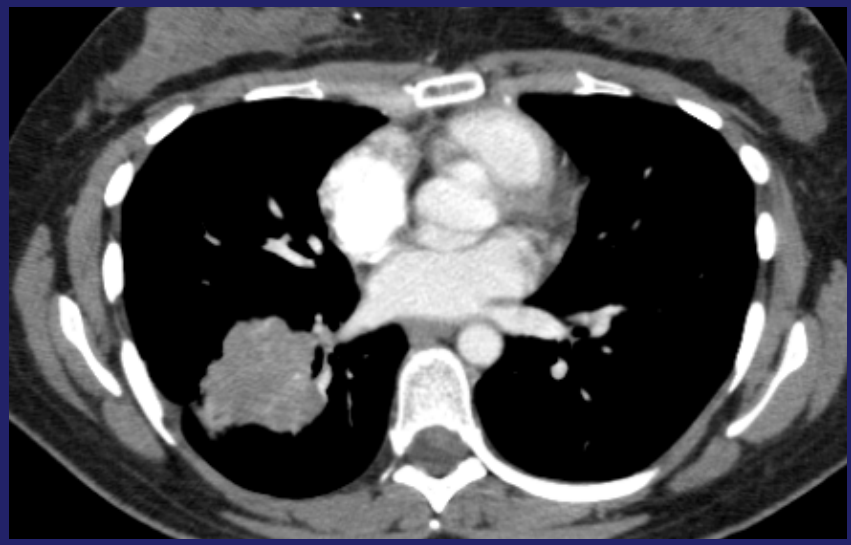
Osimertinib and Brain Metastasis

Roy S. Herbst MD, PhD
Yale Cancer Center

Case

- 39-year-old woman never-smoker presents with dry cough.
- PS = 1.
- CT scan: RLL lung mass (5.7 cm).
- PET CT – RLL mass and subcarinal node, FDG avid.
- EBUS with FNA of subcarinal node positive for lung adenocarcinoma. TTF1+.
- 3 Liver metastases are seen.
- EGFR exon 19 deletion is present.
- Brain MRI negative for intracranial metastatic disease.

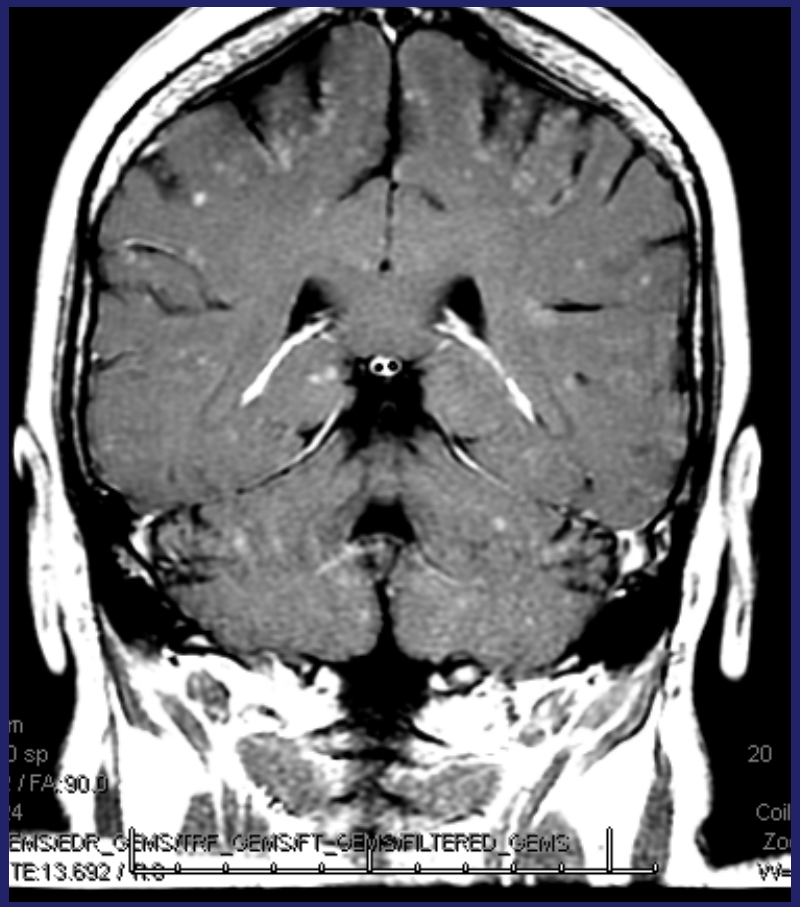


Case

The patient receives erlotinib with no evidence of disease 2 years later.

Case

- After 2 years she develops subtle word finding difficulties. MRI of the brain shows leptomeningeal carcinomatosis with innumerable superficial cortical metastases.
- PET-CT shows a continued complete response outside of the CNS.



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IASLC
International Association for the Study of Lung Cancer
IASLC 17TH WORLD CONFERENCE ON LUNG CANCER
WWW.IASLC.ORG DECEMBER 4–7, 2016 VIENNA, AUSTRIA

Randomised Phase III study of osimertinib vs platinum-pemetrexed for *EGFR* T790M-positive advanced NSCLC (AURA3)

Vassiliki A Papadimitrakopoulou[1], Yi-Long Wu[2], Myung-Ju Ahn[3], Suresh S Ramalingam[4], Marina Chiara Garassino[5], Hye Ryun Kim[6], Frances A Shepherd[7], Hiroaki Akamatsu[8], Willemijn SME Theelen[9], Chee Khoon Lee[10], Martin Sebastian[11], Alison Templeton[12], Marcelo Marotti[12], Serban Ghiorghiu[12], Tony Mok[13]

[1]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China; [3]Samsung Medical Center, Seoul, Republic of Korea; [4]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [5]Medical Oncology Department, Thoracic Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [6]Department of Internal Medicine, Division of Medical Oncology, Yonsei University College of Medicine, Seoul, Republic of Korea; [7]Princess Margaret Cancer Centre, Toronto, Canada; [8]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan; [9]Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [10]St George Hospital, Clinical Research Unit, Division of Cancer Services, Pitney Clinical Sciences Building, Kogarah, New South Wales, Australia; [11]University Hospital Frankfurt, Goethe University, Frankfurt am Main, Germany; [12]AstraZeneca, Cambridge, UK; [13]Key Laboratory of South China, Department of Clinical Oncology, The Chinese University of Hong Kong, Sha Tin, Hong Kong

Presented by VA Papadimitrakopoulou at the World Conference on Lung Cancer 2016
Plenary Session: PL03 Presidential Symposium (abstract PL03.03)

AURA3 study design

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour *EGFR* T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

R 2:1

Osimertinib (n=279)
80 mg orally
QD

Platinum-pemetrexed (n=140)
Pemetrexed 500 mg/m^2 + carboplatin AUC5 *or* cisplatin 75 mg/m^2
Q3W for up to 6 cycles
+ optional maintenance pemetrexed#

Endpoints

Primary:

- PFS by investigator assessment (RECISTv1.1)

Secondary and exploratory:

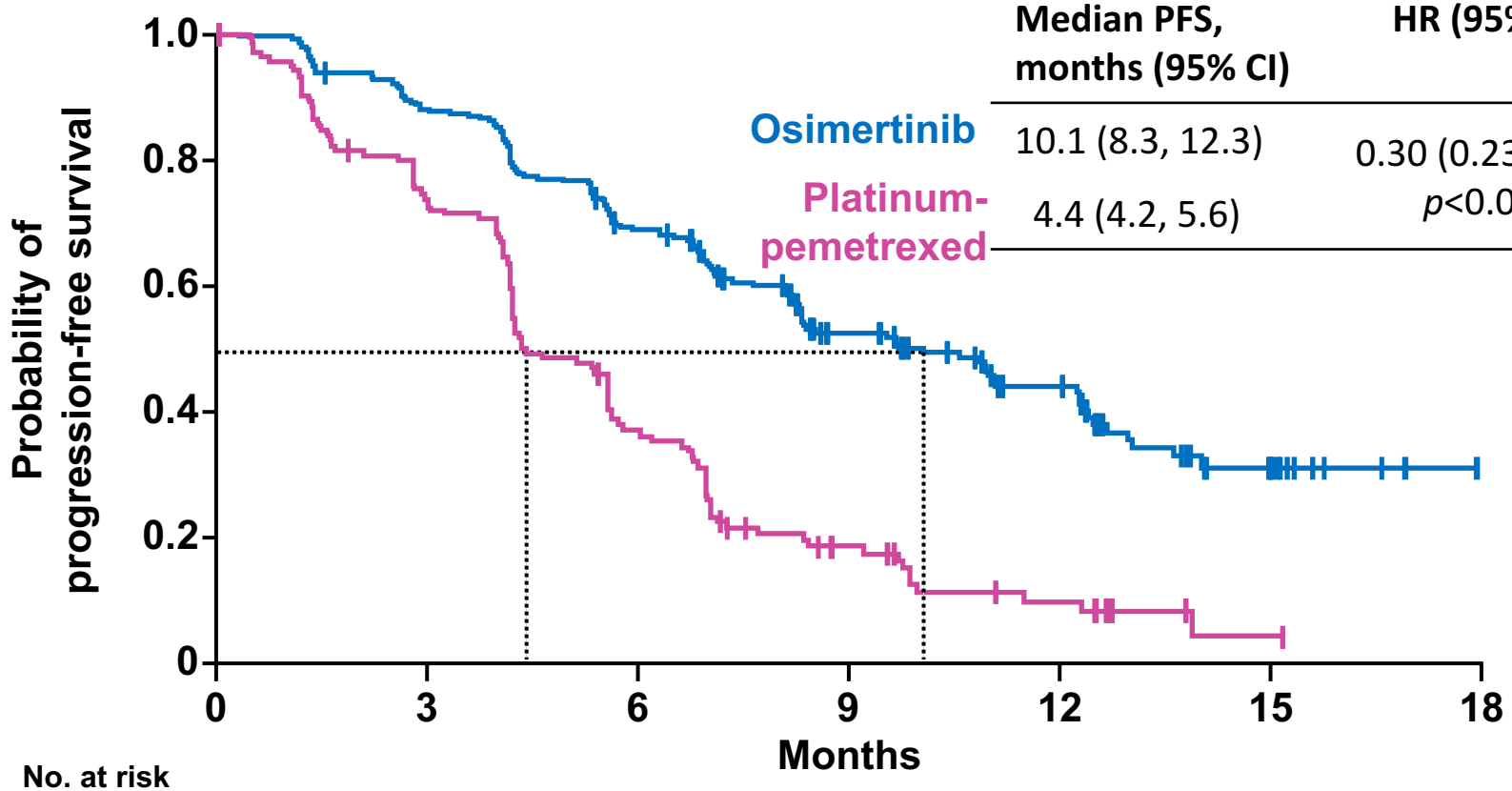
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

- Patients were stratified at randomisation based on ethnicity (Asian/Non-Asian)
- RECISTv1.1 assessments performed every 6 weeks until objective disease progression; patients could receive study treatment beyond RECISTv1.1 defined progression as long as they experienced clinical benefit
- With 221 events of progression or death, the study would have 80% power to reject the null hypothesis of no significant difference in duration of PFS between the two treatment groups, assuming a treatment effect HR of 0.67 at 5% two-sided significance

*Defined as not requiring corticosteroids for 4 weeks prior to study treatment; #For patients whose disease had not progressed after 4 cycles of platinum-pemetrexed
HR, hazard ratio; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria In Solid Tumors; WHO, World Health Organization

AURA3 primary endpoint: PFS by investigator assessment



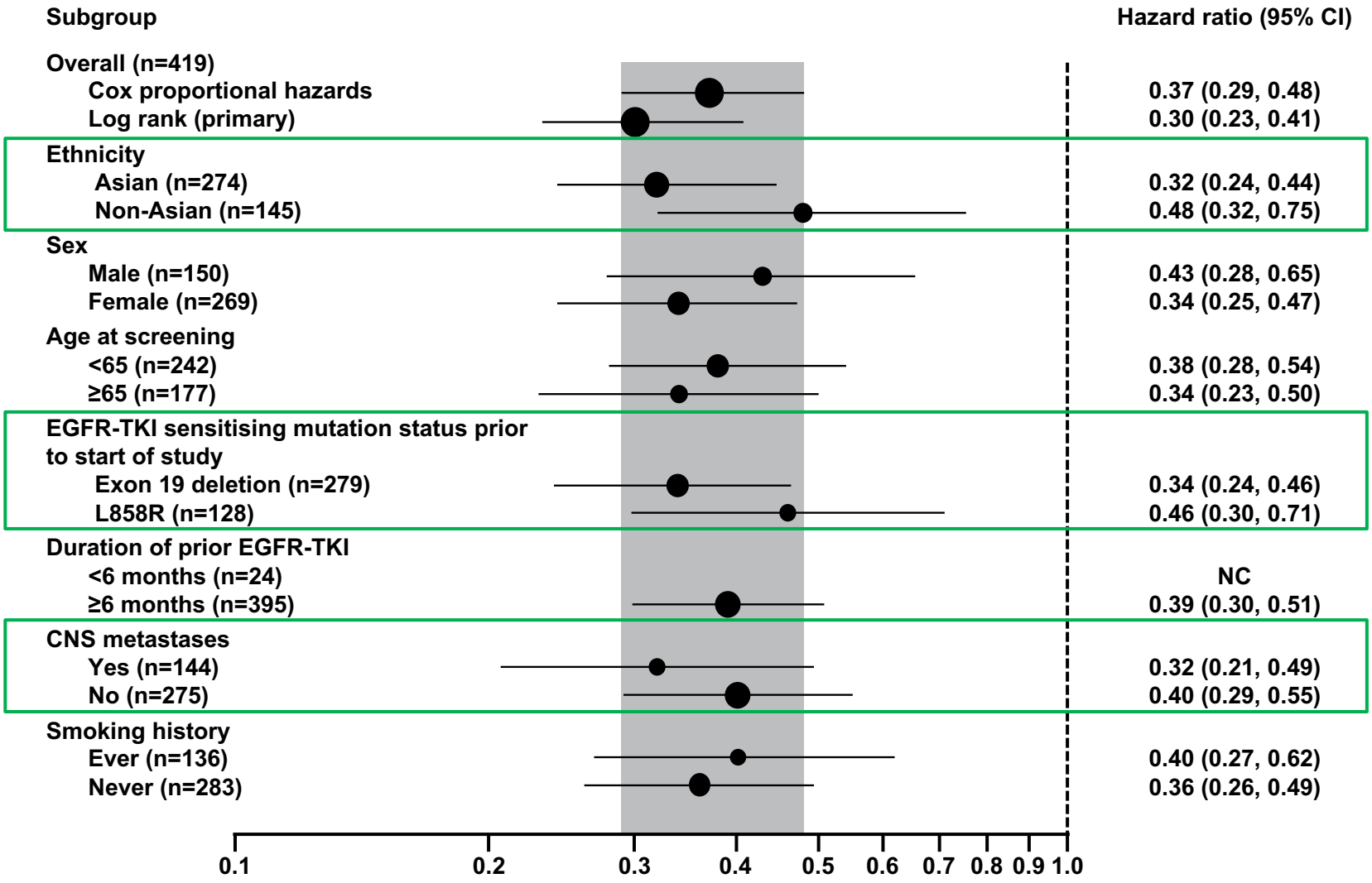
	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3, 12.3)	0.30 (0.23, 0.41)
Platinum-pemetrexed	4.4 (4.2, 5.6)	*p*<0.001

No. at risk							
Osimertinib	279	240	162	88	50	13	0
Platinum-pemetrexed	140	93	44	17	7	1	0

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

PFS benefit with osimertinib observed across all subgroups in AURA3

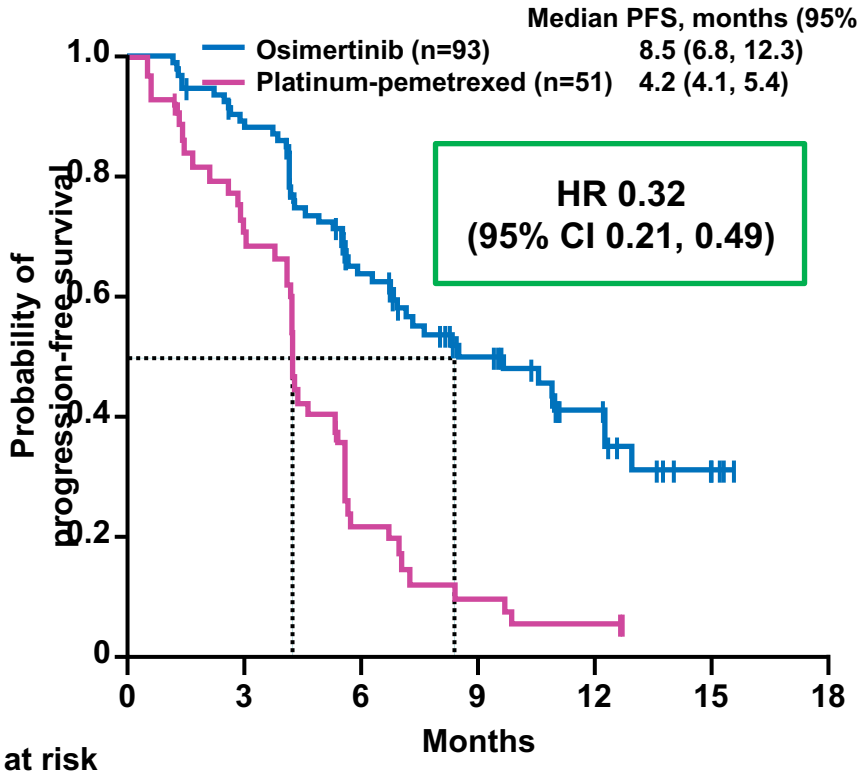


Population: intent-to-treat

HR <1 implies a lower risk of progression on osimertinib 80 mg. Cox proportional hazards model includes randomised treatment, the subgroup covariate of interest, and the treatment by subgroup interaction. Size of circle is proportional to the number of events. Overall population analysis was performed using a Cox proportional hazards model and the primary analysis (U and V statistics) from stratified log-rank test. If there were <20 events in a subgroup then the analysis was not performed; NC, non-calculable

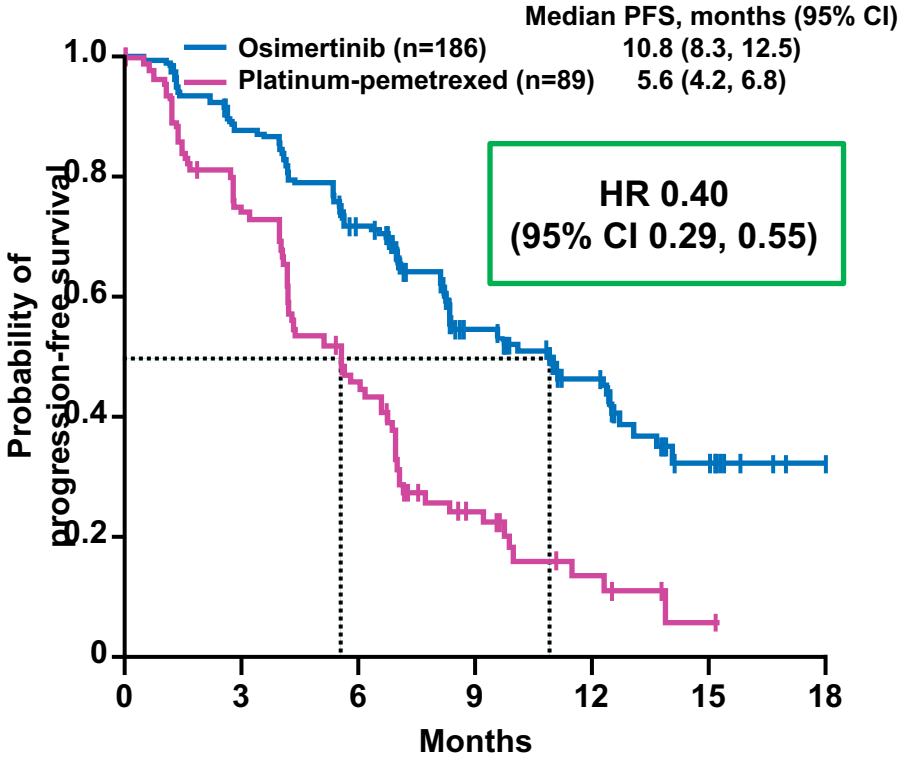
PFS benefit in AURA3 patients with CNS metastases at baseline

With CNS metastases



No. at risk							
Osimertinib	93	80	46	27	14	4	0
Platinum-pemetrexed	51	32	9	4	2	0	0

Without CNS metastases



Osimertinib	186	160	116	61	36	9	0
Platinum-pemetrexed	89	61	35	13	5	1	0

Population: intent-to-treat

Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.

Tick marks indicate censored data. CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy.

Properties of Brain Penetrating EGFR Inhibitors

	Osimertinib	AZD3759
Structure	Pyrimidine	Quinazoline
Inhibit T790M ?	Yes	No
Dose	80 mg approved 20 – 240 mg tested	50 – 500 mg
Brain penetration – preclinical models	$K_{puu,\ brain}$ = 0.39[1]	$K_{puu,\ brain}$ = 1.3[3]
Brain penetration - humans	$K_{puu,\ CSF}$ = 0.5[2]	$K_{puu,\ CSF}$ = 1.0[4]

Gefitinib $K_{puu,\ brain}$ = 0.021

Kpuu = the ratio of the unbound tissue (brain) concentration over the unbound plasma concentration

[1]Ballard et al. CCR, *in press*; [2]Ballard et al. Personal Communication; [3]Zeng et al. J Med Chem 2015; [4]Ahn et al. ASCO 2016

Osimertinib activity in patients with leptomeningeal disease from non-small cell lung cancer: updated results from the BLOOM study

James Chih-Hsin Yang[1], Dong-Wan Kim[2], Sang-We Kim[3], Byoung Chul Cho[4], Jong Seok Lee[5], Xin Ye[6], Xiaolu Yin[6], Zhenfan Yang[6], Haiyi Jiang[6], Myung-Ju Ahn[7]

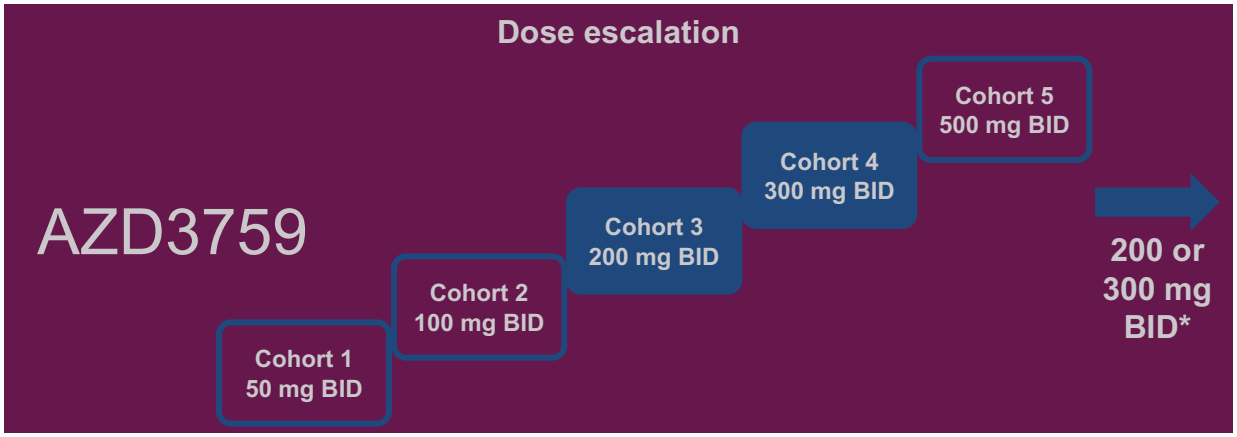
[1]National Taiwan University Hospital, Taipei, Taiwan;
[2]Seoul National University Hospital, Seoul, Republic of Korea;
[3]Asan Medical Center, Seoul, Republic of Korea;
[4]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea;
[5]Seoul National University, Bundang Hospital, Seongnam, Republic of Korea;
[6]Astrazeneca, Shanghai, China; [7]Samsung Medical Center, Seoul, Republic of Korea

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: James Chih-Hsin Yang

Presented By James Yang at 2016 ASCO Annual Meeting

Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD3759 or osimertinib in patients with EGFR mutation-positive advanced NSCLC



Dose expansion cohorts

Leptomeningeal metastasis

- EGFR-TKI naïve or pre-treated patients

Brain metastasis

- EGFR-TKI naïve patients

Osimertinib
160 mg QD

Leptomeningeal metastasis cohort

- EGFR-TKI pre-treated patients

T790M positive leptomeningeal metastasis cohort

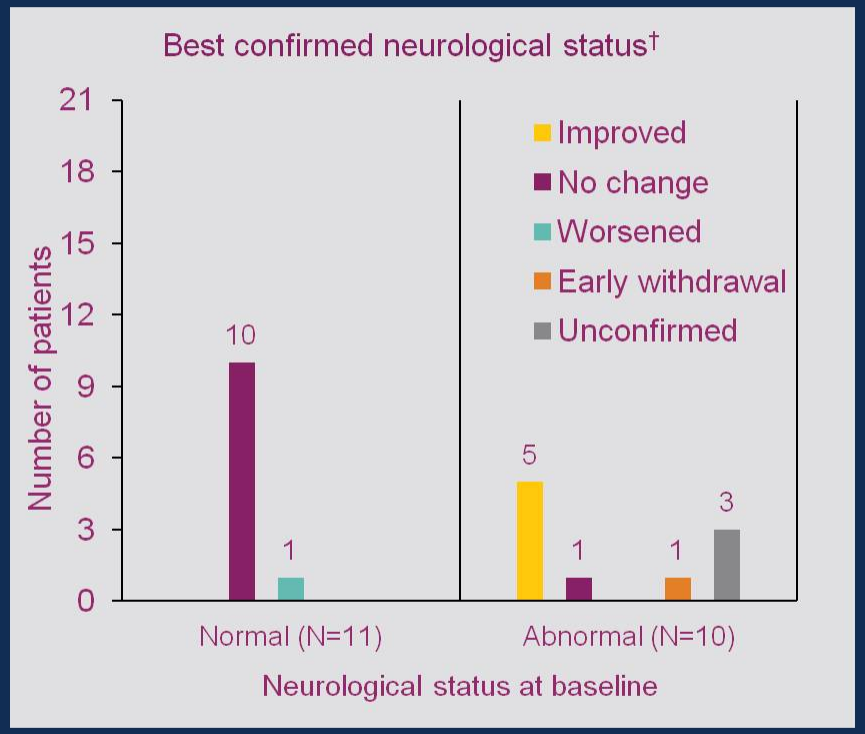
*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy

Osimertinib activity across LM assessments

Efficacy assessments were conducted on 21 patients

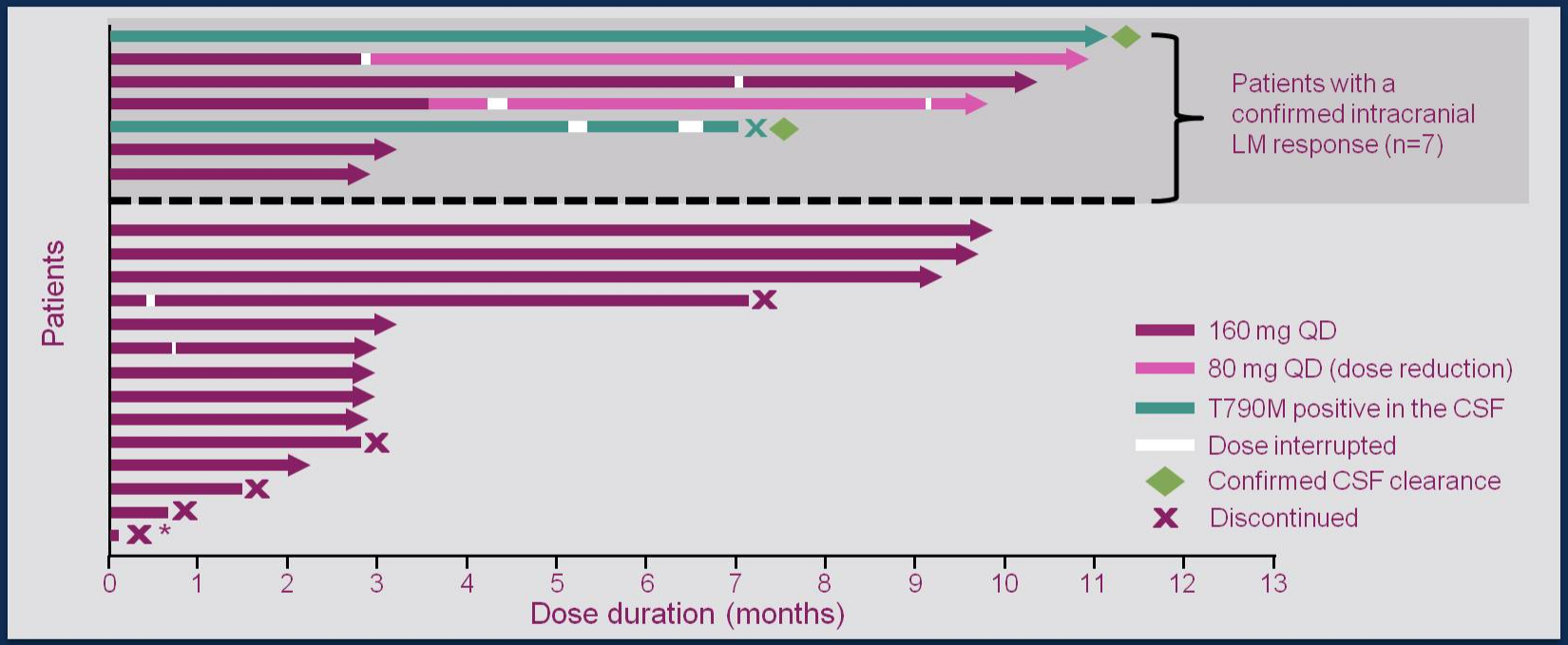
- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	



Population: efficacy, n=21.*Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

Time on treatment



Fifteen patients are ongoing treatment at time of data cut-off (March 10, 2016)
7 of whom have been on treatment for >9 months

*Patient died due to aspiration pneumonia. Arrows represent observations at the time of data cut-off.
Two patients experienced AEs leading to dose reduction: one patient had skin pruritus and one patient had neutropenia

Phase I study (BLOOM) of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM)

Myung-Ju AHN[1], Dong-Wan KIM[2], Tae Min KIM[2], Chia-Chi LIN[5], Jayantha RATNAYAKE[5], David J CARLILE[3], Xiaolu YIN[4], Zhenfan YANG[4], Haiyi JIANG[5], James Chih-Hsin YANG[6]

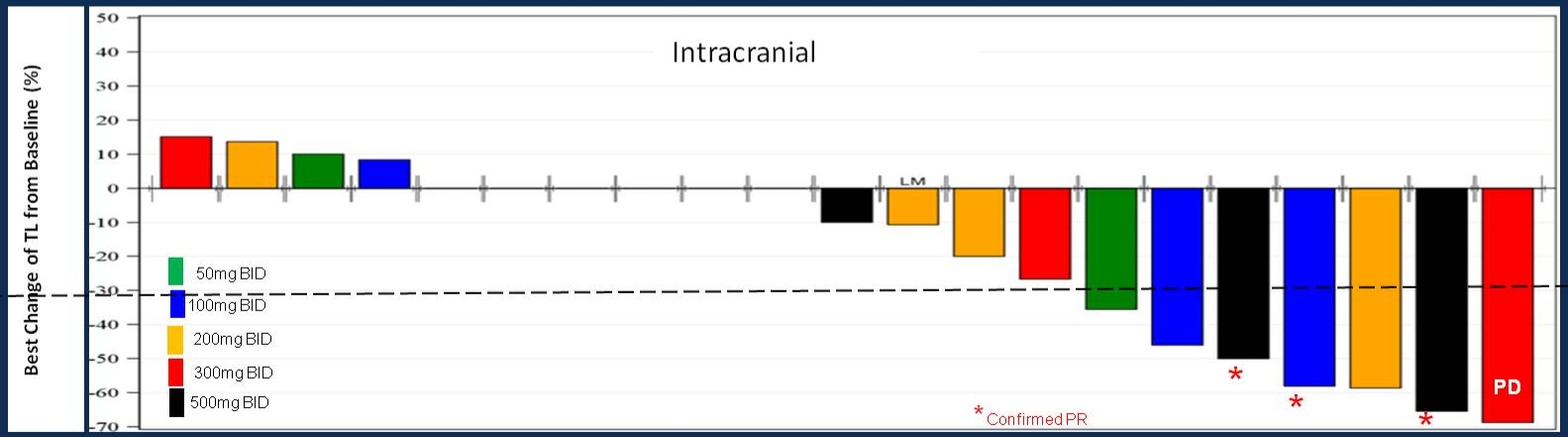
1. Samsung Medical Center, South Korea; 2. Seoul National University Hospital, South Korea; 3. Early Clinical Development, AstraZeneca; 4. Asia & Emerging Markets iMed, AstraZeneca; 5. Global Medicine Development, AstraZeneca; 6. National Taiwan University Hospital, Taiwan

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Myung-Ju Ahn

Anti-tumor activity

- 21 patients with measurable BM lesions were heavily pre-treated and had progressed both extracranially and intracranially on entering the study. 13 out of 21 patients had EGFR TKI as immediate prior treatment.
- Tumor shrinkage in the brain (target lesion) was observed in 11 patients at doses ≥50mg BID, with 3 confirmed PR and 3 unconfirmed PR by IA.
- 8 out of 22 patients with measurable extracranial lesions had tumor shrinkage, with one unconfirmed PR by IA.



Summary of Findings

- Brain Mets (AZD3759)
  - 6 PRs (3 confirmed/3 unconfirmed) in 21 patients
  - 13/21 had immediate prior EGFR TKIs; 7 /21 prior WBXRT
- Leptomeningeal Carcinomatosis (AZD3759 & Osimertinib)
  - Neurologic improvement and responses observed
  - > 50% (14/26) had prior WBXRT
  - 100% had prior systemic EGFR TKIs
  - Clearing of CSF cytology observed in many patients

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WWW.IASLC.ORG DECEMBER 4–7, 2016 VIENNA, AUSTRIA

CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two Phase II trials

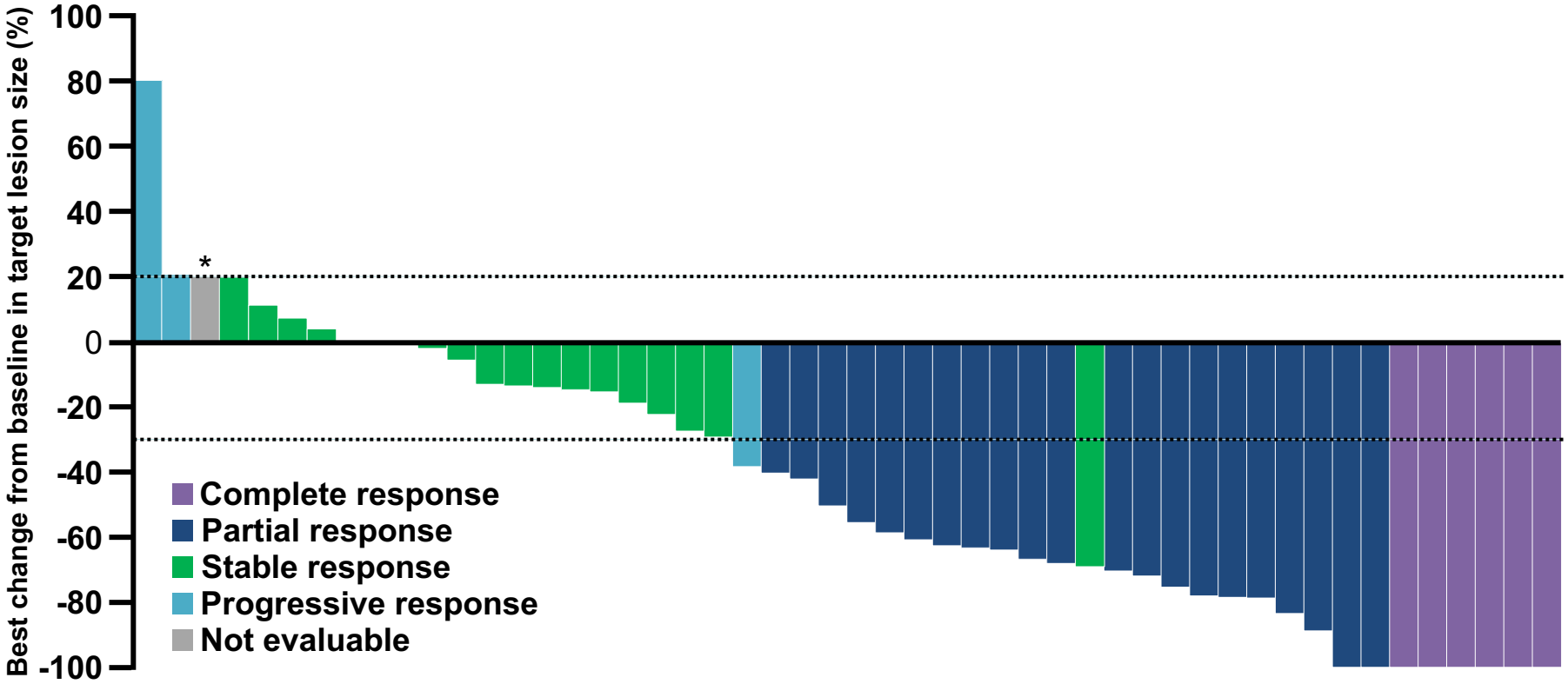
Glenwood Goss[1], Frances A Shepherd[2], Myung-Ju Ahn[3], Lyudmila Bazhenova[4], Lucio Crinò[5], Filippo De Marinis[6], Enriqueta Felip[7], Alessandro Morabito[8], Rachel Hodge[9], Mireille Cantarini[10], Tetsuya Mitsudomi[11], Pasi A Jänne[12], James Chih-Hsin Yang[13]

[1]The Ottawa Hospital Cancer Centre, University of Ottawa, Ottawa, Canada; [2]University Health Network, Princess Margaret Cancer Centre, Toronto, Canada; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]UC San Diego Health, Moores Cancer Center, California, USA; [5]Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy;[6]European Institute of Oncology, Milan, Italy; [7]Vall D'Hebron Institute of Oncology, Barcelona, Spain; [8]Istituto Nazionale Tumori di Napoli, Naples, Italy; [9]AstraZeneca, Cambridge, UK; [10]AstraZeneca, Macclesfield, UK; [11]Kinki University Faculty of Medicine, Osaka-Sayama, Japan; [12]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, USA; [13]Cancer Research Center, National Taiwan University, Taipei, Taiwan

Presented by Glenwood Goss at the World Conference on Lung Cancer 2016
Session MA15: Novel Strategies in Targeted Therapy (abstract ID: MA16.11)

CNS target lesions show shrinkage from baseline

- **The CNS ORR was 54% (95% CI 39, 68)**
- **Median best percentage change from baseline in CNS target lesion size was -53%**
  (range: -100% – +80%)



Population: evaluable for response. Scans were performed every 6 weeks
*represents imputed values
CI, confidence interval

CNS overall response rate was encouraging

Patients evaluable for CNS response (n=50)	
CNS ORR*, % Complete response, n (%) Partial response, n (%) Stable disease ≥6 weeks, n (%) Progressive disease, n (%) Not evaluable, n (%)	54 (95% CI 39, 68) 6 (12) 21 (42) 19 (38) 3 (6) 1 (2)
CNS DCR, %	92 (95% CI 81, 98)
CNS response based on prior brain RT status*	
Prior RT ≤6 months before first dose, n	19 / 50
CNS ORR, % Complete response / partial response, %	32 (95% CI 13, 57) 11 / 21
No prior RT or RT >6 months before first dose, n	31 / 50
CNS ORR, % Complete response / partial response, %	68 (95% CI 48, 83) 13 / 55

DCR is calculated from the percentage of patients with a best overall CNS response of complete response, partial response, or stable disease at ≥6 weeks, prior to CNS progression

No objective response includes stable disease, non-evaluable and disease progression

*Responses required confirmation after 4 weeks

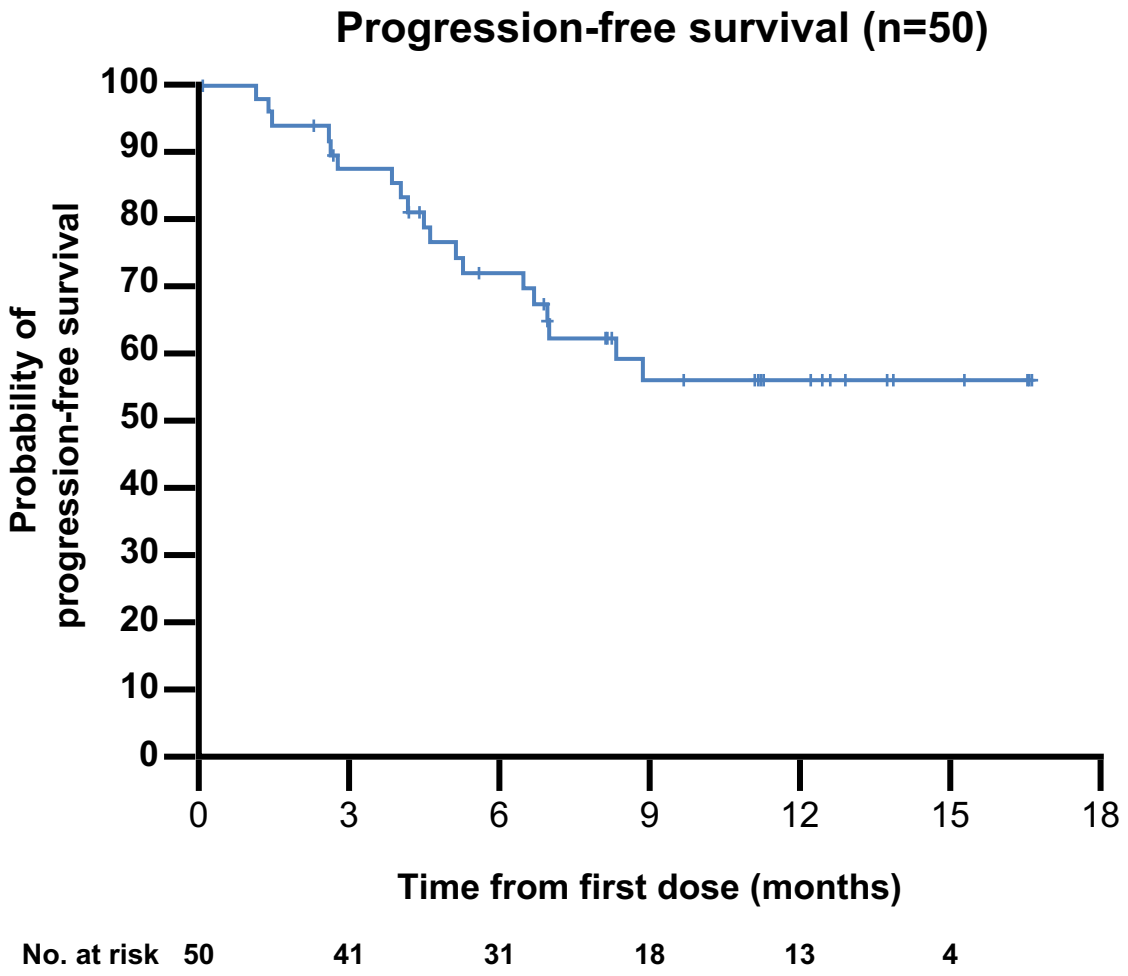
- **Confirmed complete response rate was 12%**
- **82% of patients responded by time of first assessment (within 6 weeks)**
- **CNS DCR was 92%**
- **CNS responses were observed regardless of prior brain radiation**

Population: evaluable for response

Scans were performed at baseline and every 6 weeks thereafter until RECIST disease progression

RT, radiation therapy

Clinically meaningful efficacy in the CNS



CNS progression or death events that do not occur at the time of analysis are censored

CNS PFS by BICR	Total (n=50)
Median follow-up for CNS PFS*	11.2 months
CNS progression or death# Maturity	19 / 50 38%
Median CNS PFS#, months	NC (95% CI 7, NC)
Progression-free at 6 months§ at 12 months§	72% (95% CI 57, 83) 56% (95% CI 40, 70)

- **At 9 months, 75% (95% CI 53, 88) of patients were estimated to remain in CNS response without progression or death**

Population: evaluable for response
*censored patients only; #only includes progression events that occurred within 19 weeks of the last evaluable assessment; § estimated by Kaplan-Meier technique

Conclusions

- **Osimertinib is an oral, potent, CNS-active, irreversible EGFR-TKI, selective for both EGFR-TKI sensitising and T790M resistance mutations**
- **In the pooled single-arm Phase II studies, patients with T790M-positive NSCLC and CNS metastases at baseline demonstrated clinically meaningful efficacy for osimertinib 80 mg daily (by blinded independent central neuroradiologist review), that was consistent with that reported for the overall patient population**
- **Osimertinib demonstrated an encouraging CNS objective response rate of 54% with a rapid onset (within 6 weeks) and CNS disease control rate of 92%**
- **CNS responses were observed regardless of prior radiotherapy status**
- **CNS progression-free survival was encouraging, with data still maturing**