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Osimertinib (AZD9291) as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts

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Disclosures

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James C-H Yang – Advisory board: Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, AstraZeneca, Astellas, Bayer, MSD, Merck Serono, Pfizer, Novartis, Clovis Oncology, Celgene

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Introduction

- EGFR-TKIs (gefitinib, erlotinib and afatinib) are recommended as first-line therapy for patients with EGFR-TKI sensitising EGFRm advanced NSCLC[1], with median progression-free survival (PFS) of 9.2–13.1 months[2–11]
- Osimertinib is an irreversible EGFR-TKI, selective for both EGFR-TKI sensitising mutations and T790M resistance mutations[12,13]
- *In vitro*, osimertinib delayed the emergence of resistance in EGFRm Ex19del PC9 cells compared with gefitinib and afatinib[14]
- Osimertinib demonstrated a deeper and more durable response compared to gefitinib in PC9 *in vivo* tumour xenograft models[12]
- Here we present updated efficacy and safety results from two Phase I expansion cohorts who received osimertinib 80 mg or 160 mg once daily as first-line treatment for EGFRm advanced NSCLC in the AURA study (NCT01802632)

1. Reck et al. Ann Oncol 2014;25:(suppl 3)iii27–iii39; 2. Fukuoka et al. J Clin Oncol 2011;29:2866–2874; 3. Rosell et al. Lancet Oncol 2012;13:239–246;
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10. Park et al. Presented at ESMO Asia 2015, LBA2_PR; 11. Douillard et al. Br J Cancer 2014;110:55–62; 12. Cross et al. Cancer Discov 2014;4:1046–1061;
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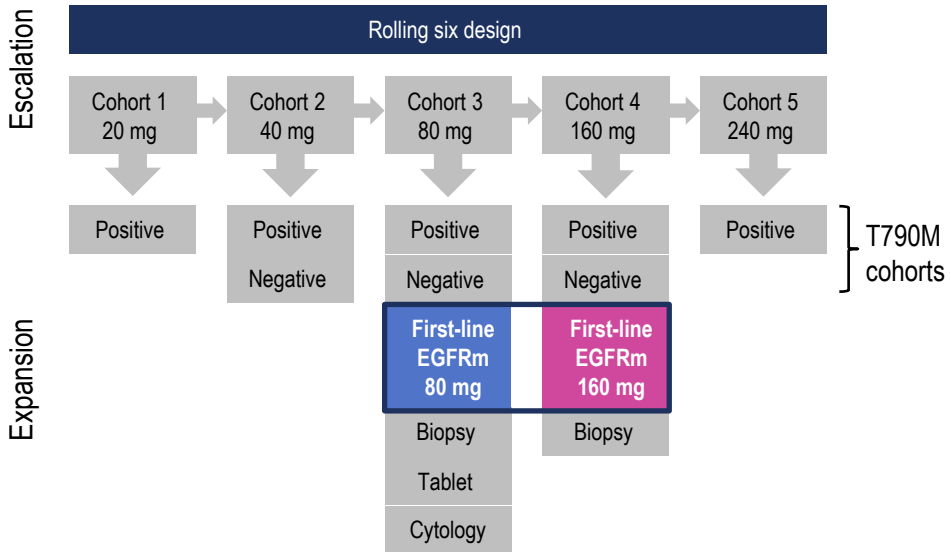
EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation-positive; Ex19del, exon 19 deletion;
NSCLC, non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

AURA Phase I dose escalation/expansion: study design

First-line cohort objective

- Safety and tolerability of osimertinib (80 mg or 160 mg qd orally) as first-line therapy for patients with EGFRm advanced NSCLC



Key inclusion criteria:

- Aged ≥18 (≥20 in Japan)
- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Measurable disease at baseline
- Patients must have EGFR mutation positive NSCLC (local test)

Key exclusion criteria:

- Prior history of ILD
- Symptomatic brain metastases

Data cut-off: 4 January 2016
Data from cohorts in grayed out boxes are not included in the analyses reported here
ILD, interstitial lung disease; qd, once-daily dosing

AURA EGFRm first-line cohorts: baseline demographics

- 60 patients received osimertinib (80 mg [n=30] or 160 mg [n=30] qd orally) and were included in the evaluable for response population*
- Data cut-off, 4 January 2016; median length of RECIST 1.1 follow-up: 16.6 months (80 mg: 16.5 months; 160 mg: 16.6 months)
- 21 (35%) patients discontinued treatment
- 39 (65%) patients are still receiving study treatment: 19 ongoing at 80 mg; 20 ongoing at 160 mg

Characteristic	80 mg n=30	160 mg n=30	Total N=60
Gender, %; Male / Female	33 / 67	17 / 83	25 / 75
Age, median (range); years	63 (40–77)	65 (38–91)	64 (38–91)
Race, % Caucasian / Asian / Other† / Not reported	20 / 77 / 3 / 0	27 / 67 / 3 / 3	23 / 72 / 3 / 2
EGFR mutation type by local test, % Ex19del / L858R / Positive subtype unknown / Other	37 / 47 / 3 / 13	43 / 37 / 13 / 7	40 / 42 / 8 / 10
De novo T790M status by central test, % Positive / negative / unknown	13 / 70 / 17	3 / 83 / 13	8‡ / 77 / 15

Population: all dosed patients; data cut-off: 4 January 2016
*Evaluable for response population: dosed patients with a baseline RECIST assessment
†Other includes Black or African American, American Indian or Alaskan native
‡A total of 5 patients had *de novo* T790M positive NSCLC by central test
RECIST, Response Evaluation Criteria In Solid Tumors

Summary of adverse events in osimertinib EGFRm first-line cohorts

AE category, all causality, n (%)	Safety analysis set*		
	80 mg n=30	160 mg n=30	Total N=60
Any AE	30 (100)	30 (100)	60 (100)
Any AE ≥Grade 3	13 (43)	15 (50)	28 (47)
Any AE leading to death	0	0	0
Any AE leading to dose interruption	8 (27)	9 (30)	17 (28)
Any AE leading to dose reduction†	3 (10)	14 (47)	17 (28)
Any AE leading to discontinuation	4 (13)	2 (7)	6 (10)
Any serious AE	11 (37)	7 (23)	18 (30)
AE category, drug-related‡			
Any AE	29 (97)	30 (100)	59 (98)
Any AE ≥Grade 3	4 (13)	6 (20)	10 (17)
Any AE leading to discontinuation	2 (7)	1 (3)	3 (5)
Any serious AE	4 (13)	1 (3)	5 (8)

Data cut-off: 4 January 2016
*Safety analysis set: all patients dosed
†Three / three patients in the 80 mg cohort had a single dose reduction to 40 mg, 13 / 14 patients in the 160 mg cohort had a single dose reduction to 80 mg, and one patient had two dose reductions, first to 80 mg then to 40 mg
‡As assessed by the investigator
AE, adverse event

All causality adverse events in osimertinib EGFRm first-line cohorts

AEs occurring in ≥25% of patients overall, n (%)	Safety analysis set*					
	80 mg n=30		160 mg n=30		Total N=60	
	Any grade	Gr ≥3	Any grade	Gr ≥3	Any grade	Gr ≥3
Rash (grouped terms)	21 (70)	0	26 (87)	1 (3)	47 (78)	1 (2)
Diarrhoea	18 (60)	0	26 (87)	2 (7)	44 (73)	2 (3)
Dry skin (grouped terms)	17 (57)	0	18 (60)	0	35 (58)	0
Paronychia (grouped terms)	11 (37)	0	19 (63)	2 (7)	30 (50)	2 (3)
Stomatitis	13 (43)	0	15 (50)	1 (3)	28 (47)	1 (2)
Constipation	10 (33)	0	7 (23)	0	17 (28)	0
Pruritus	8 (27)	0	8 (27)	0	16 (27)	0
Decreased appetite	8 (27)	0	7 (23)	0	15 (25)	0
Nausea	7 (23)	1 (3)	8 (27)	0	15 (25)	1 (2)
Select AEs						
ILD (grouped terms)†	3 (10)	0	0	0	3 (5)	0
Hyperglycaemia	1 (3)	0	2 (7)	0	3 (5)	0
QT prolongation	2 (7)	0	3 (10)	0	5 (8)	0

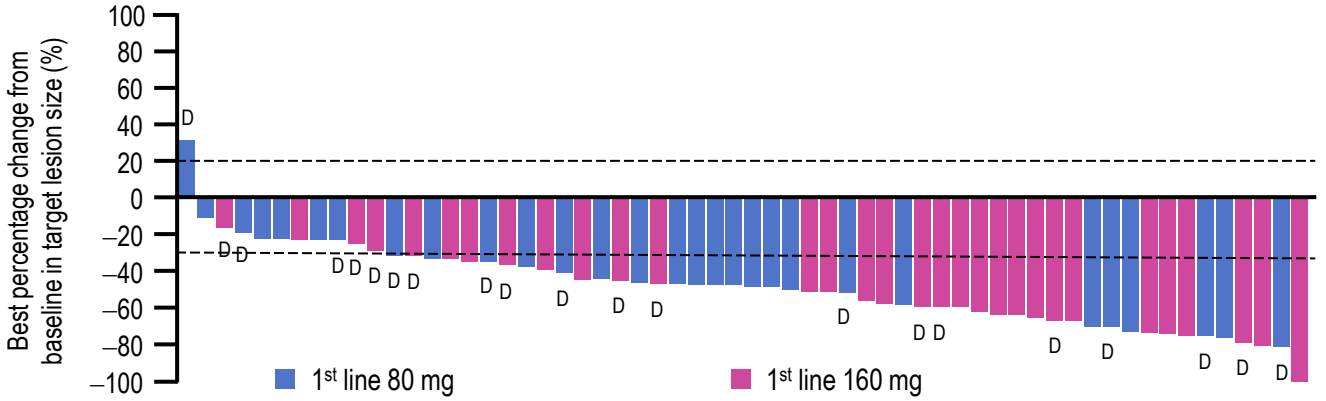
Data cut-off: 4 January 2016

*Safety analysis set: all patients dosed

†As of June 1, 2015, of more than 1200 patients across all studies dosed with osimertinib, ILD grouped term events were reported in approximately 2.9% of patients (35 events): nine Grade 1,six Grade 2, 18 Grade ≥3, two currently ungraded. Of these, a total of four patients are reported to have died due to ILD (Grade 5)

Gr, grade

Tumour response to osimertinib in EGFRm first-line cohorts (investigator assessed)



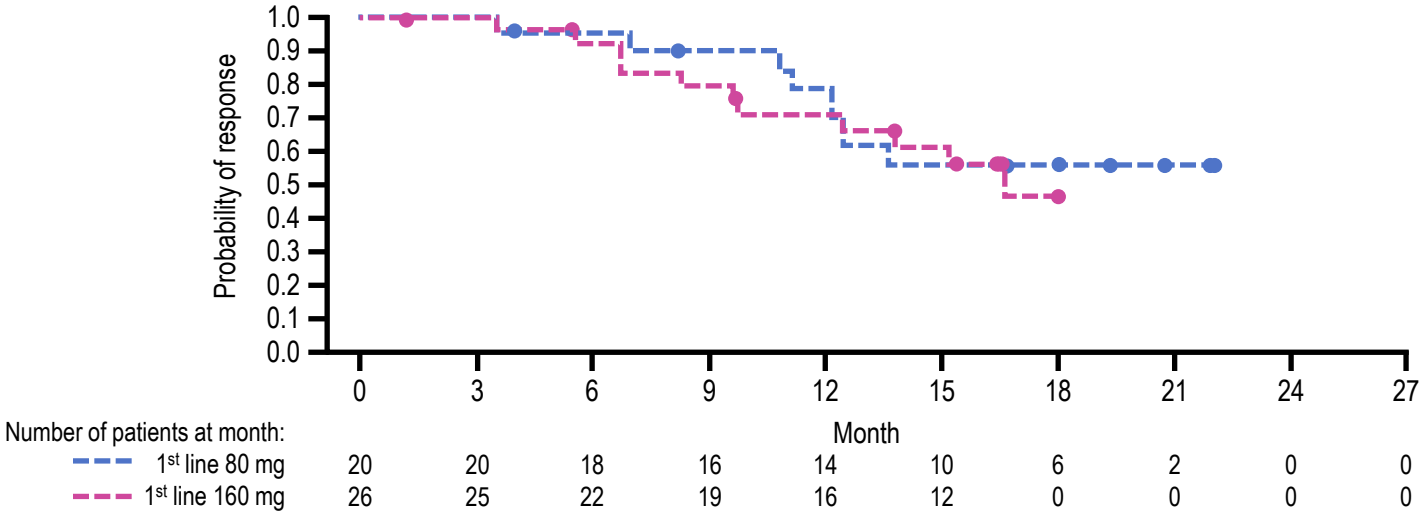
	80 mg n=30	160 mg n=30	Total N=60
Confirmed ORR	67% (95% CI 47, 83)	87% (95% CI 69, 96)	77% (95% CI 64, 87)
Disease control rate*	93% (95% CI 78, 99)	100% (95% CI 88, 100)	98% (95% CI 89, 100)
Best objective response			
Complete response	0	2	2
Partial response	20	24	44
Stable disease ≥6 weeks	8	4	12
Progressive disease	2	0	2

Population: evaluable for response; data cut-off: 4 January 2016 RECIST 1.1, programmatically calculated from investigator-recorded tumour measurement

*Complete response, partial response, stable disease

CI, confidence interval; D, discontinuation; ORR, objective response rate

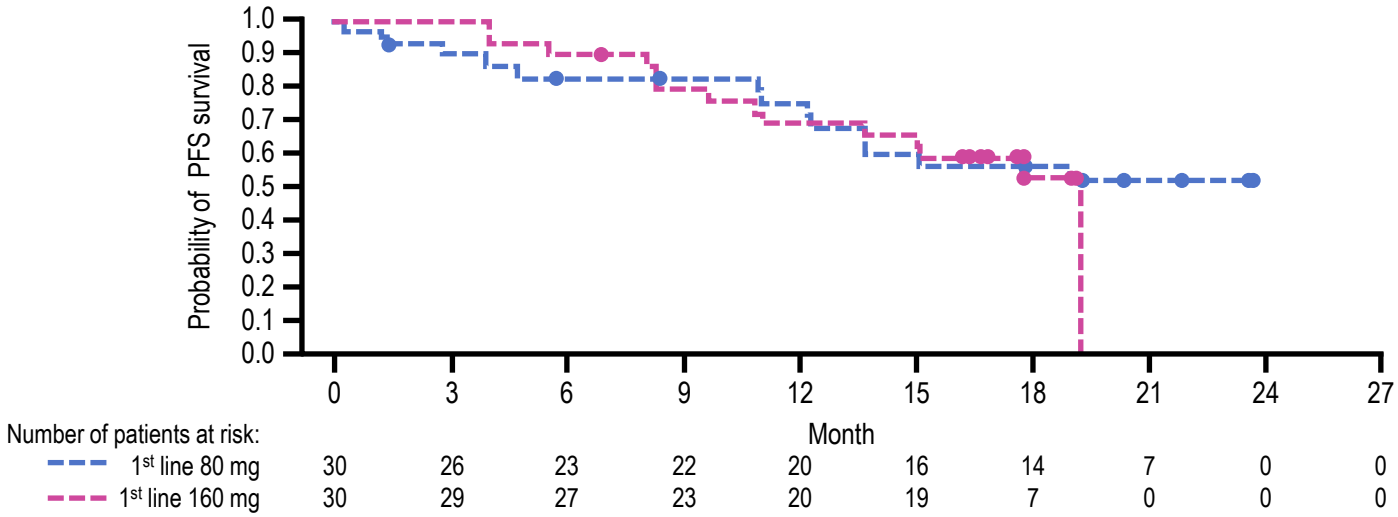
DoR in osimertinib EGFRm first-line cohorts (investigator assessed)



	80 mg n=20	160 mg n=26	Total N=46
Median DoR,* months (95% CI)	NC (12.2, NC)	16.7 (9.7, NC)	NC (12.5, NC)
Maximum DoR, months	22.1 ongoing	18.0 ongoing	22.1 ongoing
Remaining in response,† % (95% CI)			
12 months	79 (52, 91)	71 (48, 85)	74 (58, 85)
18 months	56 (31, 75)	NC	53 (36, 67)

Population: evaluable for response and patients with objective response; data cut-off: 4 January 2016
Circles on the Kaplan-Meier plot denote censored observations
*Duration of response is the time from first documentation of response until date of progression or death or last evaluable RECIST assessment for patients who do not progress
†Calculated using Kaplan-Meier technique
DoR, duration of response; NC, not calculable

PFS in osimertinib EGFRm first-line cohorts (investigator assessed)



	80 mg n=30	160 mg n=30	Total N=60
Median PFS,* months (95% CI)	NC (12.3, NC)	19.3 (11.1, 19.3)	19.3 (13.7, NC)
Remaining alive and progression-free,† % (95% CI)			
12 months	75 (55, 88)	69 (49, 83)	72 (59, 82)
18 months	57 (36, 73)	53 (32, 70)	55 (41, 67)

Population: safety analysis set; data cut-off: 4 January 2016
Progression events that do not occur within 14 weeks of the last evaluable assessment (or first dose) are censored
Circles on the Kaplan-Meier plot denote censored observations
*Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
†Calculated using the Kaplan-Meier technique

Clinical outcome in patients with *de novo* T790M positive NSCLC

- A total of 5 (8%) patients had *de novo* T790M positive NSCLC at study entry (central testing)*

Dose	Gender, M/F	Race	Age, years	Best objective response	DoR, months
80 mg	F	Asian	50	Partial response	12.2+
80 mg	F	Asian	60	Partial response	12.5
80 mg	F	Caucasian	61	Partial response	16.8+
80 mg	F	Caucasian	49	Partial response	20.7+
160 mg	M	Asian	59	Partial response	18.0+

*1 patient with single *de novo* T790M mutation without co-existing sensitising mutation, 4 patients with T790M/L858R co-existing sensitising mutation; +, response ongoing in 4/5 patients

Conclusions

- In treatment-naïve patients with EGFRm locally advanced or metastatic NSCLC, osimertinib treatment results in high ORR, promising PFS and manageable tolerability profile

- In the overall population:
  - Confirmed ORR was 77%, with a median PFS of 19.3 months
  - 55% of patients were progression free at 18 months
  - Median duration of response has not yet been reached

- The Phase III FLAURA study (NCT02296125) in treatment-naïve patients with EGFRm advanced NSCLC is ongoing; comparing osimertinib 80 mg once daily versus current standard of care EGFR-TKIs (gefitinib/erlotinib)

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