docetaxel at 70 mg/m^2, cisplatin at 70 mg/m^2 on day 1, and fluorouracil at 750 mg/m^2 on days 1–5, repeated every three weeks. Patients in arm C (CF-RT) receive two courses of cisplatin at 75 mg/m^2 on day 1 and fluorouracil at 1000 mg/m^2 on days 1–4, repeated every four weeks concurrently with radiotherapy at 41.4Gy/23fr. This trial is designed to demonstrate the superiority of preoperative DCF and/or CF-RT over CF in terms of overall survival. We assumed three-year survival with preoperative CF to be 63% and expected a 10% increase in three-year survival for DCF and CF-RT. The sample size was calculated as a total of 501 patients (167 patients per arm) with a study-wise one-sided alpha level of 5%, power of 70% for each pair comparison, an accrual period of 6.25 years, and a follow-up period of three years. This trial was registered as UMIN000009482 and started in December 2012. Clinical trial information: UMIN000009482.

TPS4153 General Poster Session (Board #32G), Sun, 8:00 AM-11:45 AM

RILOMET-1: An international phase III multicenter, randomized, double-blind, placebo-controlled trial of rilotumumab plus epirubicin, cisplatin, and capecitabine (ECX) as first-line therapy in patients with advanced MET-positive gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

David Cunningham, Salah-Eddin Al-Batran, Irina Davidenko, David H. Ilson, André M. Murad, Niall C. Tebbutt, Yizhou Jiang, Elwyn Loh, Sarita Dubey, RILOMET-1 investigators; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Krankenhaus Nordwest, University Cancer Center, Frankfurt, Germany; Clinical Oncology Dispensary, Krasnodar, Russia; Memorial Sloan-Kettering Cancer Center, New York, NY; Hospital das Clínicas da Universidade Federal e Minas Gerais, Horizonte, Brazil; Austin Health and University of Melbourne, Heidelberg, Australia; Amgen, Inc., Thousand Oaks, CA; Amgen, Inc., South San Francisco, CA

Background: Rilotumumab is an investigational, fully human monoclonal antibody to hepatocyte growth factor/scatter factor that inhibits signaling through the MET receptor. In a randomized phase II study in patients with advanced G/GEJ adenocarcinoma, addition of rilotumumab every 3 weeks (Q3W) to ECX showed trends toward improved overall survival (OS) and progression-free survival (PFS) compared with ECX alone. In patients with high tumor MET expression and high rilotumumab exposure, the treatment effect of rilotumumab combined with ECX was significantly enhanced. **Methods:** In this phase III study, patients (planned N=450) are randomized 1:1 to ECX (intravenous [IV] epirubicin 50 mg/m^2 on day 1, IV cisplatin 60 mg/m^2 on day 1, and oral capecitabine 625 mg/m^2 twice daily on days 1−21) plus double-blind rilotumumab 15 mg/kg or placebo IV Q3W. Randomization is stratified by disease extent (locally advanced vs metastatic) and Eastern Cooperative Oncology Group (ECOG) score (0 vs 1). Key eligibility criteria include previously untreated, pathologically confirmed unresectable locally advanced or metastatic G/GEJ adenocarcinoma; ECOG score 0 or 1; ≥18 years old; MET-positive by centralized immunohistochemistry; HER2-negative; adequate organ function; and ≥6 months since neoadjuvant/adjuvant therapy. The primary endpoint is OS. Key secondary endpoints include PFS, 12-month survival rate, objective response, OS in MET expression tertiles, safety, and pharmacokinetics. An exploratory objective is to assess associations between outcomes and tumor and circulating biomarkers. Enrollment began in November 2012, and the trial continues to accrue. An independent data monitoring committee will conduct planned interim reviews for safety and efficacy. Status: recruiting participants. Sponsored by Amgen Inc. Clinical trial information: NCT01697072.

TPS4154 General Poster Session (Board #32H), Sun, 8:00 AM-11:45 AM

A UGT1A1 genotype-directed phase II toxicity and efficacy-finding study of irinotecan combined with S-1 as first-line treatment in advanced gastric cancer.

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Background: The best chemotherapy regimen for advanced gastric cancer (AGC) is uncertain, but promising findings have been reported with Irinotecan (IRI) plus S-1. However, IRI can induce severe neutropenia or diarrhea associated with homozygosity of the UGT1A1*28 or UGT1A1*6 alleles. This trial was designed to compare the toxicity and efficacy on different doses of IRI combined with S-1 according to UGT1A1 genotype as first-line chemotherapy in AGC in Chinese patients. **Methods:** Previously untreated patients with histologically proven gastric or gastroesophageal junction adenocarcinoma, aged between 18 and 75 years with ECOG performance status 0-2 were classified according to UGT1A1 genotype: wild-type (none of *28 or *6 allele); heterozygous (only one of *28 or *6 allele); or homozygous (*28/*28, *6/*6, or double heterozygous for *28 and *6). Patients were randomized (1:1) to receive either low or high dose of IRI given i.v. (90 min) on day 1 in each genotype group. The low and high dose of IRI were 80mg/m^2 and 200 mg/m^2 in the wild-type group, 80 mg/m^2 and 150 mg/m^2 in the heterozygous group, 40 mg/m^2 and 80 mg/m^2 in the homozygous group. S-1 was administered orally at a dose level set on the basis of the body surface area (BSA): 40 (BSA$<$1.25 m^2), 50 (BSA$\geq$1.25 to$<$1.5 m^2) or 60 mg (BSA$\geq$1.5 m^2) twice a day on day1-7. Courses were repeated every 2 weeks, unless disease progression, unacceptable toxicity or patient refusal. The primary endpoint was to explore the safety and efficacy on different doses of IRI combined with S-1 according to UGT1A1 polymorphism. Based on the frequency of UGT1A1*28 and UGT1A1*6 gene polymorphism in Asian gastrointestinal cancer patients, the chi-square test and fisher exact test were used to evaluate the planned sample size which is 100 in total: 40 for the wild-type, 40 for the heterozygous and 20 for the homozygous group. Until now, 8 patients have been enrolled. Clinical trial information: ChiCTR-OCH-12002472.

TPS4155 General Poster Session (Board #33A), Sun, 8:00 AM-11:45 AM

MetGastric: A randomized phase III study of onartuzumab (MetMAb) in combination with mFOLFOX6 in patients with metastatic HER2-negative and MET-positive adenocarcinoma of the stomach or gastroesophageal junction.

David Cunningham, Yung-Jue Bang, Josep Tabernero, Manish A. Shah, Florian Lordick, Stephen Paul Hack; Royal Marsden NHS Foundation Trust, Surrey, United Kingdom; Seoul National University Hospital, Seoul, South Korea; Vall d'Hebron University Hospital, Barcelona, Spain; Weill Cornell Medical College; New York Presbyterian Hospital, New York, NY; University Cancer Center Leipzig, Leipzig, Germany; Genentech, Inc., South San Francisco, CA

Background: Dysregulation of the HGF/MET pathway in patients with gastroesophageal cancer (GEC) is associated with diminished survival and poor prognostic features, such as nodal and organ metastasis, disease stage and tumor invasiveness. Preclinical data suggest that inhibition of the HGF/MET axis may increase the anti-tumor properties of platinum agents by overcoming HGF-mediated resistance mechanisms. Overexpression and inappropriate activation of the MET pathway has been shown to promote peritoneal metastasis in murine models of GEC. Overexpression of HGF or MET has also been linked to metastatic spread to the liver and peritoneum in patients with GEC. Clinical studies suggest that antibody-based inhibitors of the HGF/MET pathway are active in GEC. Onartuzumab, a monovalent monoclonal antibody, specifically binds to the MET receptor preventing HGF binding thereby inhibiting signal transduction. The most commonly reported adverse events associated with onartuzumab are grade 1–3 peripheral edema, hypoalbuminemia and fatigue. **Methods:** MetGastric is a randomized placebo-controlled, international phase III study in patients with previously untreated metastatic GEC. Only patients with tumors classified as both HER2-negative and MET-positive (by IHC) are eligible. Patients will be randomized (1:1) to receive mFOLFOX6 plus onartuzumab or mFOLFOX6 plus placebo. A maximum of 12 cycles of mFOLFOX6 are permitted. Onartuzumab or placebo will be continued until disease progression. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, overall response rate, safety and correlative biomarker studies. Primary and secondary analyses will include all randomized patients, analyzed according to treatment arm assignment and MET IHC score. Safety will be assessed in all patients who receive at least one dose of study treatment. This study is open for accrual. Clinical trial information: NCT01662869.

TPS4156 General Poster Session (Board #33B), Sun, 8:00 AM-11:45 AM

ST03: A randomized trial of perioperative epirubicin, cisplatin plus capecitabine (ECX) with or without bevacizumab (B) in patients (pts) with operable gastric, esophagogastric junction (OGJ), or lower esophageal adenocarcinoma.

Elizabeth Catherine Smyth, Ruth E. Langley, Sally P. Stenning, Laura Stevenson, Claire Robb, William H. Allum, Heike Grabsch, Derek Alderson, Angela M. Riddell, Thomas Crosby, Robert Mason, Michael Griffin, Wasat Mansoor, Fareeda Y. Coxon, Stephen Falk, Debra Furniss, Gary William Middleton, Katherine Anne Sumpter, Jane M. Blazeby, David Cunningham; The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; Medical Research Council Clinical Trials Unit, London, United Kingdom; Leeds Institute of Molecular Medicine, Leeds, United Kingdom; Queen Elizabeth Hospital, Birmingham, United Kingdom; Velindre Hospital, Cardiff, United Kingdom; Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; Royal Victoria Infirmary, Newcastle, United Kingdom; Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; Northern Centre for Cancer Care, Newcastle Upon Tyne, United Kingdom; Bristol Haematology and Oncology Centre, Bristol, United Kingdom; Weston Park Hospital, Sheffield, United Kingdom; St Lukes Cancer Centre, Guildford, United Kingdom; Northern Centre for Cancer Care, Newcastle, United Kingdom; University of Bristol, Bristol, United Kingdom

Background: Perioperative ECX chemotherapy is a standard of care for localised operable gastric/OGJ/ lower oesophageal adenocarcinoma (Cunningham, NEJM 2006). In combination with chemotherapy B, a monoclonal antibody targeting VEGF-A, results in improved response rates (RR) and progression free survival in advanced gastric cancer (Ohtsu, JCO 2011). ST03 aims to assess the safety and feasibility (stage I, 200 pts) and efficacy (stage II) of the addition of B to perioperative ECX chemotherapy. **Methods:** ST03 is a multicentre, open-label, phase II/III randomised trial open at 106 UK centres. Eligibility criteria are histologically proven, untreated, resectable, lower oesophageal, OGJ or gastric adenocarcinoma; age $\geq$18 years; WHO PS 0-1; and adequate cardiac ejection fraction (EF). Exclusion criteria are TIA/CVA or MI $\leq$1 year; uncontrolled hypertension; $\geq$ Grade 2 NYHA heart failure; recent gastrointestinal inflammatory conditions or major surgery/trauma/open biopsy $<$28d of study entry. Pts receive 3 pre- and 3 postoperative ECX (epirubicin 50 mg/m2 iv D1, cisplatin 60 mg/m2 iv D1 and capecitabine 1250mg/m2/D1-21) +/- B 7.5mg/kg D1 q3wk during chemotherapy, then 6 B q3wk (investigational arm). Surgery is pre-specified and laparoscopic procedures allowed only after quality assurance review. All specimens undergo central pathology review; blood and tissue collection for translational studies is ongoing. Stage I Safety results including cardiac EF have been reported (Okines Ann Oncol 2012). The stage II primary outcome measure is overall survival. Secondary outcome measures are RR, resection rate, disease free survival, toxicity, and QoL. MRI and PET substudies are ongoing. 877 of 1,100 pts have been recruited, accrual expected to complete in Q4 2013. A pilot study within ST03 randomising HER2 positive pts to ECX $\pm$ lapatanib (L) opened Q1 2013 and will assess safety, HER2 positivity rate and feasibility in 40 pts randomised between standard ECX and modified ECX+L. Trial sponsored and co-ordinated by the MRC Clinical Trials Unit and funded by Cancer Research UK (CRUK06/025, NCT00450203). Clinical trial information: NCT00450203.

TPS4157 General Poster Session (Board #33C), Sun, 8:00 AM-11:45 AM

INTEGRATE: A randomized phase II double-blind placebo-controlled study of regorafenib in refractory advanced esophagogastric cancer (AOGC)—A study by the Australasian Gastrointestinal Trials Group (AGITG).

Nick Pavlakis, David Goldstein, Katrin Marie Sjoquist, Andrew Martin, Eric Tsobanis, Sonia Yip, Jenny Shannon, Matthew E. Burge, Michelle F. Cronk, Niall C. Tebbutt, Andrew Strickland, Lara Rachel Lipton, Timothy Jay Price, Louise M. Nott, Dean Laurence Harris, Margot J. Burnell, Thierry Alcindor, Yung-Jue Bang, Yoon-Koo Kang, Christopher J. O'Callaghan; Royal North Shore Hospital, Sydney University, Sydney, Australia; Prince of Wales Hospital, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, Camperdown, Australia; NHMRC Clinical Trials Centre, Sydney, Australia; Nepean Cancer Care Centre, Kingswood, Australia; Royal Brisbane and Women's Hospital, Herston, Australia; Nambour General Hospital, Nambour, Australia; Austin Health and University of Melbourne, Heidelberg, Australia; Monash Medical Centre, East Bentleigh, Australia; Western Hospital, Footscray, Australia; The Queen Elizabeth Hospital, Woodville, Australia; Royal Hobart Hospital, Hobart, Australia; Christchurch Hospital, Christchurch, New Zealand; Saint John Regional Hospital, Saint John, NB, Canada; McGill University Health Centre, Montreal, QC, Canada; Seoul National University Hospital, Seoul, South Korea; Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; NCIC Clinical Trials Group, Kingston, ON, Canada

Background: Advanced Oesophago-Gastric Carcinoma (AOGC) has a poor prognosis, and there is no established standard treatment following failure of first or second line chemotherapy (CT). Regorafenib (BAY 73-4506)(REG) is an oral multi-kinase inhibitor which targets kinases involved in angiogenesis (VEGFR1-3, TIE-2), tumor microenvironment (PDGFR-β, FGFR), and oncogenesis (RAF, RET and KIT), and has shown activity in other solid tumours. Following promising results in colon cancer and GIST, this study will determine if regorafenib has sufficient activity and safety to warrant further evaluation in a phase III trial as a second or third line therapy for AOGC. **Methods:** International (Australia & New Zealand (ANZ); Canada (NCIC CTG), Korea) randomised phase II, double-blind, placebo-controlled trial with 2:1 (REG:placebo) randomisation and stratification by: (1) Lines of prior chemotherapy for advanced disease (1 vs. 2). (2) Geographic region. Eligible patients with histological confirmation of OGC, with measurable metastatic or locally advanced disease that is refractory to, or relapsed following, first or second line CT, will receive best supportive care plus 160mg REG or matching placebo orally on days 1-21 of each 28 day treatment cycle until disease progression or prohibitive adverse events. Primary endpoint is progression free survival (PFS). Secondary endpoints: PFS by baseline VEGF, response rate, overall survival, safety, quality of life and exploratory plasma angiogenesis and tissue growth factor biomarkers. 150 patients will be randomized in a 2:1 (REG:PBO) ratio. This will provide 90% power to detect a PFS rate at 2 months in the REG arm $\geq$ 66% versus $<$ 50%. If 16 of 33 (evaluable) REG participants have progressed by 2 months, then the study will be reassessed or stopped. Results: As of January 2013, 19 of 29 planned ANZ sites are open, with 10 patients enrolled. Regulatory approval has been received for 16 sites in Canada and 7 sites in Korea. 4 Korean sites have received ethics approval with recruitment expected to commence in early April 2013. Clinical trial information: ACTRN12612000239864.

TPS4158 General Poster Session (Board #33D), Sun, 8:00 AM-11:45 AM

POWER: An open-label, randomized phase III trial of cisplatin and 5-FU with or without panitumumab (P) for patients (pts) with nonresectable, advanced, or metastatic esophageal squamous cell cancer (ESCC).

Markus Hermann Moehler, Ingo Ringshausen, Ralf Hofheinz, Salah-Eddin Al-Batran, Lothar Mueller, Peter C. Thuss-Patience, Kersten Borchert, Aysun Karatas, Ralph Keller, Anja Klein, Anne Kranich, Baruch Brenner, Sylvie Lorenzen, Manfred P. Lutz, Richard Greil, Josep Tabernero, Eric Van Cutsem, Ullrich Graeven; Johannes Gutenberg University Mainz, Mainz, Germany; Klinikum rechts der Isar, Technical University Munich, Munich, Germany; University Hospital Mannheim, Mannheim, Germany; Krankenhaus Nordwest, Frankfurt, Germany; Oncological Practice, Leer, Germany; Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum, Department of Hematology, Oncology and Tumor Immunology, Palliative Care Unit, Berlin, Germany; University Hospital Rostock, Rostock, Germany; AIO der Deutschen Krebsgesellschaft e.V., Berlin, Germany; GSO mbH, Hamburg, Germany; EORTC, Brussels, Belgium; Universitätsklinikum der PMU, Salzburg, Austria; Vall d'Hebron University Hospital, Barcelona, Spain; UZ Leuven, Gasthuisberg Campus, Leuven, Belgium

Background: More than 50% of pts with esophageal cancer have locally advanced or metastatic disease at the time of initial diagnosis. For this group chemotherapy is increasingly used intending local and distant tumor control, improvement of quality of life (QoL) and longer survival. Previous data suggested that EGFR-targeting antibodies may be safely combined with cisplatin and 5-FU, and in addition may increase the efficacy of the standard cisplatin/5-FU regimen [Lorenzen et al, *Ann Oncol*2009; 20(10): 1667-1673]. **Methods:** In this open-label, randomized (1:1), multicenter, multinational phase III trial pts with nonresectable, advanced or metastatic ESCC, not eligible for definitive radiochemotherapy, are included. Pts have measurable or non-measurable disease according to RECIST 1.1 and an ECOG PS 0-1. Previous chemotherapy of ESCC in the metastatic setting, concurrent radiotherapy involving target lesions and previous exposure to EGFR-targeted therapy are excluded. Pts receive either CTX (cisplatin 100 mg/m^2 on day 1 and 5-FU 1000 mg/m^2/d on day 1-4) or CTX + P (9 mg/kg on day 1). Cycles are repeated every 3 weeks until progression of disease. Tumor assessment is performed every 9 weeks. The primary objective is to demonstrate superiority of CTX + P over CTX alone in terms of overall survival. Secondary endpoints are progression-free survival, 1-year survival, response rate, safety and tolerability, and QoL. A translational analysis in tumor tissue and serum samples is included. 300 pts are planned to be enrolled for a power of 90% to reject the null hypothesis in which the median overall survival in the control and experimental groups are 6 and 9 months, respectively. 18 pts have been enrolled to date. A Data Monitoring Board will review safety data after 40, 100 and 200 pts. The clinical trial registry number is NCT1627379. Clinical trial information: NCT01627379.

TPS4159 **General Poster Session (Board #33E), Sun, 8:00 AM-11:45 AM**

Metiv-HCC: A phase III clinical trial evaluating tivantinib (ARQ 197), a MET inhibitor, versus placebo as second-line in patients (pts) with MET-high inoperable hepatocellular carcinoma (HCC).

Armando Santoro, Camillo Porta, Lorenza Rimassa, Ivan Borbath, Bruno Daniele, Richard S. Finn, Jean-Luc Raoul, Lawrence H. Schwartz, Aiwu Ruth He, Jorg Trojan, Markus Peck-Radosavljevic, Giovanni Abbadessa, Terri Robin Goldberg, Jordi Bruix; Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy; IRCCS San Matteo University Hospital Foundation, Pavia, Italy; Cliniques Universitaires Saint-Luc, Brussels, Belgium; G. Rummo Hospital, Benevento, Italy; University of California, Los Angeles, Geffen School of Medicine, Los Angeles, CA; Paoli-Calmettes Institute, Marseille, France; Columbia University Medical Center/New York Presbyterian Hospital, New York, NY; Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; Johann Wolfgang Goethe University, Frankfurt, Germany; Medizinische Universitaet Wien, Vienna, Austria; ArQule, Inc., Woburn, MA; Daiichi Sankyo Co., Ltd., Edison, NJ; BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain

Background: Tivantinibis a selective, non-ATP competitive, oral inhibitor of MET, the tyrosine kinase receptor for hepatocyte growth factor (HGF). MET over-expression is associated with poor prognosis in HCC patients. A phase Ib study (Santoro et al, Br J Cancer, 2013) with tivantinib 360mg BID revealed no worsening of liver function in cirrhotic HCC pts. A randomized, placebo-controlled phase 2 study identified HCC patients with high tumor MET expression at immunohistochemistry (IHC) as the target population for tivantinib in second line (overall survival: 7.2 months on tivantinib, 3.8 months on placebo, HR: 0.38, $p=0.01$), and selected 240mg BID as the appropriate dose for HCC patients (Santoro et al, Lancet Oncol, 2013). **Methods:** Enrollment forthis phase III clinical trial (ARQ 197-A-U303, NCT01755767) has begun.Eligible pts must present with Child Pugh A; ECOG performance score <1; inoperable RECIST 1.1 measurable disease; adequate bone marrow, liver and kidney functions; no prior liver transplant. Pts must have progressed after or not tolerated one prior line of systemic therapy including sorafenib and their tumor samples must be deemed MET-High by IHC at a central laboratory to be eligible. Approximately 303 pts are randomized 2:1 to receive tivantinib 240mg PO twice daily or placebo. Pts are stratified by vascular invasion, metastases, and alphafetoprotein level, and they are evaluated by CT or MRI scan at 8-week intervals. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival and safety. Treatment continues until confirmed disease progression or unacceptable toxicity. Pts discontinued from study treatment will be followed for survival. Participating centers are located in Europe, Australia, New Zealand, and the Americas. This trial is expected to complete enrollment by mid-2015, and an interim analysis is planned when approximately 60% of OS events are reached. Clinical trial information: NCT01755767.

TPS4160 General Poster Session (Board #33F), Sun, 8:00 AM-11:45 AM

Open-label, phase I/randomized, phase II trial of the triple angiokinase inhibitor, nintedanib, versus sorafenib in previously untreated patients with advanced hepatocellular carcinoma (HCC).

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Background: While sorafenib is established as the standard first-line treatment for patients with advanced HCC, its use can be complicated by the occurrence of drug-related adverse events (AEs). Nintedanib, a potent, oral triple angiokinase inhibitor that targets VEGF, PDGF and FGF signaling (as well as Flt3 and RET), has demonstrated clinical activity in various advanced solid tumors with a relatively low incidence of AEs typically associated with angiogenesis inhibitors (e.g. skin toxicity, hypertension, hemorrhage, and hematologic toxicity) and is currently in phase III for non-small cell lung cancer and ovarian cancer. In the Phase I, dose-finding stage of this ongoing, multicenter, open-label Phase I/II trial (NCT01004003), 200mg twice daily (bid) was established as the maximum tolerated dose of nintedanib in previously untreated patients with advanced HCC (Palmer D, et al. Ann Oncol 2012;23(Suppl 9):ix245[Abs 740P]). Nintedanib had an acceptable liver AE profile; the most common AEs were mild/moderate gastrointestinal toxicities. **Methods**: The randomized Phase II stage of the trial aims to assess the efficacy, safety, and pharmacokinetics of nintedanib in comparison with sorafenib. Eligible patients have pathologically confirmed, measurable HCC that is not amenable to local therapy, ECOG Performance Status of ≤ 2, Child-Pugh score of 5–6 (Class A), AST/ALT levels $\leq 2\times$ upper limit of normal, and no prior systemic therapy. Patients are being stratified by macrovascular invasion and/or extrahepatic spread and then randomized 2:1 to receive nintedanib 200mg bid or sorafenib 400mg bid in continuous 28-day cycles until progression or unacceptable toxicity. Overall, 93 patients were randomized between Sept 2011 and Nov 2012. The primary endpoint is time to progression (TTP) by independent review, according to RECIST 1.0. TTP will be estimated in the treated set by Kaplan–Meier methodology with treatment effects compared using a Cox proportional hazards model. Secondary endpoints include overall survival, tumor response, progression-free survival, safety and pharmacokinetics. Results are due late 2013. Clinical trial information: NCT01004003.

TPS4161^ General Poster Session (Board #33G), Sun, 8:00 AM-11:45 AM

Phase IIb randomized trial of Pexa-Vec (pexastimogene devacirepvec; JX-594), a targeted oncolytic vaccinia virus, plus best supportive care (BSC) versus BSC alone in patients with advanced hepatocellular carcinoma who have failed sorafenib treatment (TRAVERSE).

Jeong Heo, Yee Chao, Derek J. Jonker, Ari David Baron, Francois Habersetzer, James Burke, Caroline Breitbach, Richard H. Patt, Riccardo Lencioni, Michel Homerin, Jean-Marc Limacher, Monika Lusky, Theresa Hickman, Lara Longpre, David H. Kirn; Pusan National University Hospital, Busan, South Korea; Taipei Veterans General Hospital, Taipei, Taiwan; The Ottawa Hospital Research Institute, Ottawa, ON, Canada; California Pacific Medical Center, San Francisco, CA; Hôpitaux Universitaires de Strasbourg- Hôpital Civil, Strasbourg, France; Jennerex, Inc., San Francisco, CA; RadMD, Doylestown, PA; Division of Diagnostic Imaging and Intervention, Pisa University Hospital and School of Medicine, Pisa, Italy; Transgene S.A., Illkirch-Graffenstaden, France

Background: Pexa-Vec is a targeted oncolytic and immunotherapeutic vaccinia virus engineered to express human granulocyte-macrophage colony stimulating factor (GM-CSF). Direct oncolysis plus GM-CSF expression stimulates tumor vascular disruption and anti-tumor immunity (*Nature Rev Cancer,* 2009). Pexa-Vec was well-tolerated in Phase 1 trials and was shown to replicate in metastatic tumors following intratumoral (IT) or intravenous (IV) administration (*Lancet Oncol,* 2008 and *Nature,* 2011). A randomized high vs low dose Phase 2 trial in 30 patients with advanced HCC, demonstrated prolonged survival in the high-dose Pexa-Vec arm (median survival 14.1 mo vs. 6.7 mo; Hazard Ratio 0.39, p=0.02) (AASLD Annual Meeting, 2011, LB1). **Methods:** TRAVERSE is a Phase 2b randomized, open-label, multi-center trial in patients with advanced HCC who have failed sorafenib treatment. Approximately 120 patients will be randomized 2:1 to Pexa-Vec plus BSC versus BSC, respectively. Randomization will be stratified by region (Asian vs. non-Asian); sorafenib intolerant vs refractory; and presence vs absence of extra-hepatic disease. The primary objective is to determine overall survival. Main inclusion criteria are advanced HCC having failed sorafenib (intolerance or radiographic progression during or $<$ 3 months following last sorafenib), Child-Pugh A-B7 (no ascites), acceptable hematologic function. Assuming a median overall survival of 4.0 months with BSC and a target hazard ratio of 0.57 (corresponding to an experimental arm median survival of 7.0 months), 73 events (deaths) will provide 70% power at 1-sided alpha = 0.05 to detect a difference in overall survival between the treatment groups using a stratified logrank test. Patients randomized to Pexa-Vec will receive a dose of 10^9 plaque forming units (pfu) IV on Day 1 followed by five IT treatments between Day 8 and Week 18. Enrollment has begun on this study with clinical trial registry number of NCT01387555. Clinical trial information: NCT01387555.

TPS4162 General Poster Session (Board #33H), Sun, 8:00 AM-11:45 AM

A randomized controlled trial comparing modified gemcitabine plus oxaliplatin (mGEMOX) to gemcitabine plus cisplatin in the management of unresectable gall bladder cancer.

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Background: In a recently conducted study we have shown that combination of gemcitabine and oxaliplatin is superior to 5 fluorouracil and leucoverine or best supportive care. (Sharma A, Dwary AD, Mohanti BK,et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer:A randomized controlled study. *J Clin Oncol*. 2010; 28: 4581-4586.) In another recent publication from UK, gemcitabine and cisplatin combination was found superior to gemcitabine alone in biliary tract cancers (J W Valle, HS Wasan, DD Palmer, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Eng J Med*. 2010;362:1273-1281.).The current study is being planned to see whether the combination of gemcitabine and oxaliplatin is equivalent (equivalence study) to gemcitabine and cisplatin in these patients. **Methods:** Primary end point of the study is overall survival in subjects receiving mGEMOX or GemCis regimen. Secondary end points are: a) Comparison of progression free survival in 2 groups; b) Response rates in two groups; c) Identification of genes predictive of responses in a subset of patients; d) To evaluate role of PET CT in GBC patients predicting disease activity. Sample size was calculated taking median survival of 9.5 months in our previous study with mGEMOX and 11.7 months with GemCis. For this total of 216 patients are required (108 in each arm); to make for major protocol violation and lost to follow up additional 22 patients in each arm will be enrolled. Thus in total 260 patients (130) in each arm will be recruited. This will have alpha and beta values of 0.05 and 0.20 respectively. So far 103 patients have been enrolled and interim analysis is being planned. Treatment protocol: Cycles will be repeated every 3 weeks. Arm A- mGEMOX. Inj Oxaliplatin 80 mg/$m^2$2 hours infusion in Dextrose 5% Day 1 and 8. Inj Gemcitabine 900 mg/m^2IV 30 minutes infusion day 1 and 8 maximum of 6 cycles. Arm B- GEMCIS. Inj Cisplatin 25 mg/m^2PO Days 1 and 8. Inj Gemcitabine 1000 mg/m^2IV 30 minutes infusion day1and 8 maximum of 8 cycles. Clinical trial information: CTRI/2010/091/001406.

TPS4163 **General Poster Session (Board #34A), Sun, 8:00 AM-11:45 AM**

Regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing following sorafenib: An ongoing randomized, double-blind, phase III trial.

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Background: Sorafenib is the accepted first-line systemic therapy for HCC, but no standard option is available for patients with tumor progression following sorafenib. An open-label phase II study suggested that REG, a multikinase inhibitor, had an acceptable safety profile and showed evidence of antitumor activity in patients with progressive HCC (Bolondi *et al. Eur J Cancer* 2011; 47 [Suppl 1]: abstract 6.576): disease control was achieved in 26/36 patients (72%) and median time to progression (TTP) was 4.3 months; median overall survival (OS) was 13.8 months. On the basis of these promising data, a phase III trial was designed. **Methods:** This randomized, double-blind, placebo (PBO)-controlled, multinational study (ClinicalTrials.gov identifier NCT01774344) will assess the efficacy and tolerability of REG *vs* PBO in patients with HCC that has progressed following sorafenib treatment (target n=530). Inclusion criteria include Barcelona Clinic Liver Cancer stage B or C disease, Child–Pugh A liver function, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1. Patients who discontinued sorafenib ≥8 weeks before study entry or who received other previous systemic therapy for HCC will be excluded. Patients will be randomized in a 2:1 ratio to receive REG 160 mg or matching PBO OD for weeks 1–3 of each 4-week cycle; all patients will also receive best supportive care. Treatment will continue until disease progression, death, intolerable toxicity, or patient/investigator decision to stop. Doses of study drug may be delayed or reduced to manage clinically significant drug-related toxicities. The primary endpoint is OS; secondary endpoints are TTP, progression-free survival, tumor response, and safety. Analysis will be according to randomized group, stratified by geographic region (Asia *vs* rest of world), ECOG PS (0 *vs* 1), alfa-fetoprotein level (<400 *vs* ≥400 ng/ml), extrahepatic disease (yes *vs* no), and macrovascular invasion (yes *vs* no). In addition, blood, plasma, and archival tissue will be assessed for pharmacokinetic and biomarker analyses, and health-related quality of life and health utility will be measured. Clinical trial information: NCT01774344.