AZD9291 a novel EGFR-TKI that overcomes T790M-mediated resistance in NSCLC

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Disclosure Slide

- AstraZeneca, BMS, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Boehringer Ingelheim

Introduction

- EGFR mutations occur in 30–40% of NSCLCs in Asian pts and in ~15% of NSCLCs in Western pts

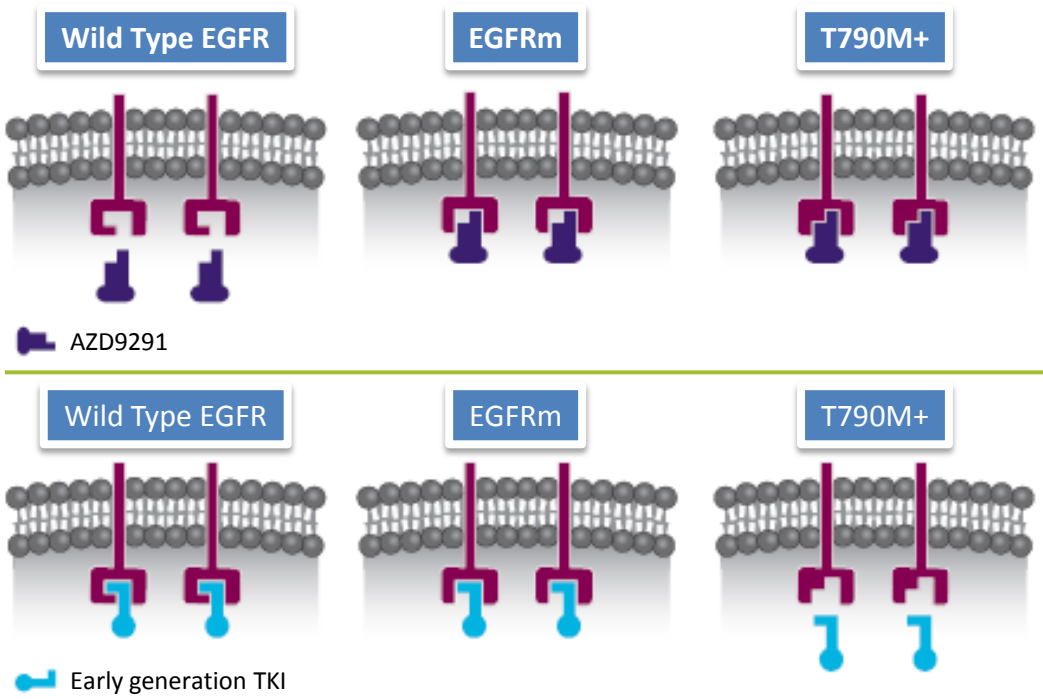
- EGFR-TKIs are approved as first-line therapy for pts who have advanced NSCLC with an EGFR-mutation[1]

- Majority of NSCLC pts with EGFR-mutation treated with a currently approved EGFR-TKI develop resistance[2–4]
  - EGFR T790M mutation is responsible for resistance in up to 60% of cases[5]
  - There are currently no approved treatments specifically for patients with T790M+ NSCLC

1. Peters et al. Ann Oncol 2012;23(Suppl 7):vii56–64; 2. Rosell et al. Lancet Oncol 2012;13:239–246;
3. Mok et al. N Engl J Med 2009;361:947–957; 4. Sequist et al. J Clin Oncol 2013;31:3327–3334;
5. Yu et al. Clin Cancer Res 2013;19:2240–2247; 6. Cross et al. Cancer Discov 2014;4:1046–1061;
7. Yang et al. ESMO 2014 Poster 449PD

AZD9291 is an oral, irreversible selective inhibitor targeting activating and T790M mutations of EGFR

AZD9291 preferentially binds the activated EGFR mutant kinase and the resistant EGFR mutant T790M kinase with a >30-fold margin vs. wild type EGFR in cells[1]



AZD9291

Effective inhibition of EGFR Ex19 del, L858R, T790M while avoiding wild-type EGFR related toxicities

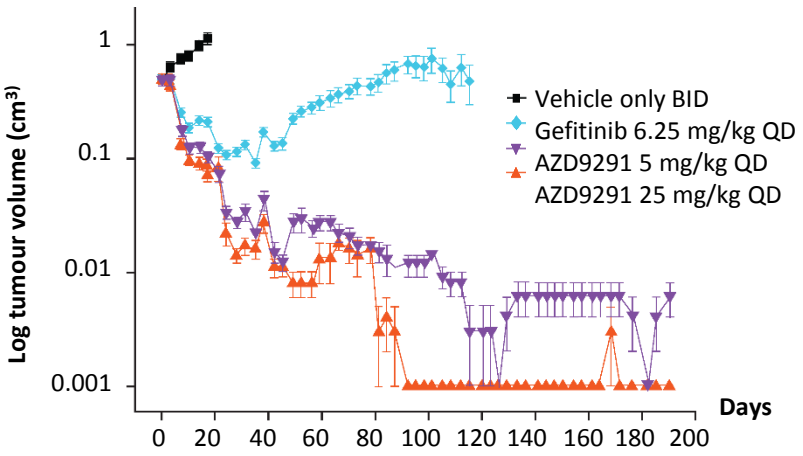
Early generation EGFR-TKIs preferentially bind the activated EGFR mutant kinase and the wild type EGFR kinase

1. Cross et al. Cancer Discov 2014;4:1046–1061;

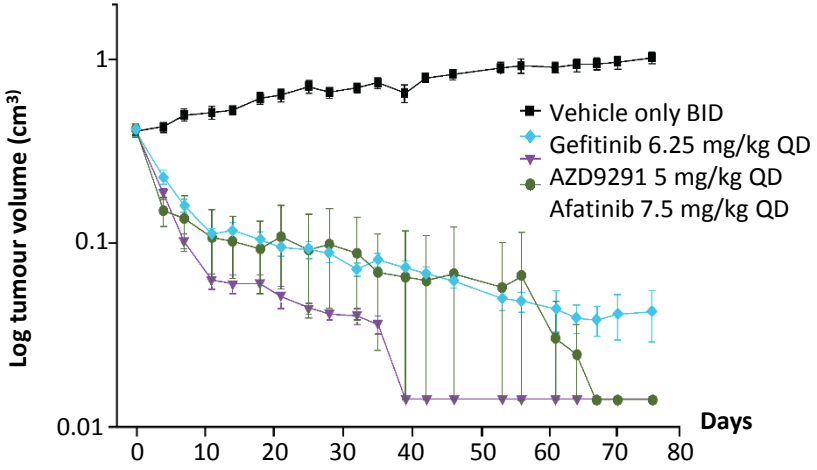
Tumour shrinkage in EGFRm+ NSCLC tumour xenografts

- AZD9291 induces sustained tumour shrinkage in PC9 and H3255 tumour xenografts

PC9 (EGFR exon 19 deletion)



H3255 (EGFR L858R)



AZD9291 at 25 mg/kg in mouse approximates to clinical exposure of 80 mg once daily, gefitinib at 6.25 mg/kg in mouse approximates to clinical exposure of 250 mg once daily; afatinib at 7.5 mg/kg in mouse approximates to clinical exposure of 40 mg once daily

QD, once daily

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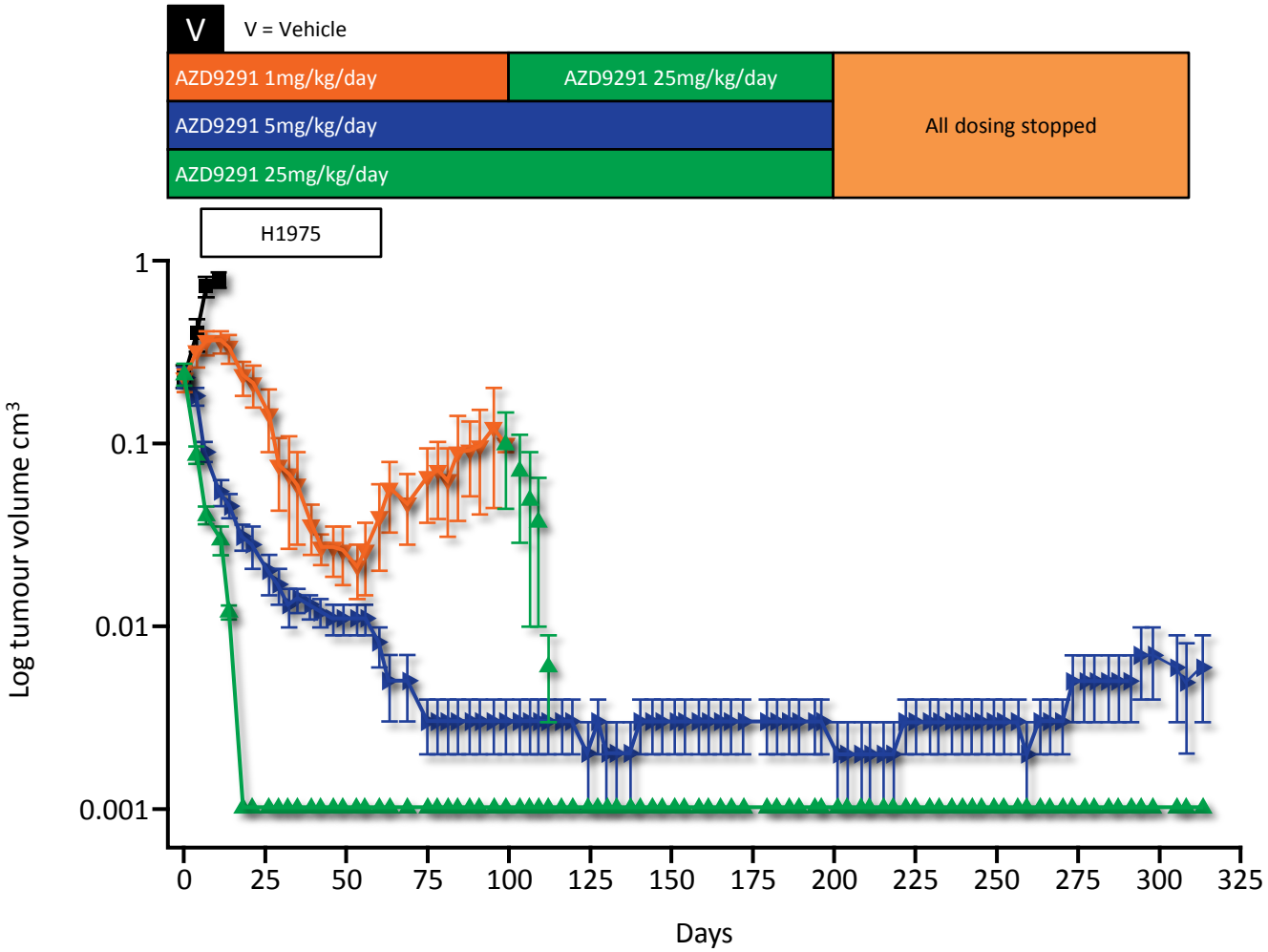
Long term dosing tumour growth inhibition study of AZD9291 in H1975 (L858R / T790M) xenograft model



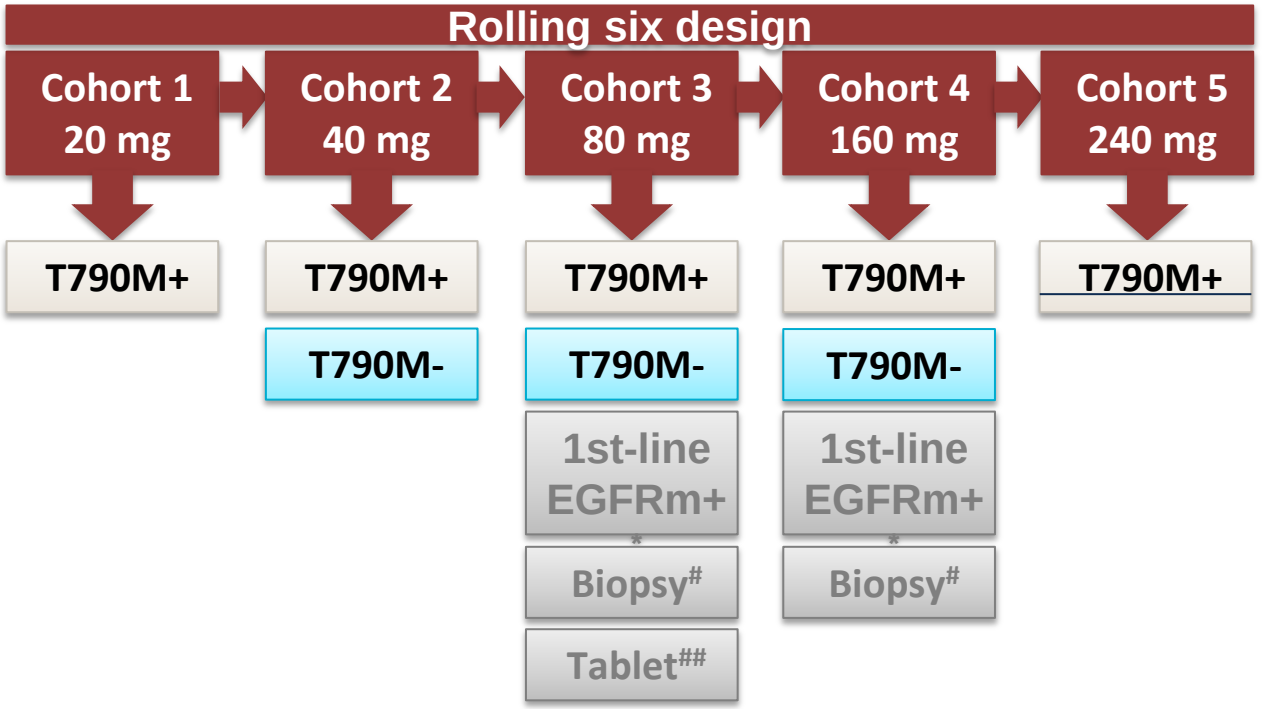
Phase I dose escalation/expansion study design

Phase I, open-label, multicenter study of AZD9291 administered once daily in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI (AURA; NCT01802632)

Primary study objective was assessment of the safety, tolerability and efficacy (ORR) of AZD9291 in EGFR-TKI-resistant pts

Escalation
Not preselected by T790M status

Expansion
Enrolment by local testing followed by central laboratory confirmation (cobas® EGFR Mutation Test) of T790M status or by central laboratory testing alone



*Prior therapy not permissible in this cohort.
#Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.

Key inclusion and exclusion criteria

- **Key inclusion criteria include**
  - Measurable disease at baseline
  - Radiological documentation of disease progression while on a previous treatment with an EGFR-TKI
  - No limit on prior EGFR or systemic regimens
  - EGFR-mutated tumor or clinical benefit from EGFR-TKI according to Jackman criteria[1]
  - Dose expansion: confirmation of tumor T790M mutation status (positive or negative) from a new biopsy sample taken after disease progression on the most recent treatment regimen
  - Patients with stable, asymptomatic brain metastases (not requiring steroids for ≥4 weeks) were allowed

- **Key exclusion criteria**
  - Prior history of ILD

Patients

- As of 1 August 2014, 253 patients were enrolled: 31 in the dose escalation cohorts and 222 in the dose expansion cohorts
  - Median age was 60 years and 62% of study participants were female
  - 62% were Asian, 36% were Caucasian
  - 60% of patients had received immediate prior EGFR-TKI therapy
  - A total of 138 patients were T790M+ by central tumour testing
  - Current median treatment duration is 6.5 months (range 0.1–16)

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Baseline demographic and disease characteristics

Characteristic	Escalation N=31	Expansion N=222
Gender, n (%) Male/Female	11/20 (35/65)	86/136 (39/61)
Age, years, median (range)	61 (39–81)	60 (28–88)
Race, n (%) Caucasian/Asian/other/missing	8/22/1/0 (26/71/3/0)	82/134/5/1 (37/60/2/0.5)
Histology, n (%) Adeno/squamous/other/missing	29/1/1/0 (94/3/3/0)	213/2/5/2 (96/1/2/1)
T790M status,* n (%) Positive/negative/unknown	Central testing not required for escalation	138/62/22 (62/28/10)
Prior lines of systemic therapy, median (range)	3 (1–12)	3 (1–12)
Prior EGFR-TKIs,# median (range)	1 (1–4)	2 (1–5)
Regimen, n (%)		
Gefitinib	22 (71)	128 (58)
Erlotinib	15 (48)	128 (58)
Afatinib	1 (3)	51 (23)
Immediate prior EGFR-TKI, n (%) Yes/no/missing	14/17/0 (45/55/0)	137/84/1 (62/38/0.5)
EGFR-TKI-sensitising mutation, n (%) Ex19del/L858R/other/none/unknown	Central testing not required for escalation	112/65/10/13/22 (50/29/5/6/10)

*Tested in a central laboratory. #Patients may have more than one prior regimen

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Safety and tolerability

- All-causality AEs were mostly mild (Grade 1/2) at all dose levels
- No DLT were reported in any of the dose escalation cohorts
- A non-tolerated dose has not been defined
- There were no observed differences in toxicity by race
- The most common AEs were diarrhoea and rash
- At the recommended Phase II dose of 80 mg once daily:
  - Grade 3 diarrhoea occurred in 1% (all grades 33%)
  - Grade 3 rash occurred in 0% (all grades 32%)
- There were six cases of potential pneumonitis-like events
  - Two occurred in non-Japanese Asian pts and four in non-Asian patients
  - To date, five have fully recovered and one is resolving with routine medical care
  - All six patients discontinued AZD9291

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All-causality adverse events, all grades

recommended Phase II dose

Patients with an AE, n (%)	20 mg N=21	40 mg N=58	80 mg N=90	160 mg N=63	240 mg N=21	Total N=253
AE by preferred term occurring in at least 10% of patients overall						
Diarrhoea	5 (24)	24 (41)	30 (33)	43 (68)	16 (76)	118 (47)
Rash (grouped term)	5 (24)	13 (22)	29 (32)	40 (63)	15 (71)	102 (40)
Nausea	3 (14)	10 (17)	16 (18)	19 (30)	7 (33)	55 (22)
Decreased appetite	7 (33)	11 (19)	14 (16)	16 (25)	6 (29)	54 (21)
Dry skin	2 (10)	9 (16)	10 (11)	25 (40)	5 (24)	51 (20)
Pruritus	2 (10)	11 (19)	15 (17)	12 (19)	7 (33)	47 (19)
Fatigue	4 (19)	15 (26)	9 (10)	11 (17)	5 (24)	44 (17)
Paronychia	2 (10)	5 (9)	11 (12)	18 (29)	6 (29)	42 (17)
Constipation	1 (5)	13 (22)	15 (17)	10 (16)	1 (5)	40 (16)
Cough	3 (14)	9 (16)	12 (13)	13 (21)	0	37 (15)
Stomatitis	1 (5)	5 (9)	9 (10)	13 (21)	3 (14)	31 (12)
Vomiting	3 (14)	4 (7)	9 (10)	7 (11)	6 (29)	29 (11)
Anaemia	0	6 (10)	11 (12)	9 (14)	2 (10)	28 (11)
Dyspnoea	2 (10)	8 (14)	9 (10)	8 (13)	0	27(11)
Upper respiratory tract infection	5 (24)	5 (9)	9 (10)	5 (8)	1 (5)	25 (10)
Headache	0	6 (10)	9 (10)	9 (14)	1 (5)	25 (10)
Select AEs of interest						
Hyperglycaemia	0	1 (2)	3 (3)	2 (3)	0	6 (2)
QT prolongation	0	2 (3)	4 (4)	4 (6)	1 (5)	11 (4)
Pneumonitis-like events*#	0	0	2 (2)	4 (6)	0	6 (2)

Dermatitis acneiform is included in the grouped rashes. *All pneumonitis-like events are undergoing full investigation and subject to change.
#As of 12 September 2014, out of more than 620 patients across all studies dosed with AZD9291, pneumonitis grouped term events have been reported in 2.09% of patients (13 events). Of these events, seven were Grade 1–2, three were Grade 3, and one Grade 5 (0.16%) and two have no CTCAE grade reported yet. Ten events were reported in second-line+ patients (five cases 160 mg, five cases 80 mg) and three events in first-line patients (all at 80 mg). Pneumonitis-like events are under investigation and subject to change

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Anti-tumour efficacy

- Among all evaluable pts, confirmed RECIST responses were observed at all dose levels (20–240 mg once daily)
- Among the 78 pts with centrally tested EGFR T790M+ and confirmed response, the longest duration of response to date is ongoing at >11 months
- Preliminary median duration of response at 80 mg was 8.2 months (95% CI 6.9, not calculable)
- Preliminary median progression-free survival
  - 9.6 months (95% CI 8.3, not calculable) in pts with centrally tested T790M+ (30% maturity, 41/138 events)
  - 2.8 months (95% CI 2.1, 4.3) in pts with centrally confirmed T790M- (71% maturity, 44/62 events)

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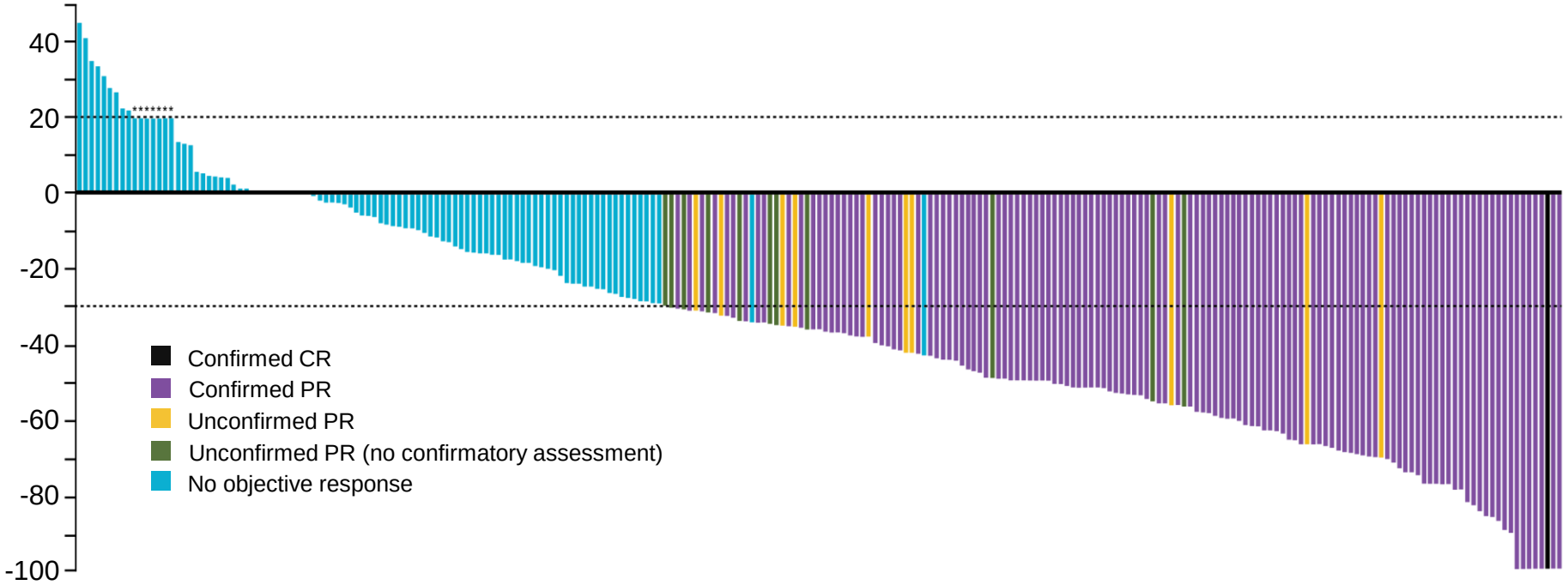
Best change in target lesion size (%) and objective response rate in overall population



- **Confirmed ORR** in the overall population was 51% (123/239; 95% CI 45, 58)
- **DCR (CR+PR+SD)** was 84% (201/239; 95% CI 79, 88)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (239)	21	58	77	62	21
ORR	52%	43%	52%	58%	52%

Patients are eligible for confirmed response if they have two post-baseline RECIST assessments or patients who withdraw/die prior to the second RECIST assessment. CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease. *Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments

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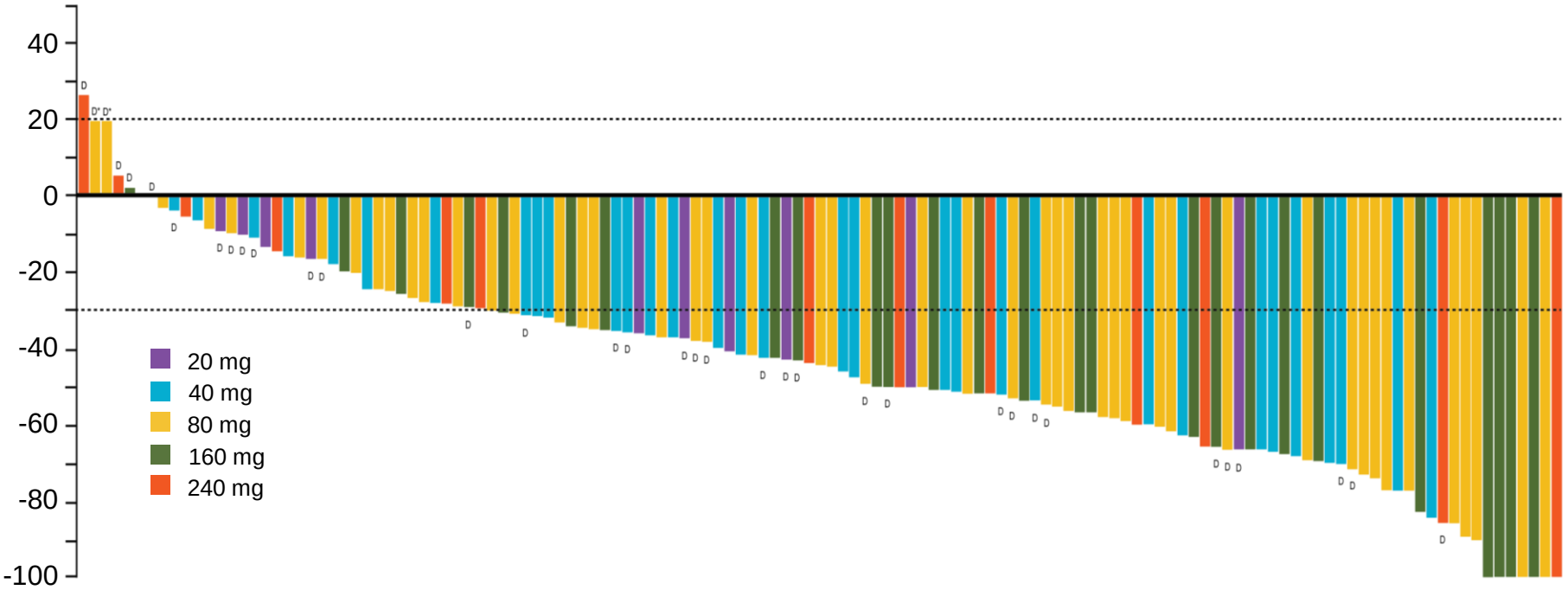
Best change in target lesion size (%) and objective response rate in T790M+ pts (central test)



- **Confirmed ORR** in pts with centrally tested T790M+ was 61% (78/127; 95% CI 52, 70)
- **DCR (CR+PR+SD)** was 95% (121/127; 95% CI 90, 98)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (127)	10	32	43	28	14
ORR	50%	59%	70%	61%	50%

Patients are eligible for confirmed response if they have two post-baseline RECIST assessments or patients who withdraw/die prior to the second RECIST assessment. CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease. *Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments

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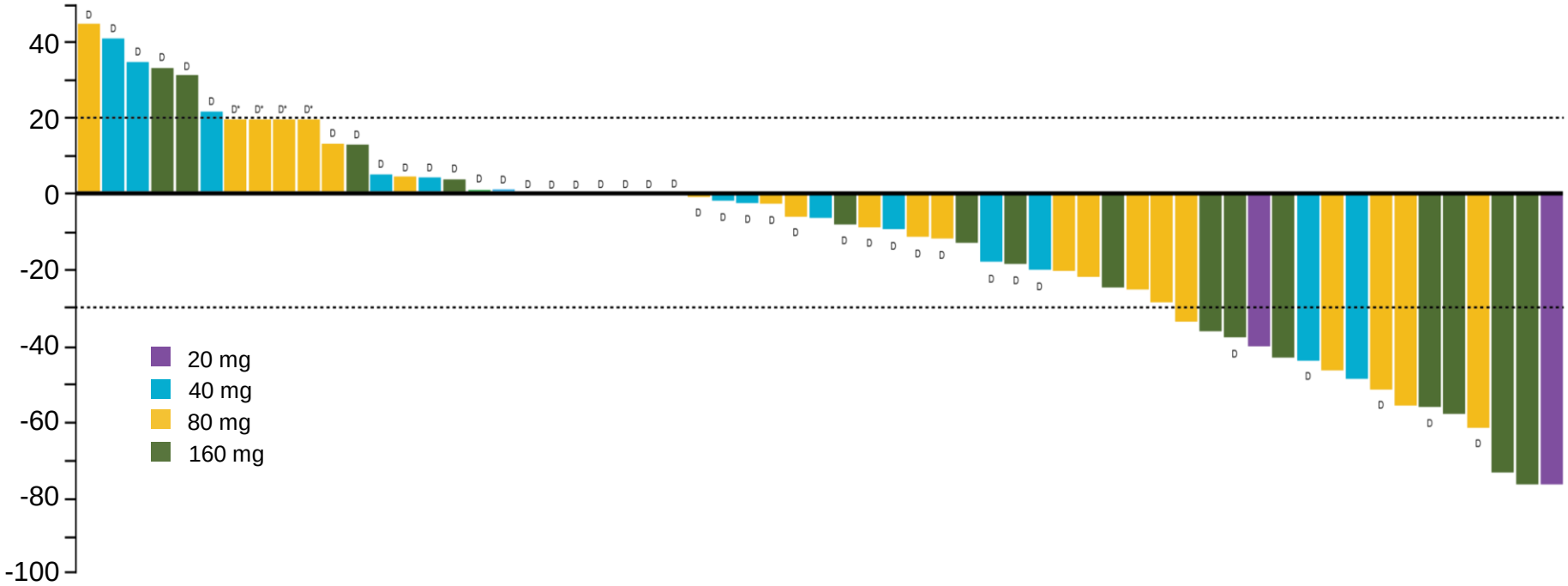
Best change in target lesion size (%) and objective response rate in T790M- pts (central test)



- **Confirmed ORR** in pts with centrally tested T790M- was 21% (13/61; 95% CI 12, 34)
- **DCR (CR+PR+SD)** was 61% (37/61; 95% CI 47, 73)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (127)	3	17	23	18	-
ORR	67%	6%	17%	33%	-

Patients are eligible for confirmed response if they have two post-baseline RECIST assessments or patients who withdraw/die prior to the second RECIST assessment. CI, confidence interval; CR, complete response; D, discontinued; DCR, disease control rate; ORR, overall response rate; PR, partial response; SD, stable disease. *Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments

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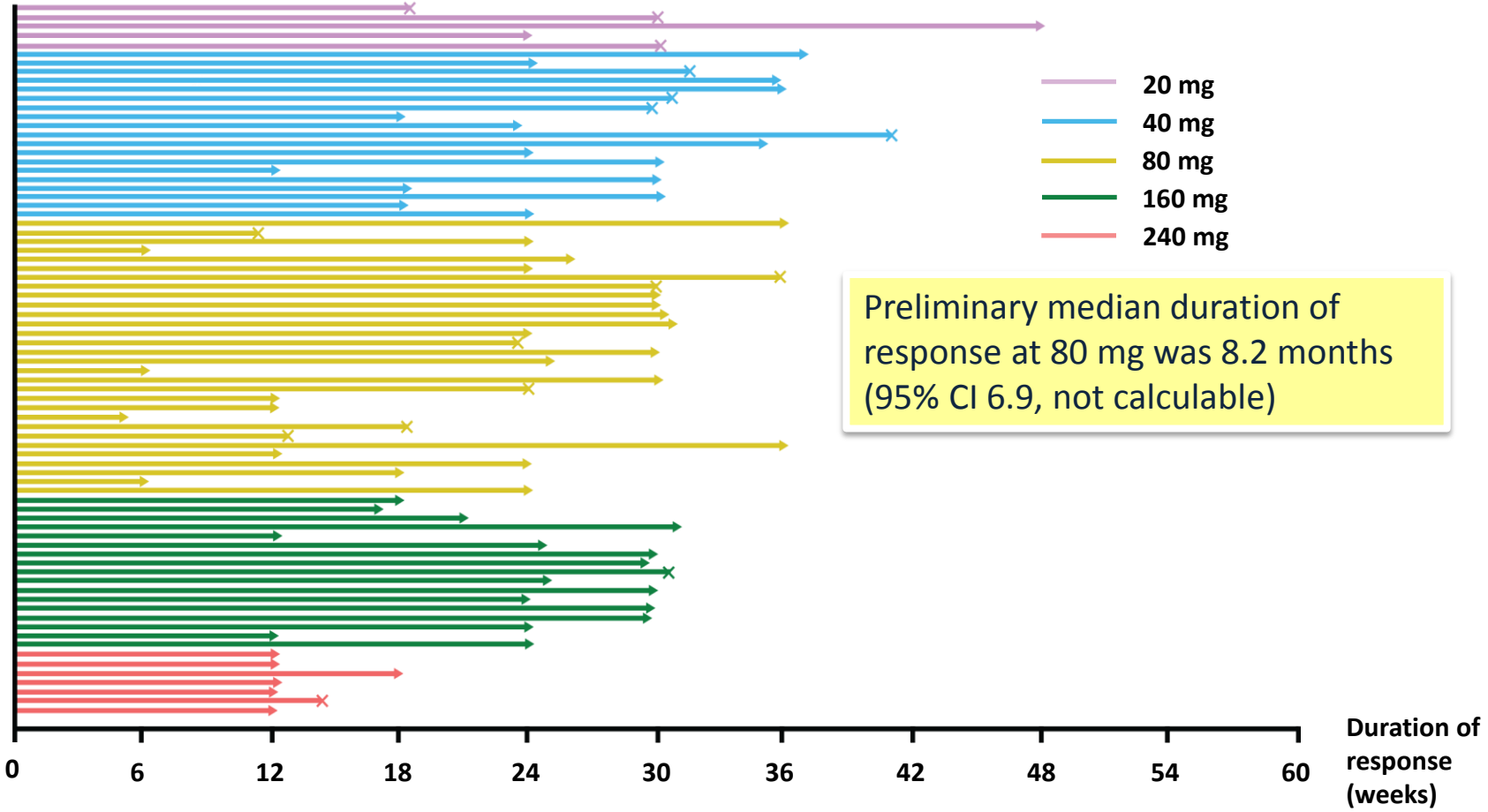
Duration of response by dose, for all patients with a response, T790M+ pts (central test)



X represents first assessment showing end of response; arrow represents censored observations

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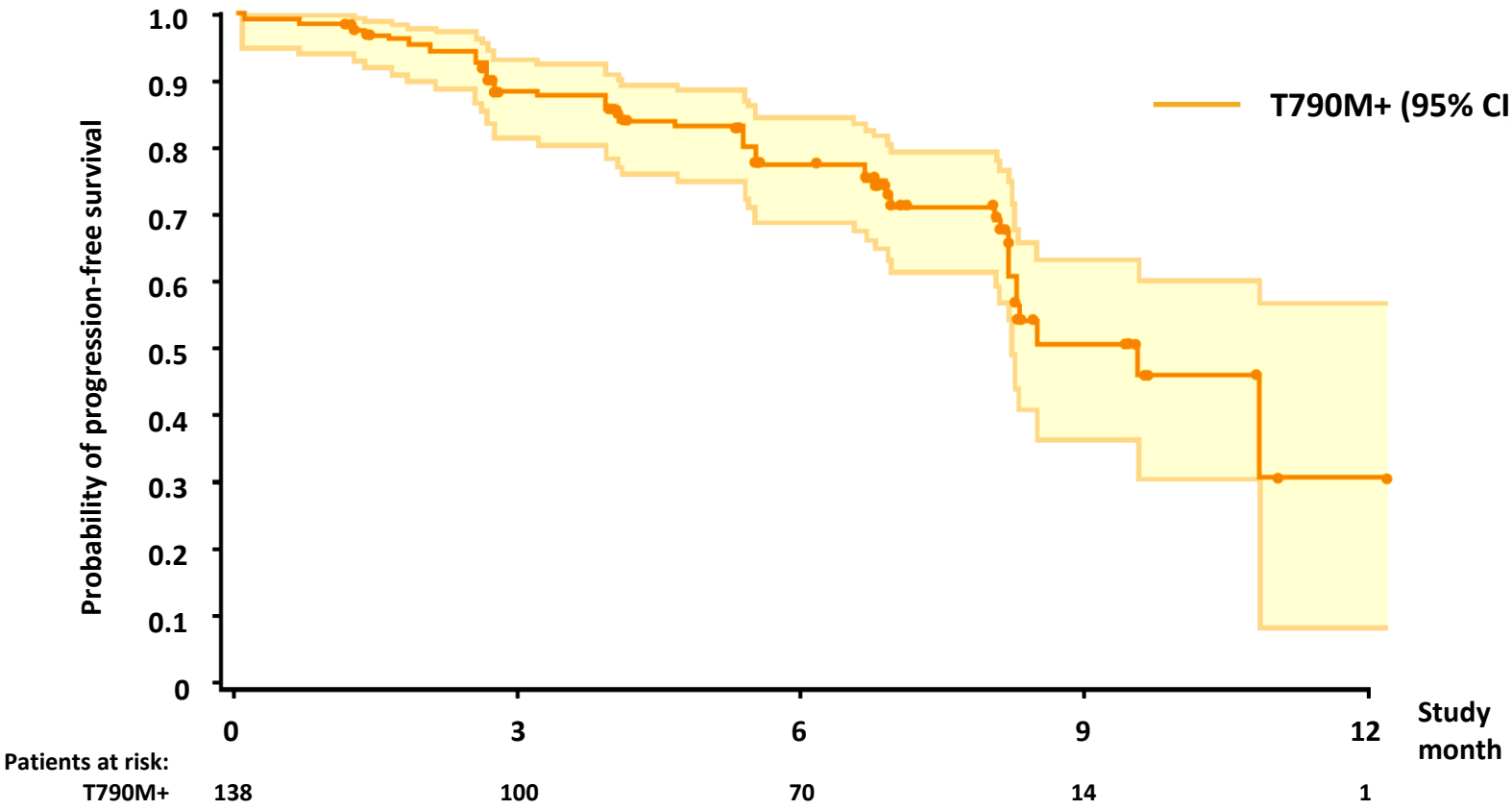
Progression-free survival in T790M+ (central test)



Preliminary median PFS 9.6 months (95% CI 8.3, not calculable)

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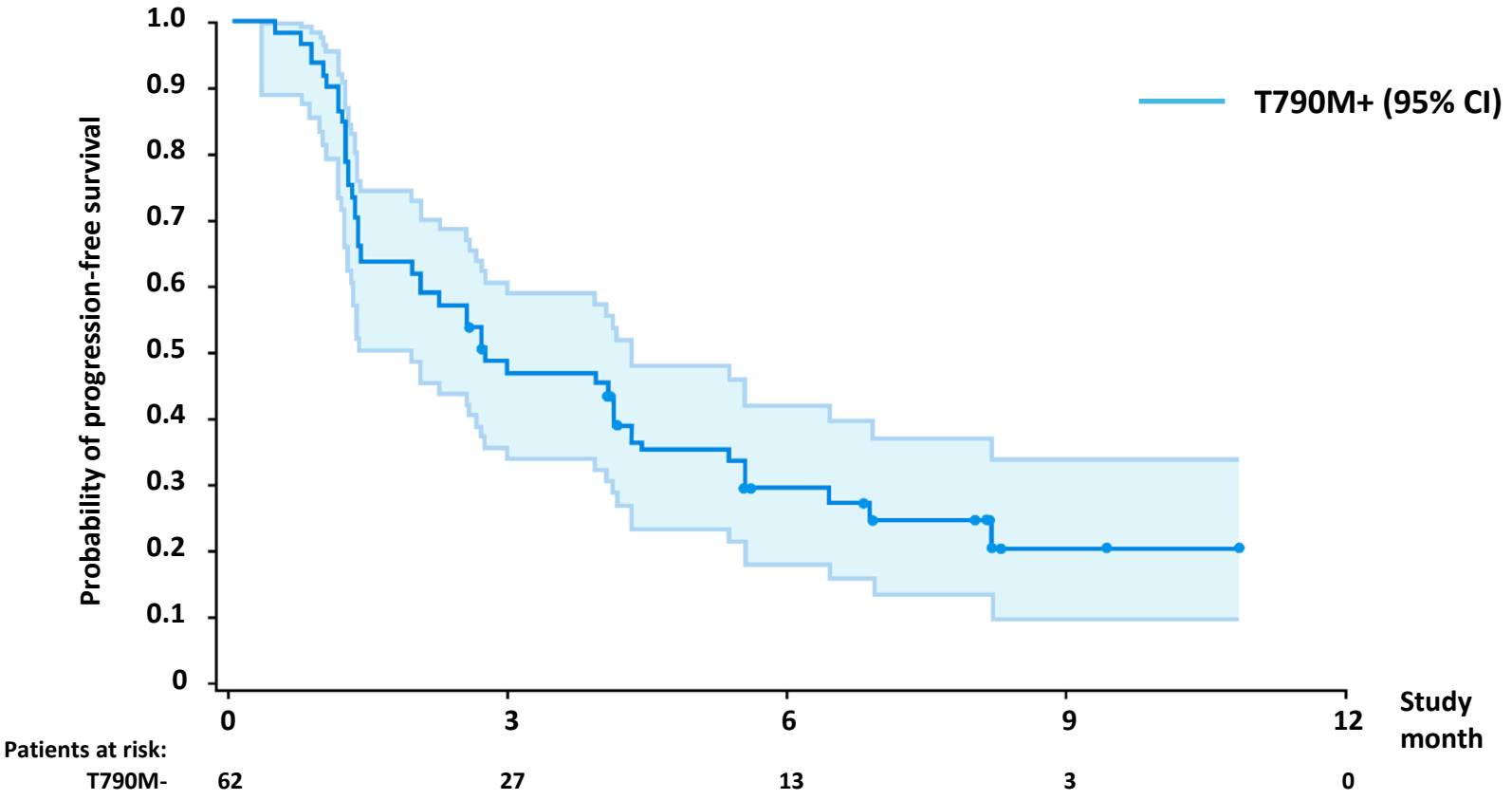
Progression-free survival in T790M- (central test)



Median PFS 2.8 months (95% CI 2.1, 4.3)

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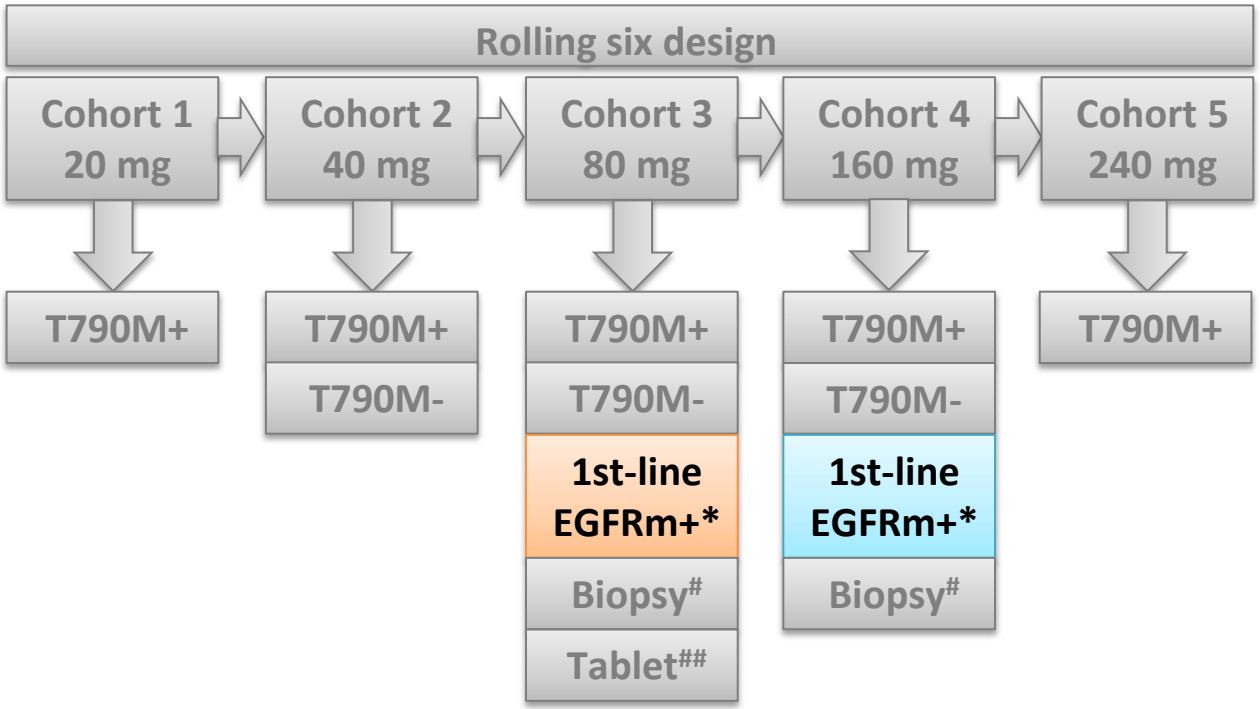
Phase I dose escalation/expansion first-line cohorts

- **Patients with a documented EGFR-TKI-sensitising mutation and who have received no prior therapy for advanced stage NSCLC were enrolled**
- **Patients received AZD9291 once daily as an 80 mg or 160 mg capsule**

Escalation
Not preselected by T790M status

Expansion
Enrollment by local testing followed by central laboratory confirmation (cobas EGFR Mutation Test) of T790M status or by central laboratory testing alone



*Prior therapy not permissible in this cohort. #Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.

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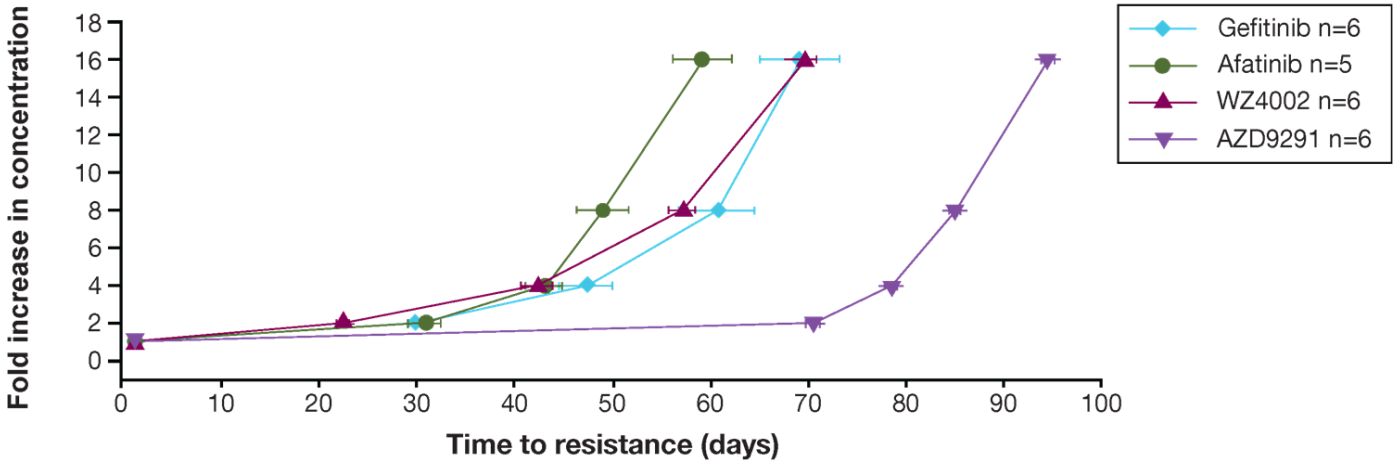
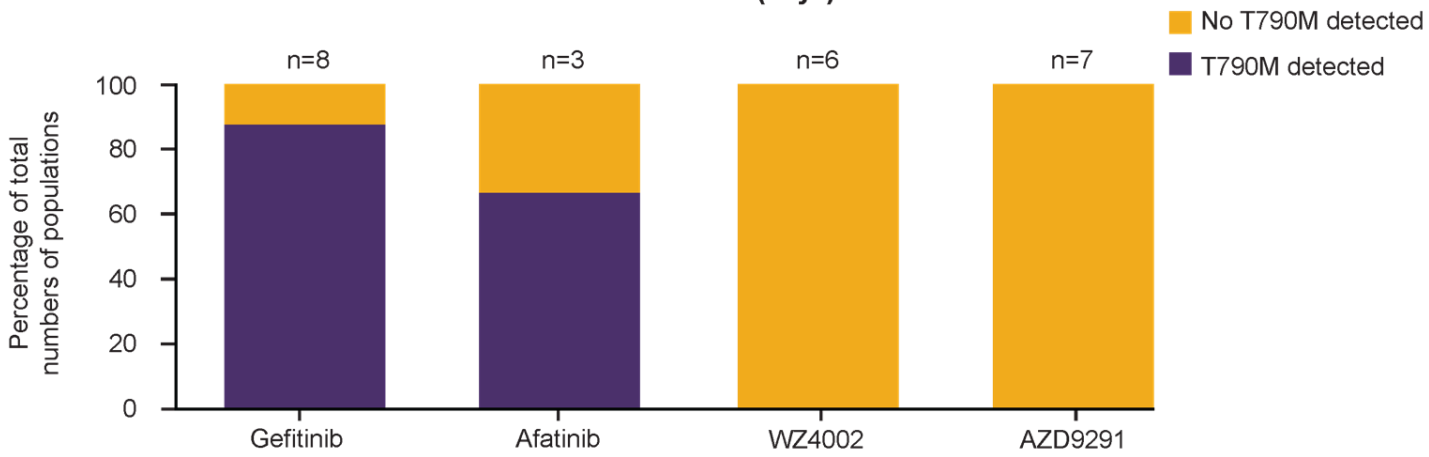
AZD92921 significantly delays resistance in EGFR-mutant

- In preclinical xenografts with EGFR-TKI-sensitising mutations, the appearance of resistance to AZD9291 is delayed compared with other EGFR-TKIs and the resistance is not dependent on T790M





IC50, half-maximal inhibitory concentration

1. Eberlein et al. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 5–9 April 2014; San Diego, CA, abstract 1722.

Patient demographics

As of the data cut-off date (1 August 2014), 30 patients had received AZD9291 at 80 mg/day and 27 at 160 mg/day

Characteristic	AZD9291 first-line cohorts N=57
Gender, n (%) Male/female	**15 / 42** (26 / 74%)
Age, years; median (range)	**63** (38 – 88)
Race, n (%) Caucasian/Asian/other/missing	**13 / 42 / 1 / 1** (23% / 74% / 2 / 2)
WHO performance status, n (%) 0/1	**33 / 24** (58% / 42)
Histology, n (%) Adeno/squamous/other/missing	**55 / 0 / 0 / 2** (96% / 0 / 0 / 4)
EGFR mutation, n (%) Exon 19 deletion/L858R/other/none/unknown	**20 / 22 / 2 / 3 / 10** (35%/39%/4/5/18)
T790M status at study entry, n (%)* Positive/negative/unknown	**5/42/10** (9%/74%/18)

*Tested in a central laboratory.

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Best objective response

Response	AZD9291 80 mg N=30	AZD9291 160 mg N=27	Total N=57
Complete response	0	0	0
Partial response	18	8	**26**
Confirmed	14	0	14
Awaiting confirmation	4	8	12
Stable disease	9	4	**13**
Progressive disease	2	0	2
Not currently evaluable	1	15	16

- **The objective response rate** (confirmed and awaiting confirmation) was 63% (26/41; 95% CI 47, 78)
- **The disease control rate** (CR + PR + SD) was 95% (39/41; 95% CI 83, 99)

16 patients currently not evaluable for response (awaiting follow-up RECIST scan) are not included in the ORR calculation
ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; CI, confidence interval

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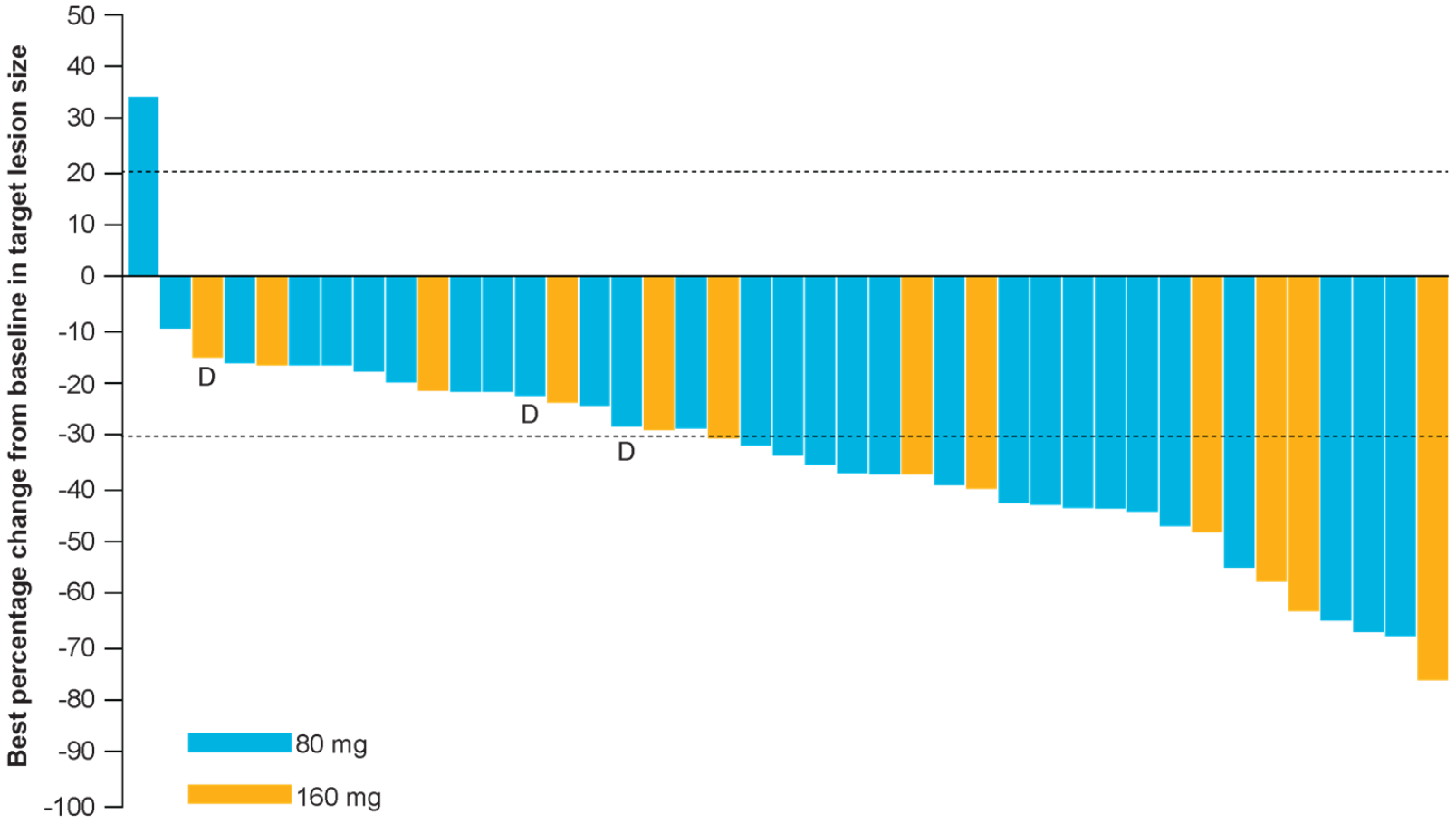
Best percentage change from baseline in target lesion of patients in the first-line cohorts (N=57)



D, discontinued

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All-causality adverse events

- The most common all-causality AEs were rash (56%) and diarrhoea (49%)
  - **No rash or diarrhoea Grade ≥3 events**; maxima for rash and diarrhoea were both Grade 2 (7% and 14% respectively)
  - **Rash incidence**: 60% at 80 mg, 52% at 160 mg
  - **Diarrhoea incidence**: 40% at 80 mg, 59% at 160 mg

	AZD9291 first-line cohort N=57	
Patients with an AE, n %	**Any grade**	**Grade ≥3**
AE by preferred term (all grades), occurring in at least 10% of patients overall		
Rash (grouped terms)*	32 (56%)	0 (0)
Diarrhoea	28 (49%)	0 (0)
Dry skin	12 (21%)	0 (0)
Stomatitis	12 (21%)	0 (0)
Pruritus	10 (18%)	0 (0)
Thrombocytopenia	7 (12%)	1 (2)
Fatigue	7 (12%)	0 (0)

*Dermatitis acneiform is included in the grouped rashes

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Conclusions

NSCLC with radiological progression while on prior therapy with EGFR-TKI

- AZD9291 demonstrates promising efficacy (confirmed ORR: 51%) in this global Phase I study
- The RR in pts with centrally confirmed T790M+ disease (80 mg confirmed ORR 70%), appears to be higher than that previously reported with platinum-containing doublet chemotherapy post EGFR-TKI (ORR 20–30%)[1–5]
- While the data are still immature (30% maturity), the current median PFS in patients with T790M+ EGFR-TKI-resistant NSCLC (9.6 months) is very encouraging
- AZD9291 was well tolerated at all dose levels tested and a non-tolerated dose has not been defined

1. Gridelli et al. J Clin Oncol 2012;30:3002–3011; 2. Goldberg et al. J Thorac Oncol 2012;7:1602–1608;
3. Maemondo et al. N Engl J Med 2010;362:2380–2388; 4. Wang et al. J Cancer Res Clin Oncol 2012;138:2069–2077;
5. Wu et al. Lung Cancer 2011;72(2):205-212

Future clinical development

AURA (NCT01802632)	• Phase II extension – further assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC
AURA 2 (NCT02094261)	• Confirmatory global Phase II – assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC
AURA 3 (NCT02151981; recruiting)	• **Phase III – AZD9291 vs platinum-based doublet** chemotherapy in second-line patients with T790M+, advanced/metastatic NSCLC who have progressed following prior therapy with an EGFR-TKI

Conclusions

For the first-line cohorts

- Early data with AZD9291 as first-line therapy in pts with EGFRm+ advanced NSCLC demonstrates clinical activity (ORR: 63%, DCR:95%) and a manageable tolerability profile

- This supports the further clinical evaluation of AZD9291 as first-line therapy of EGFRm+ advanced NSCLC

Future clinical development

AURA (NCT01802632)	• Phase II extension – further assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC
AURA 2 (NCT02094261)	• Confirmatory global Phase II – assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC
FLAURA (NCT02296125)	• AZD9291 Versus Gefitinib or Erlotinib in EGFRm+ advanced NSCLC patients

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