肺鳞癌分子靶向治疗:曙光乍现

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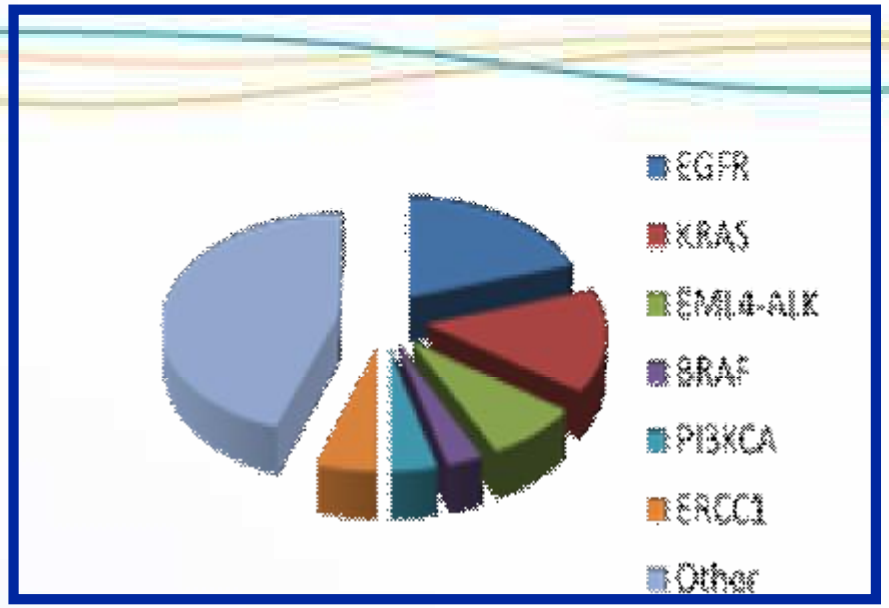
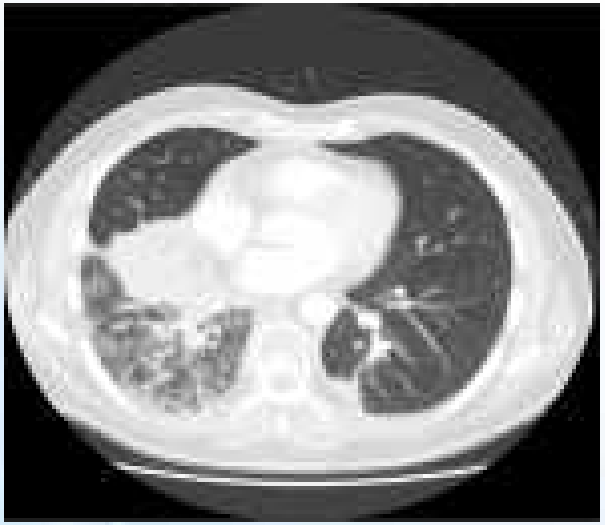
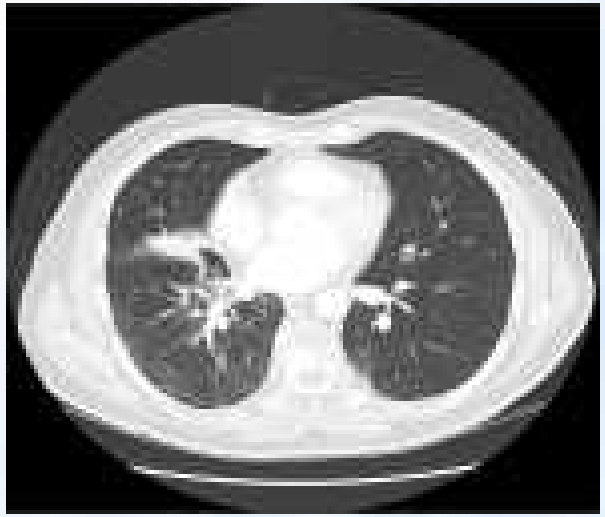
对肺腺癌分子遗传学特点的了解导致其临床治疗的变革与进步



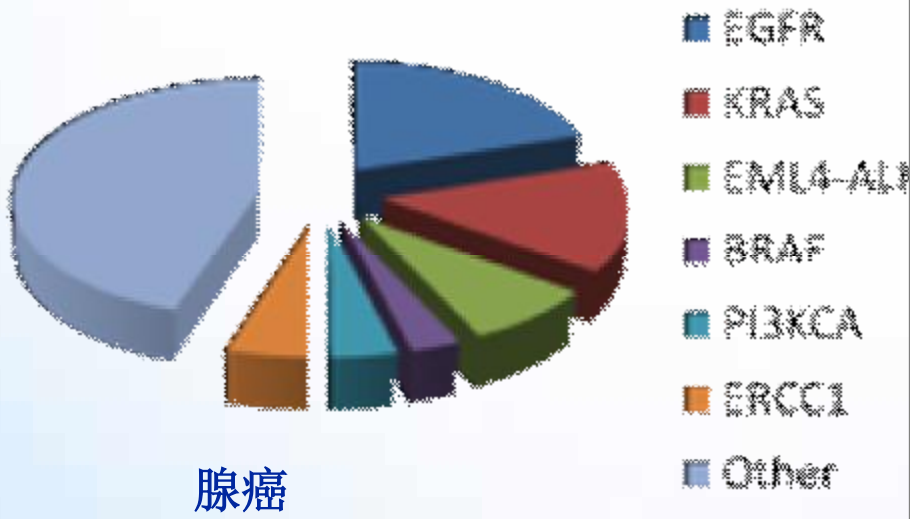
超过50%的肺腺癌已被确定有特异的靶基因



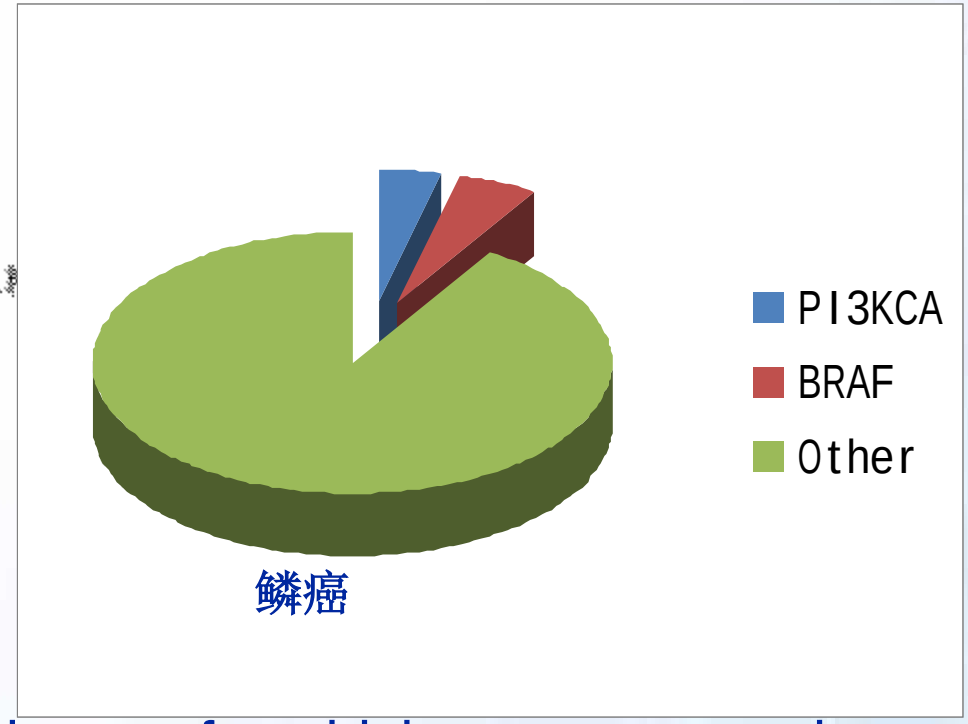
易瑞沙治疗



Current state of knowledge of targetable alterations in lung adenocarcinoma versus squamous cell lung cancer



腺癌



鱗癌

Compared to lung adenocarcinoma, for which many targeted treatment are available, there are no genomically-targeted therapies for lung squamous carcinomas...and few targets

肺癌发生率-组织学类型
1998-2002

	男性		女性	
人群	鳞癌	腺癌	鳞癌	腺癌
澳大利亚	27%	29%	17%	37%
加拿大	30%	31%	18%	41%
法国	41%	26%	20%	44%
日本	33%	41%	11%	69%
韩国	46%	26%	17%	59%
瑞典	29%	30%	17%	40%
英国	40%	18%	28%	24%
美国	27%	31%	18%	38%

Youlden DR, et al. J Thorac Onco., 2008;3:819-831

肺癌新的治疗选择
2000-1020

腺癌	鳞癌
一线	
厄罗替尼	
贝伐单抗	
培美曲赛	
二线或三线	
培美曲赛	(培美曲赛)
厄洛替尼	厄洛替尼
Crizotinib (EML4-ALK)	

鳞癌相关靶向治疗药物临床试验

药物	试验	结果
Bevacizumab	Phase II	增加严重的肺出血发生几率
Sorafenib	Phase III ESCAPE	增加死亡风险
Motesanib	Phase III MONET	增加咯血风险
Ceditranib	Phase II BR24	未增加疗效及毒性
Figitumumab	Phase III ADVIGO (2)	无组织学特异性相关发现， 无获益但增加毒性反应

一项肺鳞癌Figitumumab靶向治疗的III期临床研究

肺癌组织学亚型标志物

	免疫组化指标	分子分型
腺癌	CK7+ CK20- TTF-1+	EGFR 突变 10%-40% FISH+ 45%-50% IHC+ 60%-90% KRAS 突变 20% P53 突变 50%-70% PI3KCA 突变 2%， amplification 6% EML4-ALK 1-13%
鳞癌	TTF1 – CK5+ CK6+ P63+	EGFR 突变 very rare 扩增 30% IHC+ 常见 P53 突变 60%-70% PI3KCA 突变 2%， 扩增 33% KRAS 突变：少见

LangerCJ，etal. J Clin Oncol. 2010;28:5311-5320.

Phase III *nab*-P/C vs P/C Study Design
Socinski MA, et al. ASCO 2010, LBA# 7511

Chemo-naïve
PS 0-1
Stage IIIb / IV
NSCLC
N = 1050

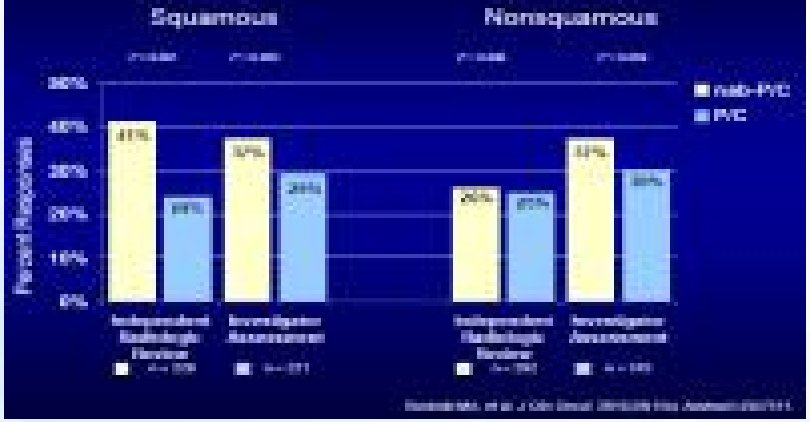
1:1

nab-Paclitaxel 100 mg/m² d1, 8, 15
Carboplatin AUC 6 d1
No Premedication
n = 525

Paclitaxel 200 mg/m² d1
Carboplatin AUC 6 d1
With Premedication of
Dexamethasone + Antihistamines
n = 525

Stratification factors:
- Stage (IIIb vs IV)
- Age (< 70 vs > 70)
- Sex
- Histology (squamous vs nonsquamous)
- Geographic region

Objective Responses by Histology



Caveolin-1 Expression in NSCLC

Histology	Cav-1 Expression (%)*
Adenocarcinoma	16.7
Adenosquamous	38.4
Squamous	67.1
Large cell	66.7

*Quantum dot IHC.
Cav-1 expression significantly associated with nodal metastases

肺鳞癌突变患者易瑞沙治疗疗效不佳

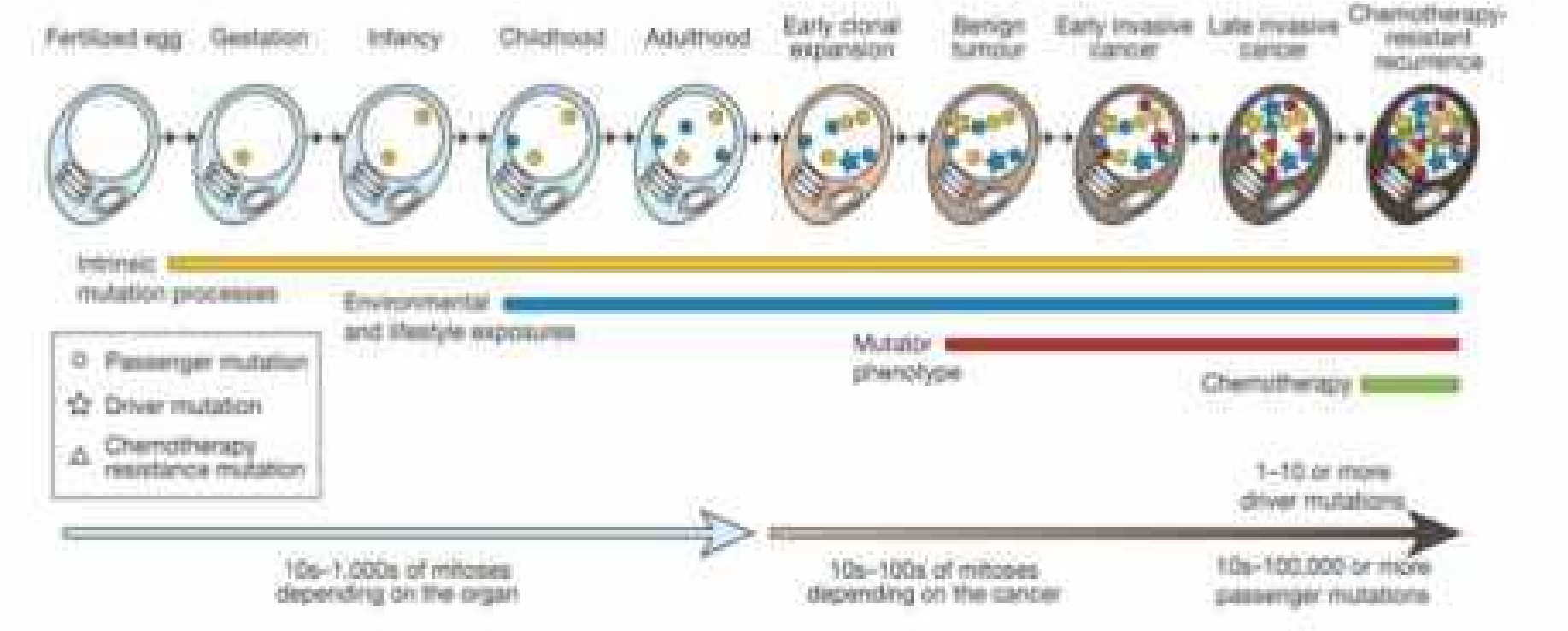
- Shukuya等利用PUBMED数据，对15项临床研究中共33例非腺癌患者进行分析。

- 其中27例为鳞癌，3例腺鳞癌，21例有EGFR突变。

- 吉非替尼治疗的有效率、疾病控制率、中位无病进展生存时间分别为27%，67%-70%和3个月，远远低于有EGFR突变的肺腺癌患者（66%，92%-93%，9.4个月）

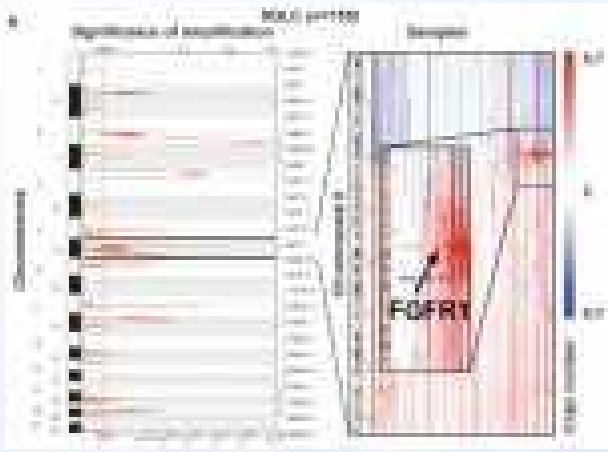
Shukuya et al, JTO, 2010

驱动突变和过客突变
（Driver or Passenger Mutations）



肺鳞癌有意义的基因扩增改变

Gene	Event Type	Drug Target
EGFR1	**Amplification**	**Yes**
SOX1	**Amplification**	**No**
CCND1	**Amplification**	**Yes**
REL	**Amplification**	**No**
PDGFRA	**Amplification**	**Yes**
EGFR	**Amplification**	**Yes**
NFE2L2	**Amplification**	**No**
MCL1	**Amplification**	**Yes**
ERBB2	**Amplification**	**Yes**
CDKN2A	**Deletion**	**Yes**
PETN	**Deletion**	**Yes**
RB	**Deletion**	**No**



Weiss et al., 2010

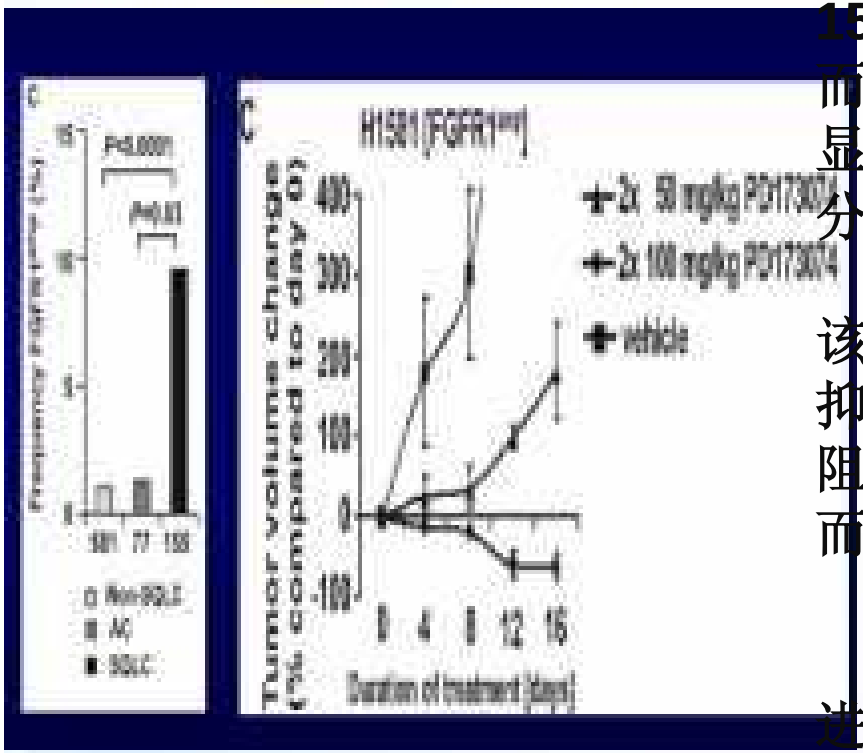
Weiss, et al, 2011

总结:肺鳞癌基因变异

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PI3KCA	Mutation	9%
PTEN	Mutation/Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%

- ü 63%SCCs能检测到明确的基因变异
- ü 需要临床前和早期临床研究证实
- ü FGFR1/2, PIK3CA, DDR2抑制剂试验正计划或进行中

FGFR1在肺鳞癌中的扩增及其抑制剂的研究



155例肺癌标本，22%存在FGFR1扩增，而581非鳞癌患者仅1%存在基因缺陷。显示FGFR1扩增可能是肺鳞癌特有的分子标志。

该研究继而分析83例肺癌细胞株中FGFR1抑制剂（PD173074）的作用，发现其能阻止其中4株肿瘤细胞的生长导致其死亡。而此4例肺癌细胞株，3例存在FGFR1扩增。

进一步动物试验显示，存在FGFR1基因缺陷的肺磷癌小鼠能从FGFR1抑制剂PD173074的治疗中获益，肿瘤明显缩小。

Weiss, et al, 2011

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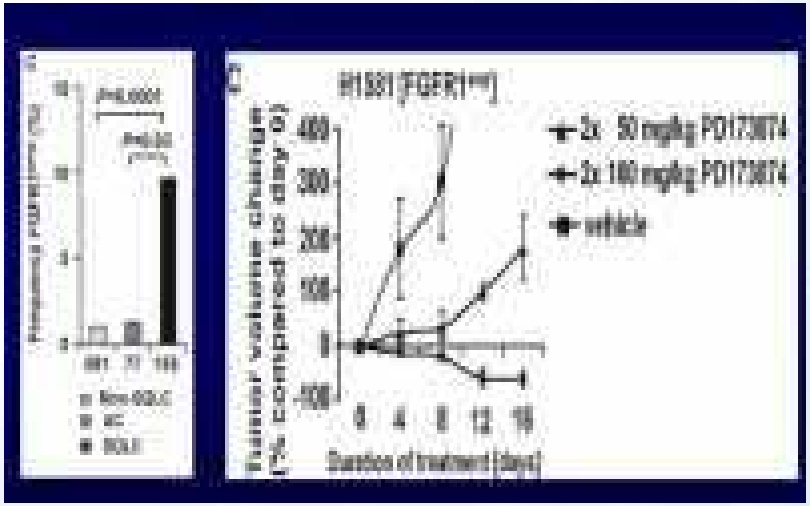
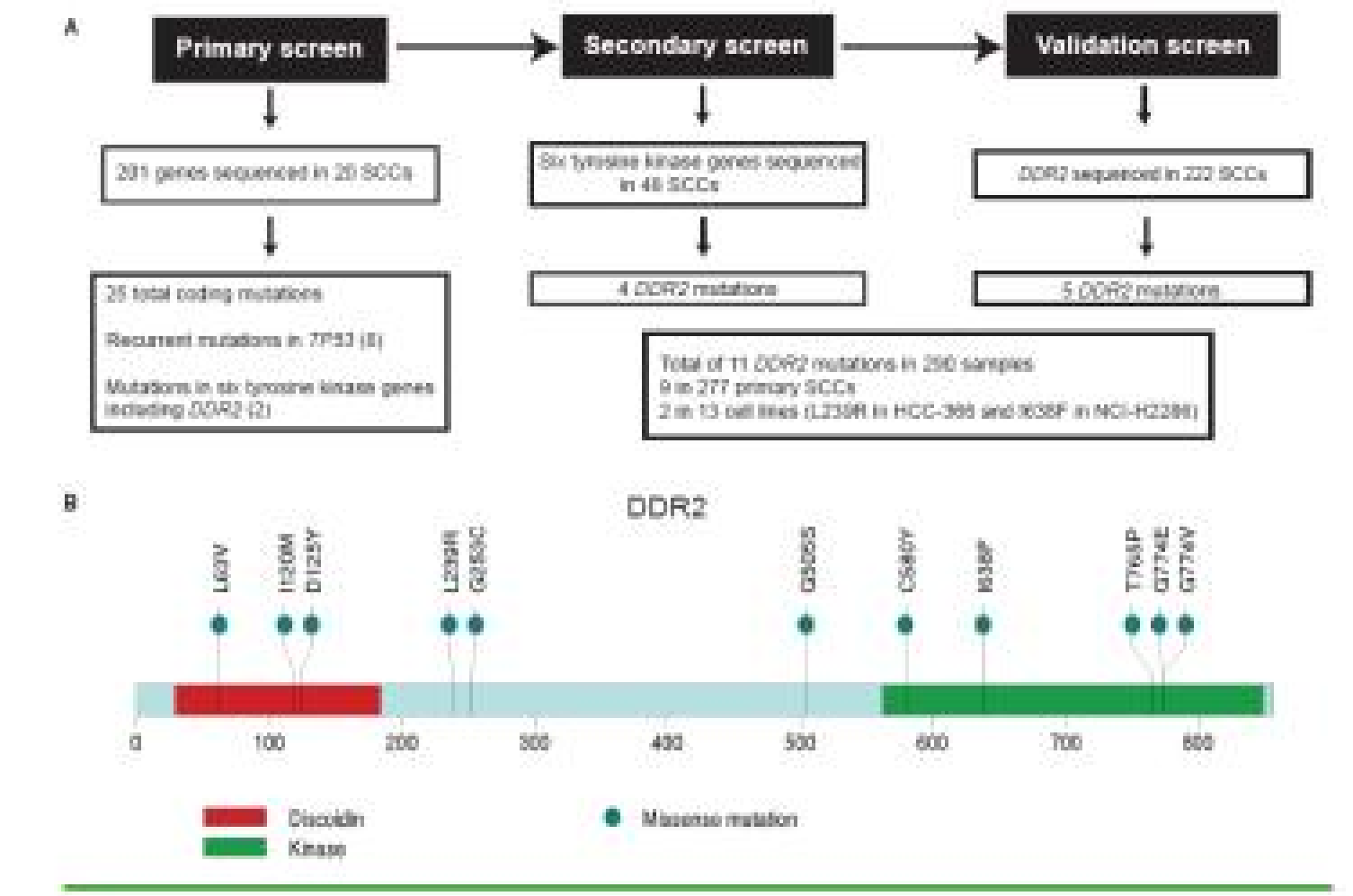


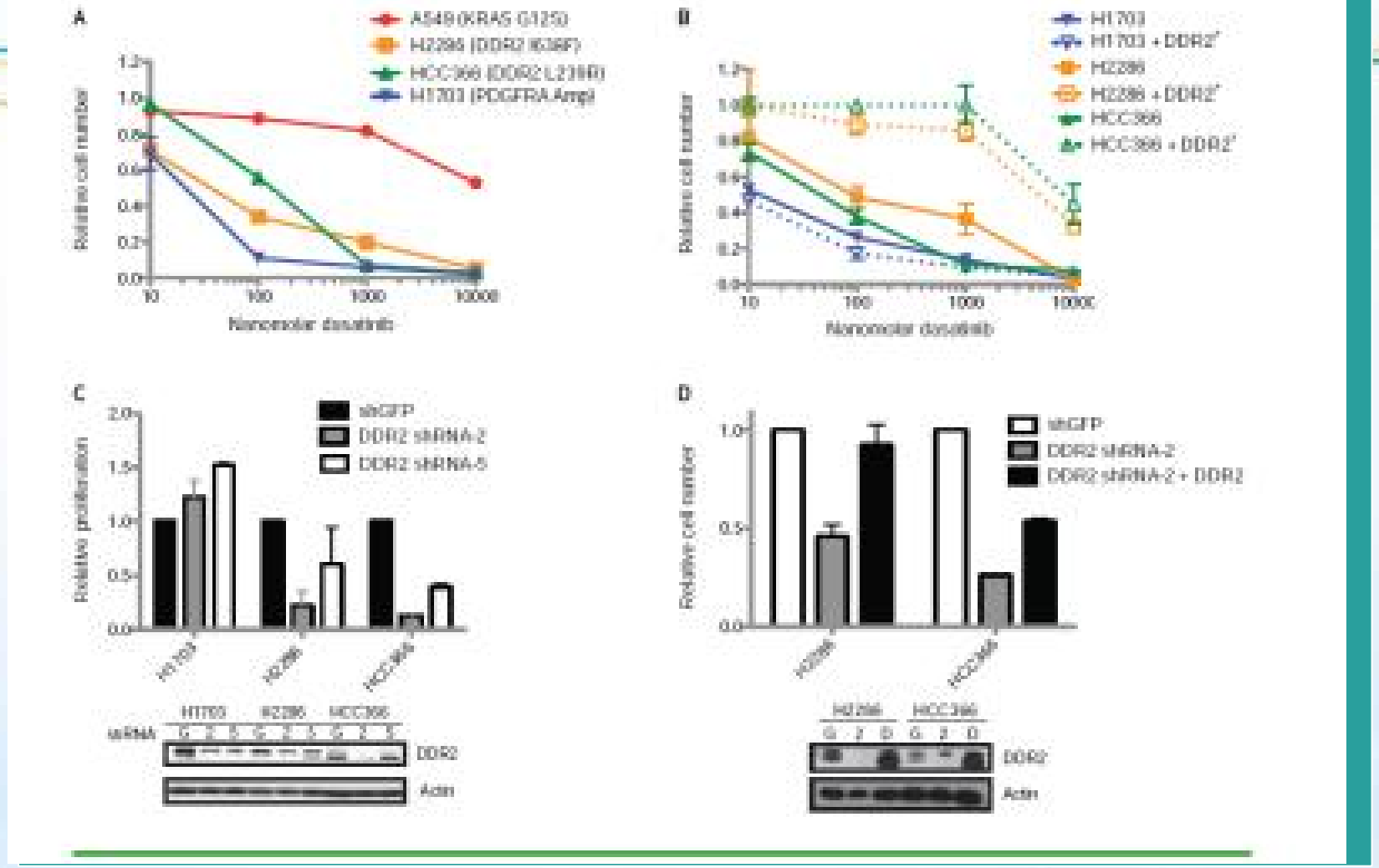
Weiss et al., 2010

肺鳞癌DDR2突变



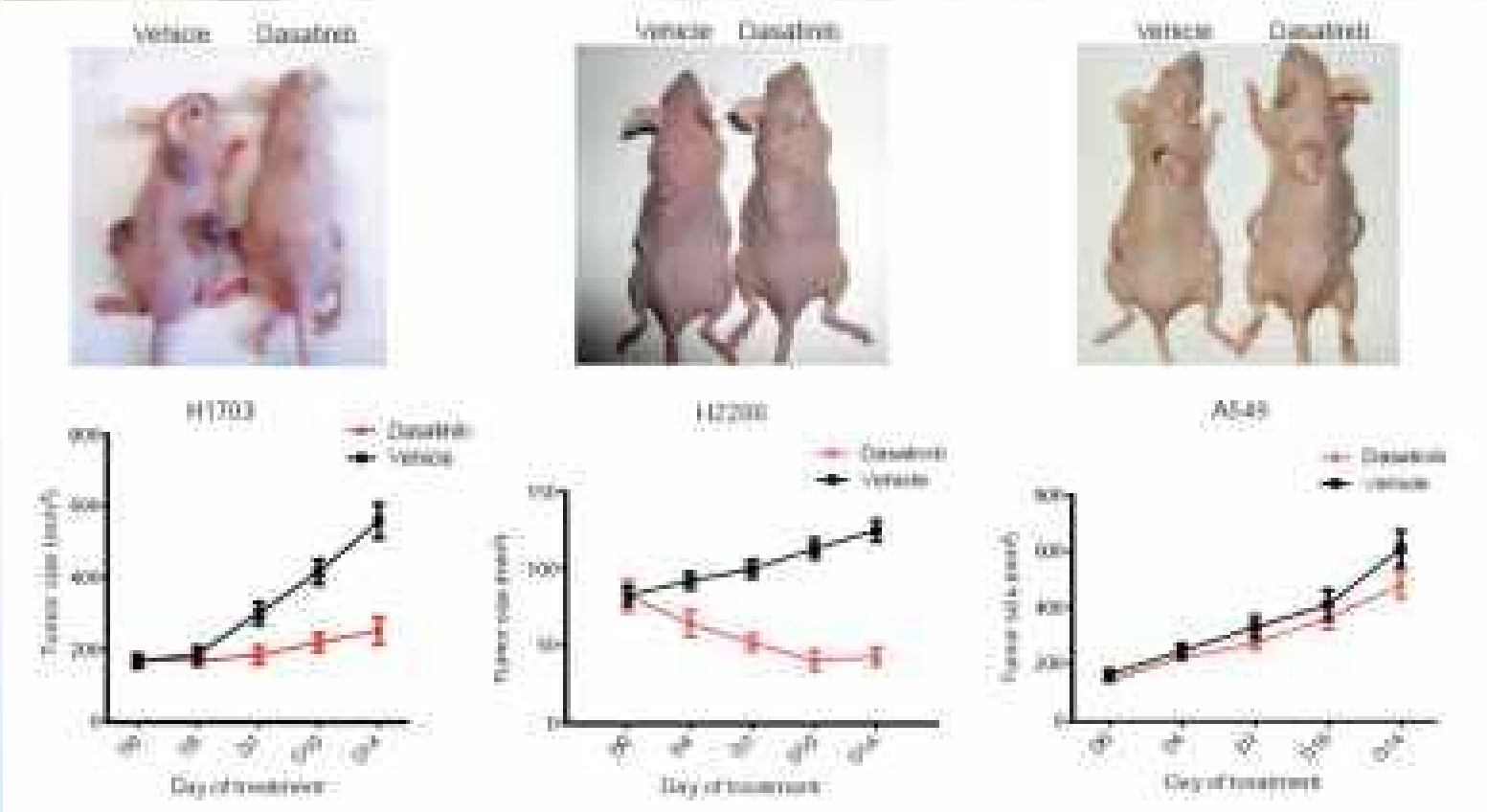
Hammerman et al, Cancer Discovery, 2011

携带DDR2突变的细胞系对其抑制剂或ShRNA敏感



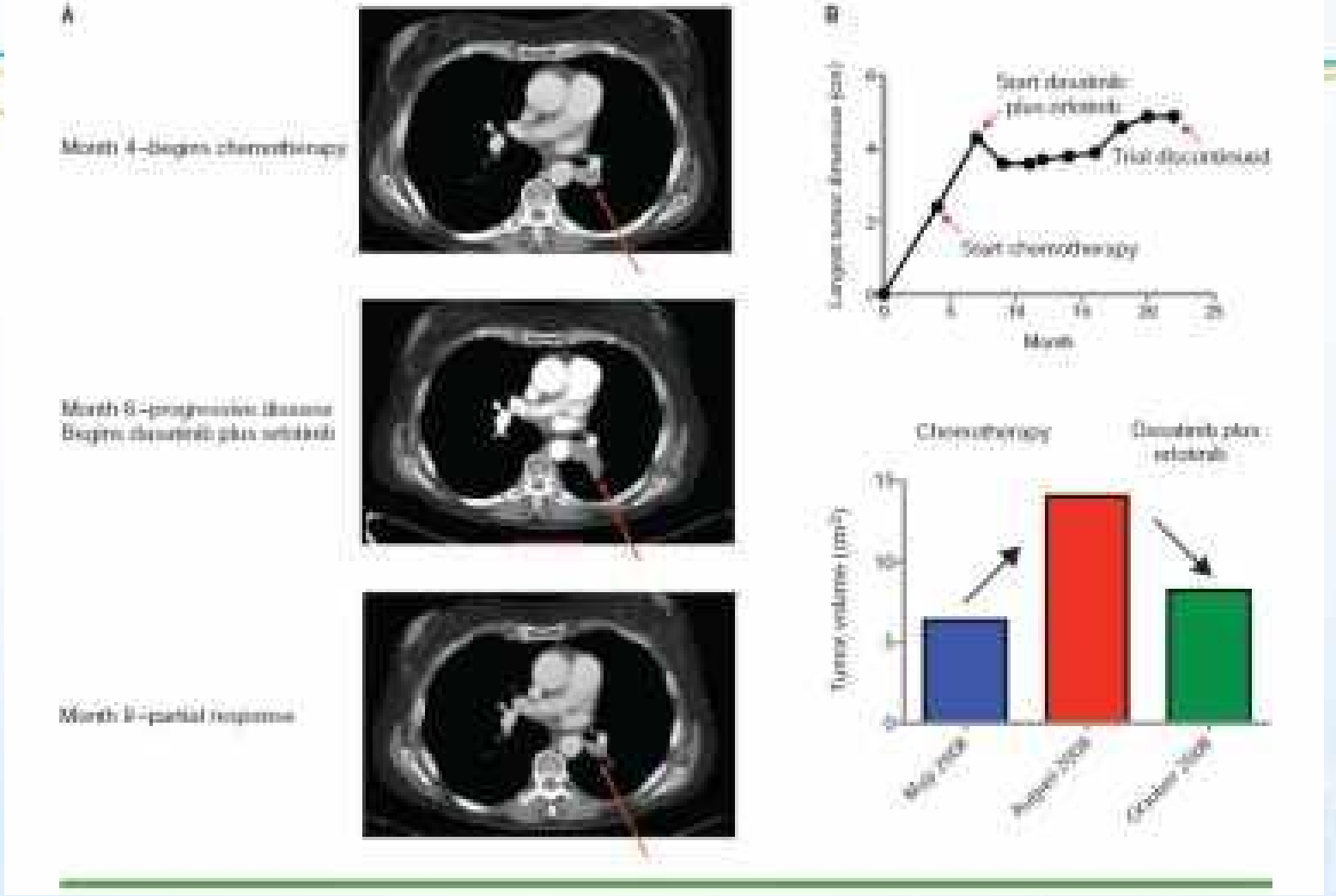
Hammerman et al, Cancer Discovery, 2011

动物实验结果



Hammerman et al, Cancer Discovery, 2011

携带DDR2突变，EGFR突变的患者对达沙替尼疗效



Hammerman et al, Cancer Discovery, 2011

Lung Cancer (2007) 58, 159–160

available at www.sciencedirect.com

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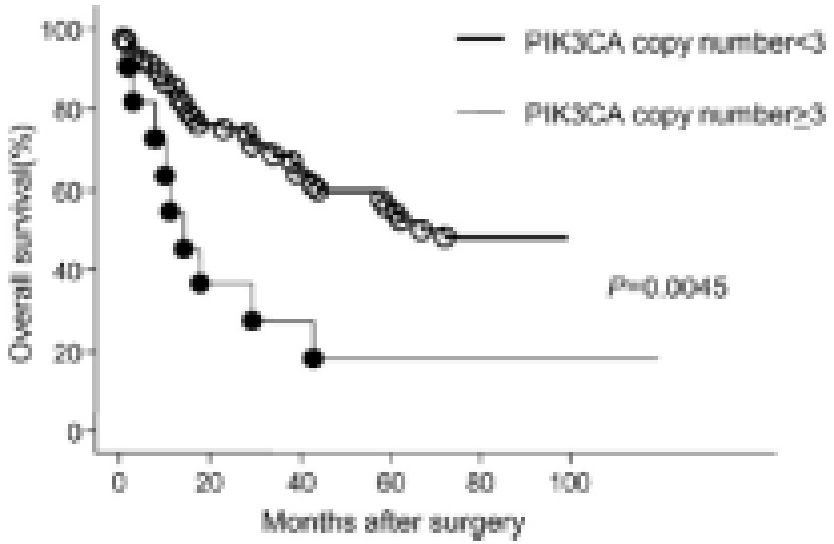
journal homepage: www.elsevier.com/locate/lungcan

ELSEVIER

LETTER TO THE EDITOR

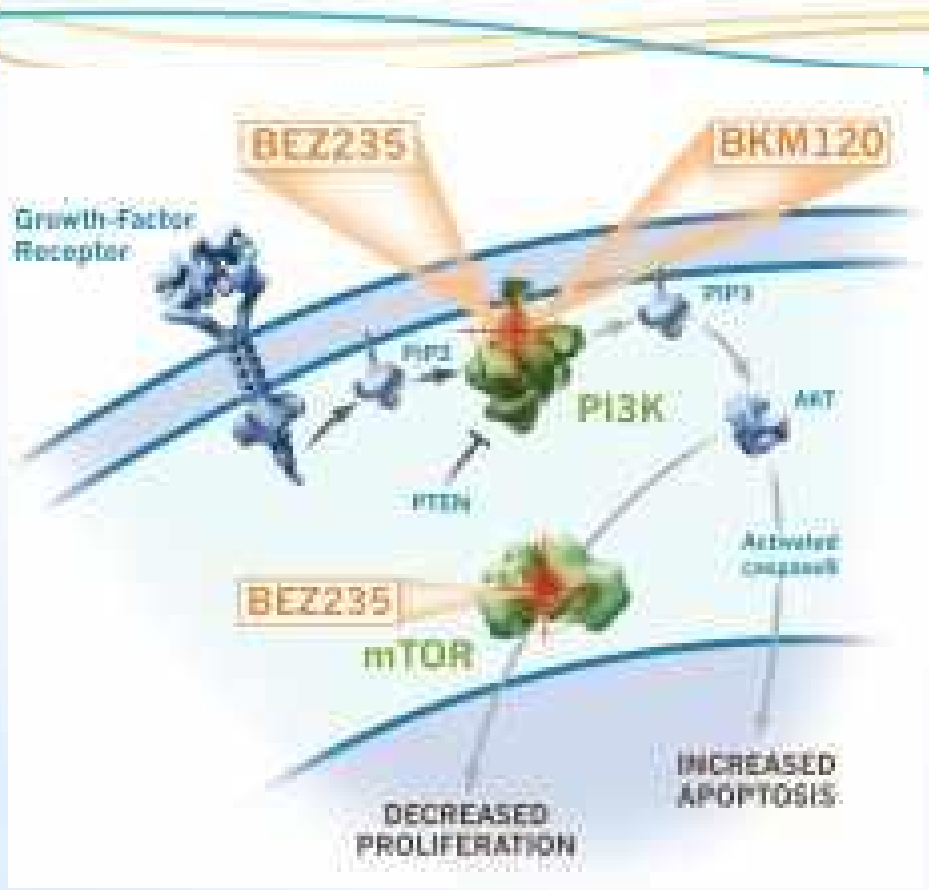
PIK3CA gene amplification in Japanese non-small cell lung cancer



92例肺鳞癌PIK3CA扩增率12%

- **男性 VS. 女性：**
  11/63 VS. 0/29 P=0.041
- **吸烟 VS. 从不吸烟：**
  11/59 VS. 0/32 P=0.021
- **鳞癌 VS. 腺癌：**
  10/28 VS. 1/64 P=0.001

BEZ235/BKM120: Blocking the PI3K Pathway



- BEZ235 is a novel, oral, potent PI3K and mTOR dual inhibitor
- BKM120 is a novel, oral selective PI3K inhibitor
- PI3K pathway regulates cell proliferation, growth, survival, and apoptosis
- PI3K pathway is mutated (activated) in many cancers
  - Mutation in PI3K
  - Via loss of PTEN or overexpression of receptor tyrosine kinases, such as EGFR & HER-2
  - Implicated in poor prognosis and survival in many cancers, including: breast, prostate, lung, glioblastoma, melanoma, bladder, endometrial carcinoma, lymphatic tumors, and others

PI3K, Phosphoinositide-3 kinase; PTEN, phosphate and tensin homolog

Wymann MP, *et al. Trends Pharmacol Sci.* 2003;**24**:366–376. Stauffer F, *et al.* AACR 2007. Abstract # 269. Ali IU, *et al. J Nat Can Inst.* 1999;**91**:1922–1932.

BEZ235 Phase I: Patient characteristics

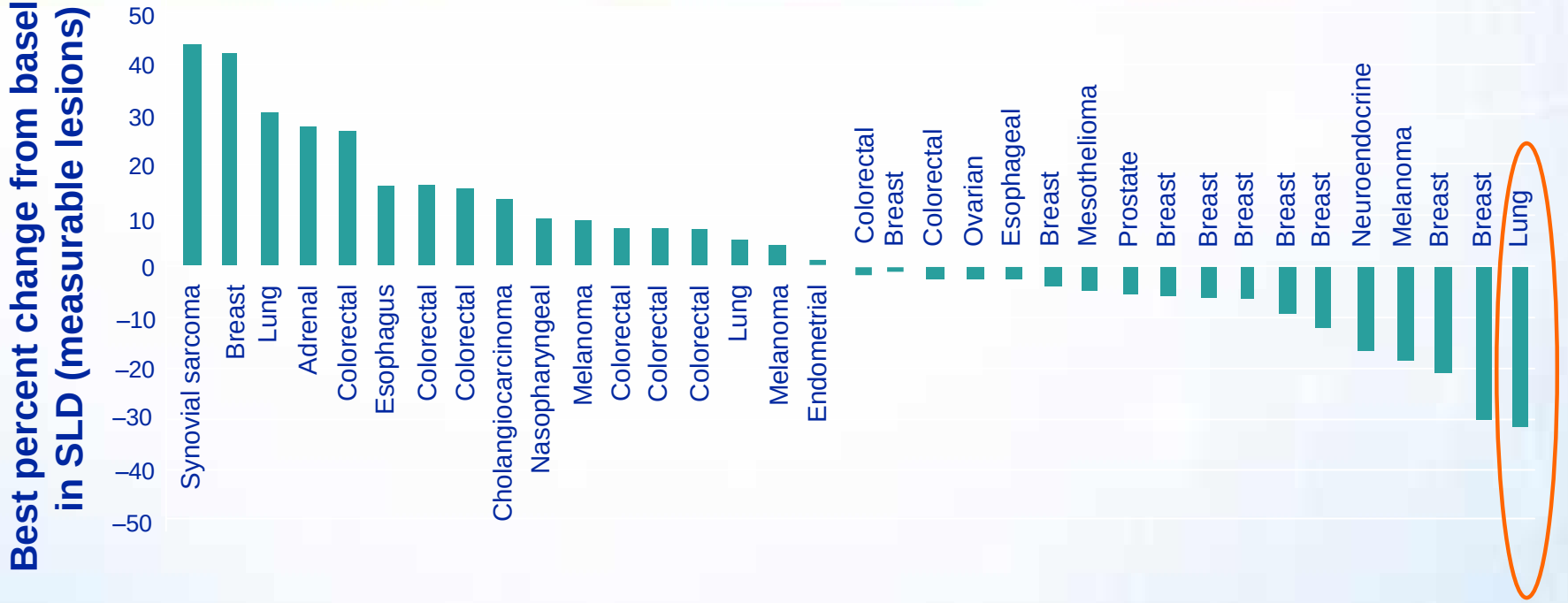
Characteristic	N=59
Median age, years (range)	55 (29 – 81)
<65 years (%)	47 (80%)
Male / Female	20 (34%) / 39 (66%)
WHO PS, 0/1	29 (49%) / 30 (51%)
Prior antineoplastic therapy	56 (95%)
Median number of regimens (range)	3 (0 – 18)
Patients with >3 prior regimens	30 (51%)

Primary tumor type	N=59
Colorectal	14 (24%)
Breast	13 (22%)
Lung	5 (9%)
Ovarian	4 (7%)
Skin melanoma	4 (7%)
Soft tissue sarcoma	3 (5%)
Prostate	2 (3%)
Endometrial	2 (3%)
Esophageal	2 (3%)
Pancreatic	2 (3%)
Head and neck	2 (3%)
Other[a]	6 (10%)

[a]One patient each (1.7%): kidney, adrenal, pleural, choroid, gallbladder, pararenal

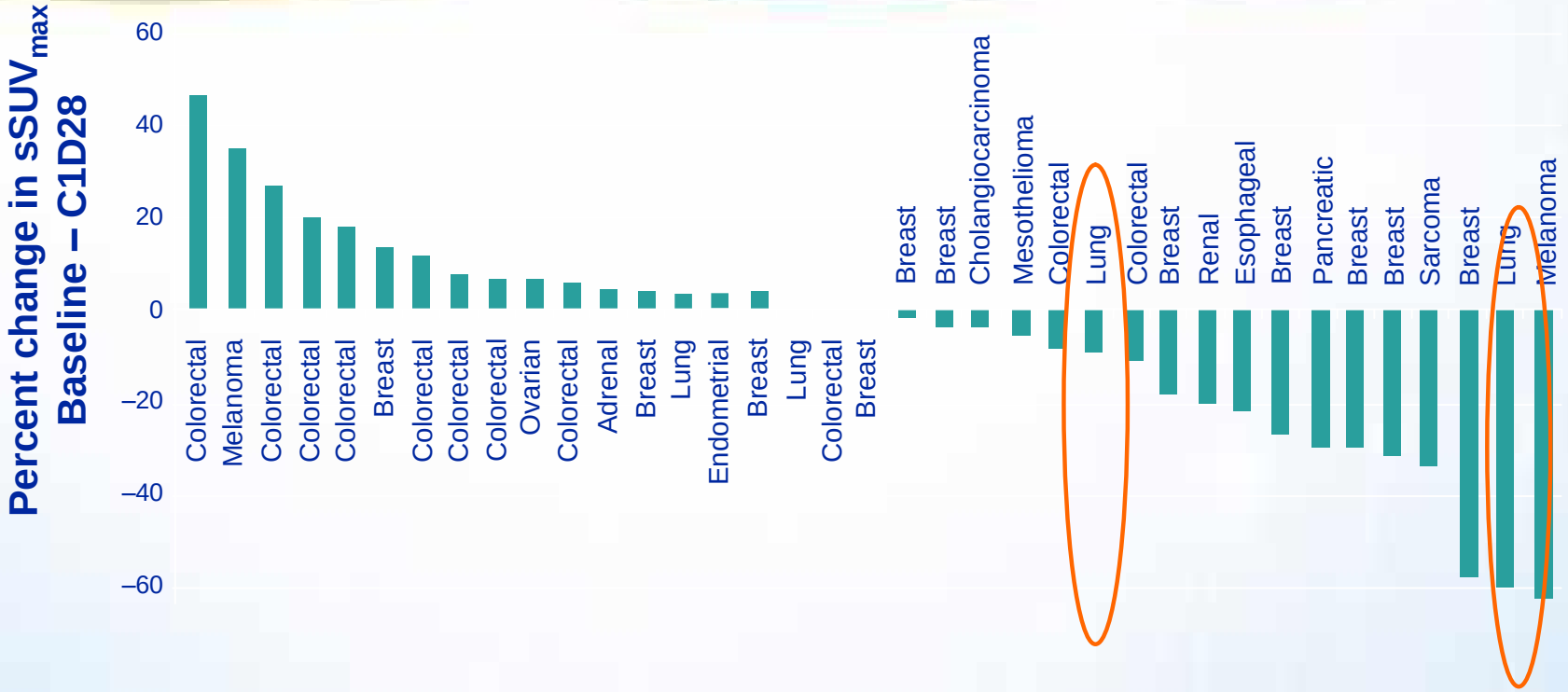
Cut-off date March 2, 2009

BEZ235 Phase I: reduction in tumor burden as per CT



- 18 out of 35 evaluable patients had tumor shrinkage as per central review

BEZ235 Phase I: tumor metabolic response as per ^{18}FDG-PET[a]

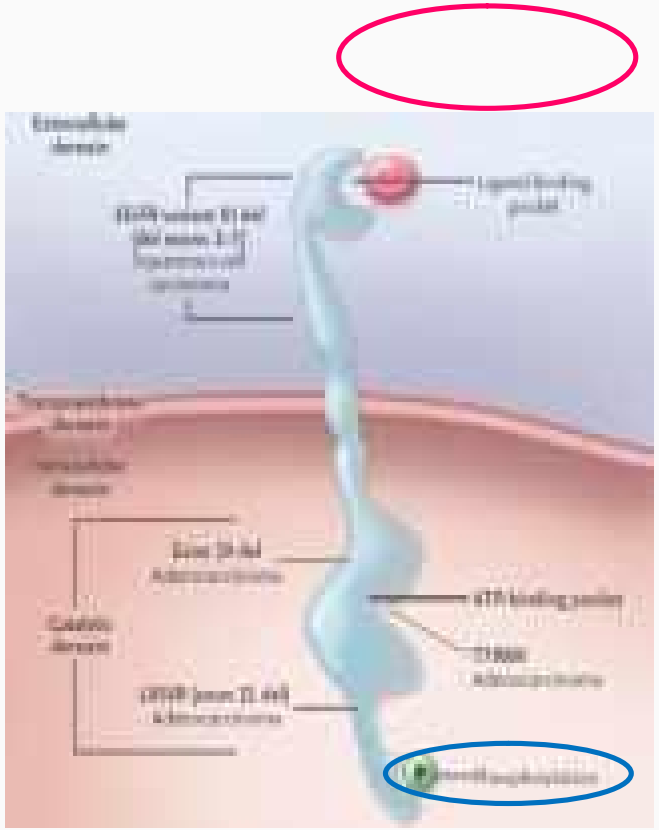


- 18 out of 37 patients demonstrated a detectable decrease in tumor ^{18}FDG-uptake as per central review

[a]End of Cycle 1

C, Cycle; D, Day

EGFR vⅢ: 潜在的分子标志-



EGFRvIII 系发生于胞外区2-7外显子突变的EGFR剪切变异体。

EGFRvIII 的剪切变异，使EGFR获得自身磷酸化的能力，在无配体情况下激活其下游经典的MAPK、ERK等通路，导致肿瘤的发生发展。

目前有关EGFRvIII的报道多见诸于神经胶质瘤、卵巢癌或头颈部肿瘤以及乳腺癌，在肺癌中的研究较少. 仅5%-10%

114例NSCLC检测结果

病理类型	病例数	EGFRvIII（+）	阳性率（%）
鳞癌	54	6	11.1
腺癌	55	2	3.64
腺鳞癌	5	0	0

总　结

肺鳞癌分子靶向治疗：曙光乍现

Gene	Frequency (%)	Drug	Reference
FGFR1 amplification	22	FGFR TKIs	Weiss et al. (6)
EGFRvIII mutations	5	EGFR TKIs	Ji et al. (10)
PIK3CA mutations	3.6	PI3K inhibitors	Yamamoto et al. (11)
EGFR kinase domain mutations	3.4	EGFR TKIs	Miyamae et al. (12)
DDR2 mutations	3.2	Dasatinib, nilotinib	Hammerman et al. (1)