EGFR TKIs in Brain Metastatases: which best therapeutic course ?

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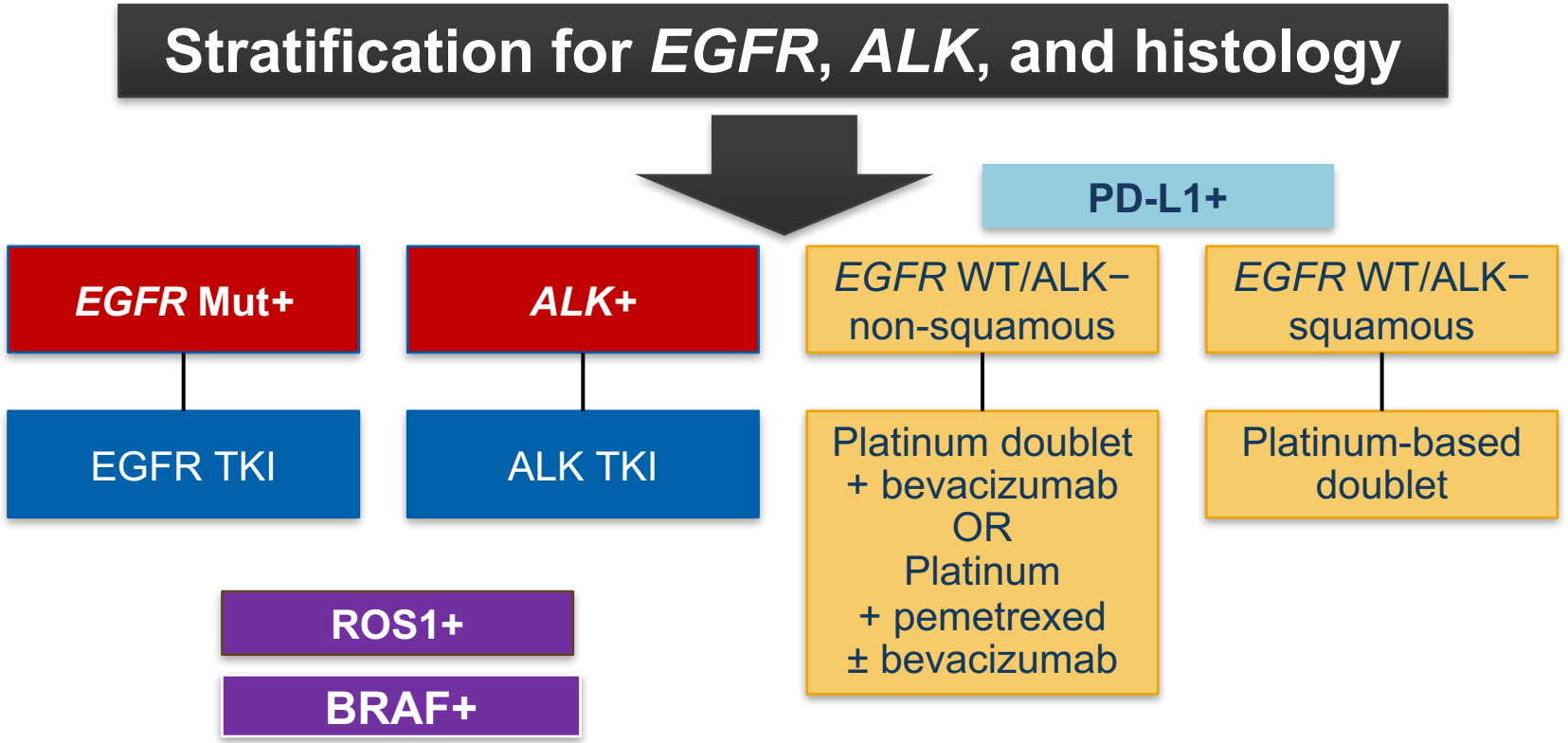
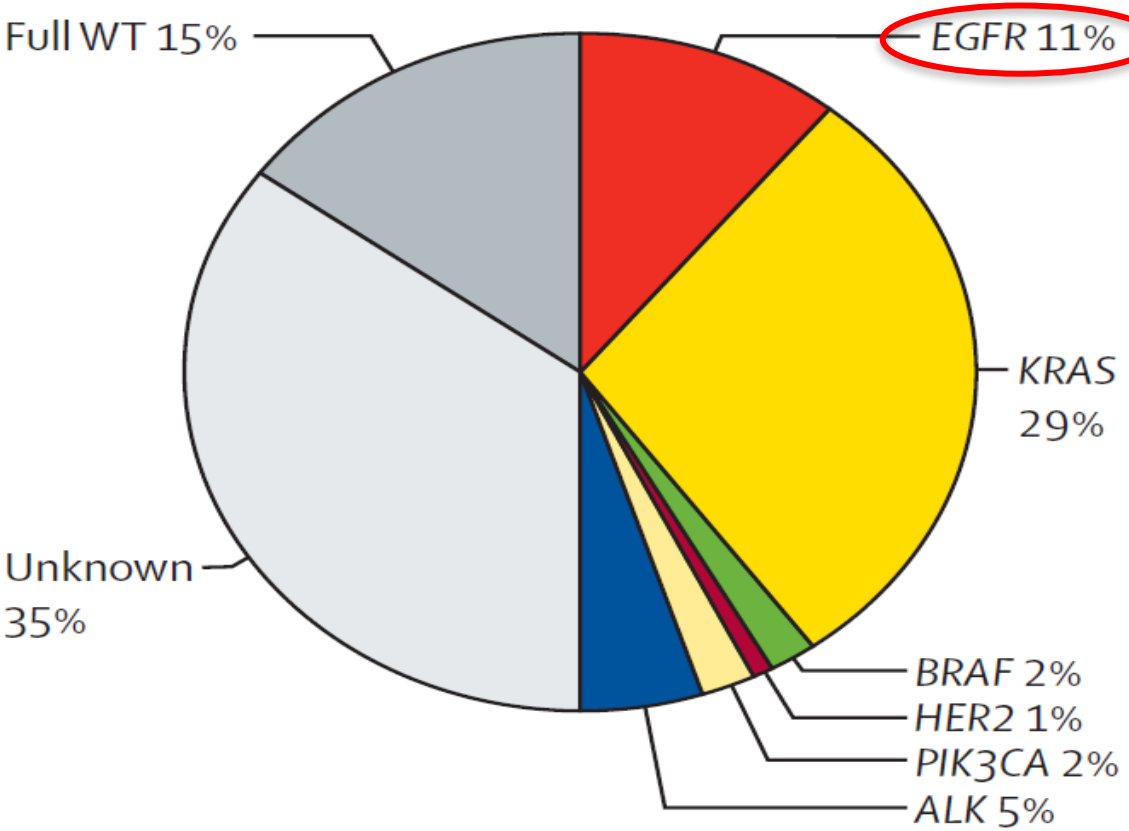
Great advances have been made in lung cancer therapy



WT, wild type.

EGFR, the most frequent targetable alteration



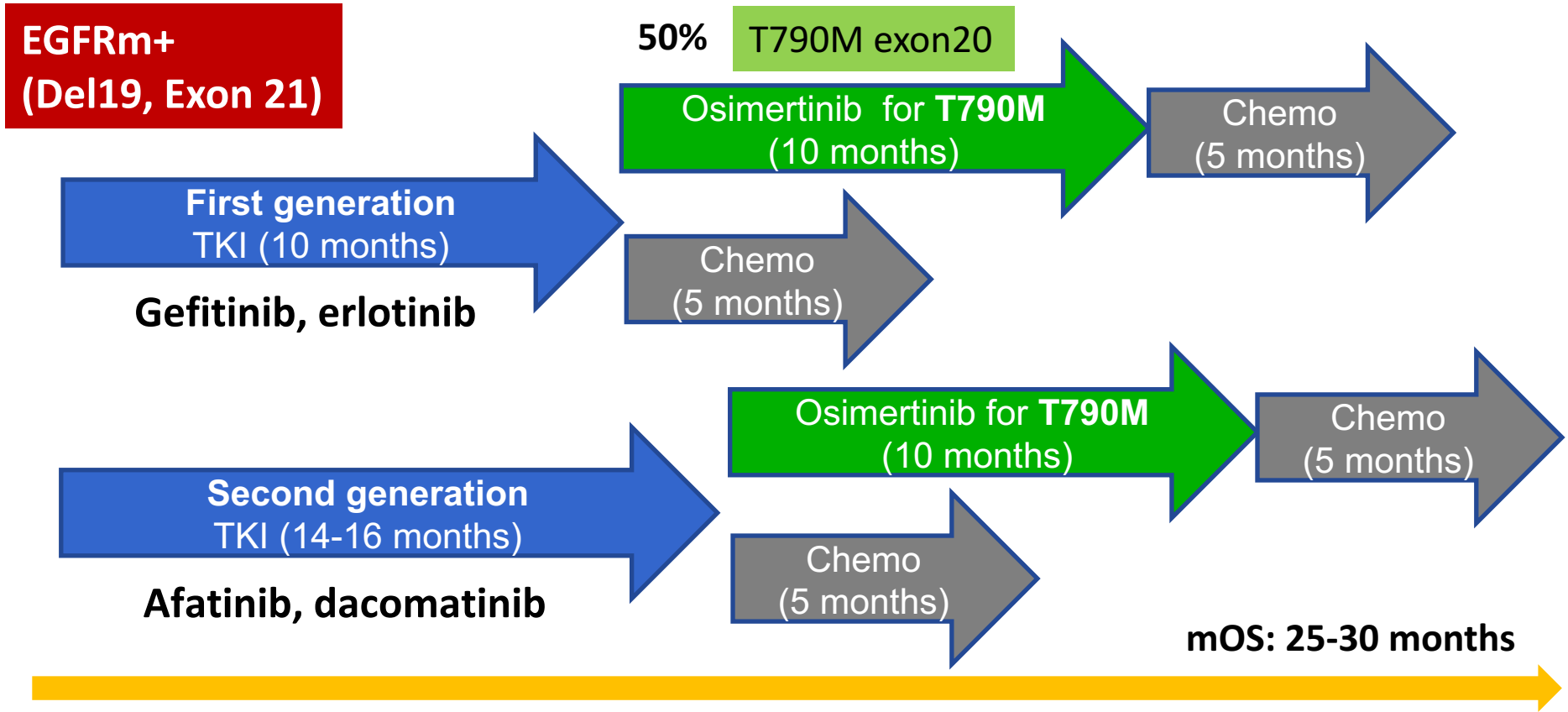
F.Barlesi et al, lancet 2016

Front-line EGFR mutant NSCLC

Trial	TKI	Chemo	Mutation	mPFS (TKI vs Chemo), p	PFS HR (95%CI)	ORR% (TKI vs Chemo)	≥G3 TKI tox (%)
	1st generation						
IPASS	Gefitinib	Carbo-Taxol	All	9.5 vs 6.3; p<0.001	0.48 (0.36-0.64)	71 vs 47	33
NEJ002	Gefitinib	Carbo-Taxol	L858R, Del19	10.8 vs 5.4; p<0.001	0.30 (0.22-0.41)	74 vs 31	41
WJTOG 3405	Gefitinib	Cis-Doce	L858R, Del19	9.2 vs 6.3; p<0.001	0.49 (0.34-0.71)	62 vs 32	NR
OPTIMAL	Erlotinib	Carbo-Gem	L858R, Del19	13.1 vs 4.6; p<0.001	0.16 (0.10-0.26)	83 vs 36	17
EURTAC	Erlotinib	Cis/Carbo-Doce/Gem	L858R, Del19	9.7 vs 5.2; p<0.001	0.37 (0.25-0.54)	58 vs 15	46
	2nd generation						
LUX-3	Afatinib	Cis-Pem	L858R, Del19	13.6 vs 6.9; p<0.0001	0.47 (0.34-0.65)	56 vs 23	49
LUX-6	Afatinib	Cis-Gem	L858R, Del19	11.0 vs 5.6; p<0.0001	0.28 (0.20-0.39)	67 vs 23	36

Mok NEJM (2009), Mitsudomi Lancet Oncol (2010); Maemondo NEJM (2010); Zhou Lancet Oncol (2011); Rossell Lancet Oncol (2012); Sequist JCO (2013); Wu Lancet Oncol (2014); NR, not reported

EGFR-TKIs based on EGFR sensitive and resistant mutations: Never ended story



CNS metastases – EGFRm+

(brain metastases and leptomeningeal metastases)

INCIDENCE of CNS metastases

- In patients with EGFRm+ NSCLC[1]: 44% (including BM and LM)

PROGNOSIS

- BM
  - Median OS[1,2]: 16-18 months
  - Cause of death[1]: 11% CNS, 35% CNS + systemic, 54% systemic
- LM
  - Median OS[3,4]: 4.5-11.0 months
  - Cause of death[5]: 28% LM, 31% LM + systemic, 41% systemic

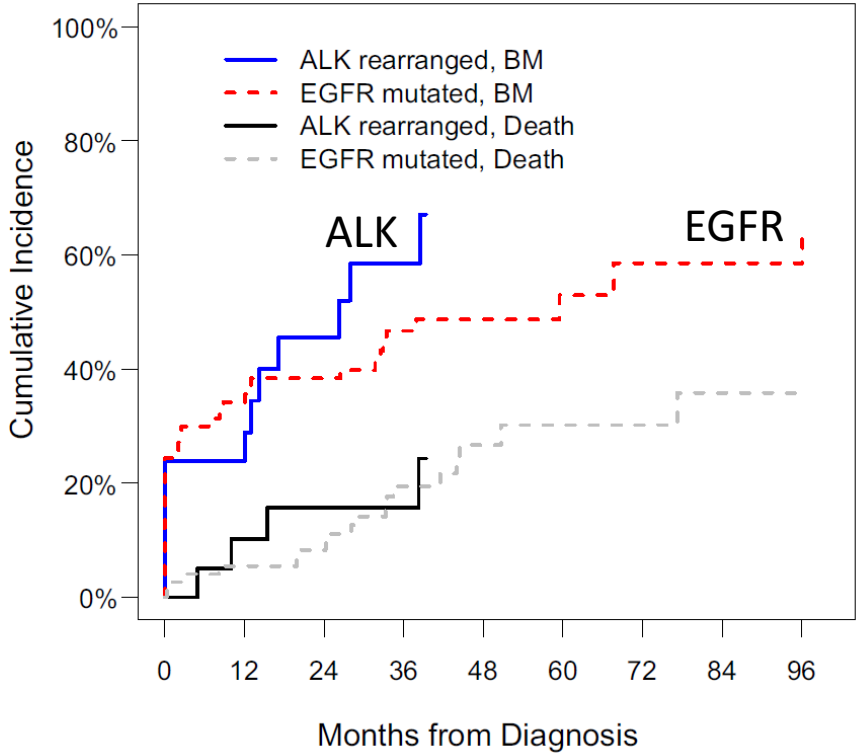
Most of these studies included small sample sizes, retrospective analyses, and case reports with inadequate power to exclude clinically relevant differences in efficacy

1. Eichler et al *Neo-Oncology* 2010;12:1193-1199. 2. Park et al *Lung Cancer* 2012;77:556-60. 3. Umemura et al *Lung Cancer* 2012;77:134-139. 4. Liao et al *J Thoracic Oncology* 2015;10:1754-61.
5. Chamerlain et al *Arch Neurol.* 1998;55:506-512. 6. Zeng Q et al *J Med Chem* 2015; 58;8200-15. 7. Yang et al *Sci Transl Med.* 2016;8:368ra172. 8. Ahn et al *ASCO 2016*.

BM in EGFR-mutated NSCLC

The cumulative incidence of post-diagnosis BM increased over time:

- 34.2% at 1 year,
- 38.4% at 2 years
- 46.7% at 3 years



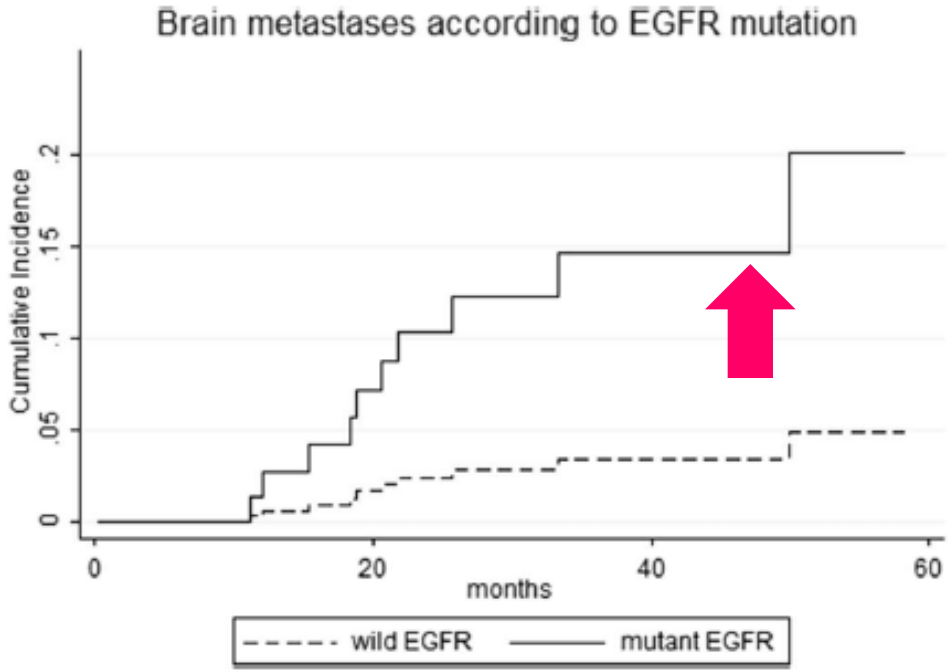
presence of BM, clinicopathologic data, and tumor genotype retrospectively compiled and analyzed from a cohort of 381 patients

Deepa Rangachari et al, lung cancer 2015

Higher risk of recurrence of brain metastasis according to EGFRm

EGFR-mutant tumor had a significantly higher risk of recurrence of brain metastasis

(hazard ratio=4.49, 95% CI: 1.20–16.80, *p*=0.026)



Cumulative risk of recurrence of brain metastasis according to *EGFR* mutation status after curative resection in patients with pulmonary adenocarcinoma

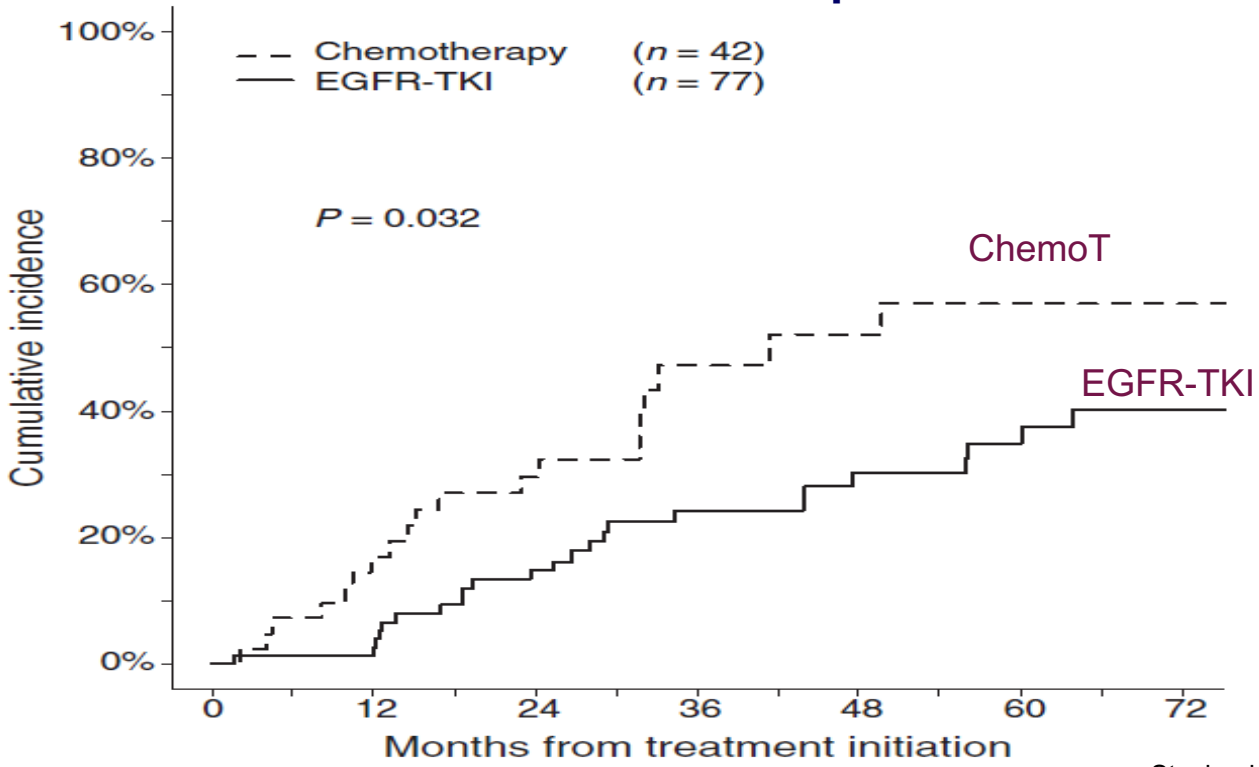
Shin DY et al, J Thorac Oncol. 2014 Feb; 9(2):195-9

Blood-brain barrier

- **For successful treatment of brain metastases, a drug must first be able to cross the BBB**
- **BBB penetration is influenced by factors such as**
  - drug's affinity for the ATP-binding cassette efflux transporters,
  - permeability glycoprotein (P-gp)
  - breast cancer-resistance protein (BCRP)
  - molecular weight of the drug
- **Chemotherapy agents and large monoclonal antibodies are generally unable to cross the BBB**

Lower rates of BM progression in EGFR+ NSCLC pts initially treated with EGFR-TKI compared with upfront chemotherapy

Patients without prior CNS involvement



Erlotinib or gefitinib

Stephanie Heon et al, CCR 2012

Select trials with EGFR-TKI therapy (1st ou 2nd generation) in NSCLC-BM

Treatment		N	Patient	RR in Brain	OS	Reference
Erlotinib		17	EGFR M+	82%	NS	Porta et al. (7)
Gefitinib Erlotinib	**or**	28	EGFRM+	83%	15.9 months	Park et al. (8)
Gefitinib		9	EGFRM+	89%	NS	Li (19)
Gefitinib Erlotinib	**or**	23	Non Smoker Asian	74%	18.8 months	Kim et al. (20)
Erlotinib		40	Non-selective	86%	11.8 months	Welsh et al. (21)
Gefitinib		41	EGFRM+	88%	21.9 months	Iuchi et al. (22)
Afatinib		32	EGFRM+, TKI-treatment history	35%	9.8 months	Hoffknecht et al. (23)

But benefit short in time…

7. Porta R, et al. Eur Respir J *37:* 624-631, 2011.
8. Park SJ, et al. Lung Cancer *77:* 556-560, 2012.
19.Li Z. J Clin Oncol 29 *(Suppl):* abstract e18065, 2011.
20. Kim JE, et al. Lung Cancer *65:* 351-354, 2009.
21.Welsh JW, et al. J Clin Oncol *31:* 895-902, 2013.
22.Iuchi T, et al. Lung Cancer *82:* 282-287, 2013.
23.Hoffknecht P, et al.. J Thorac Oncol *10:* 156-163, 2015.

Current EGFR TKIs cannot effectively treat CNS and LM at the approved doses

	CSF concentration	CSF penetration rate
Gefitinib	**3.7 +/- 1.9 ng/ml**	1.13 +/- 0.36%
Erlotinib	**28.7 +/- 16.8 ng/ml**	2.77 +/- 0.45%

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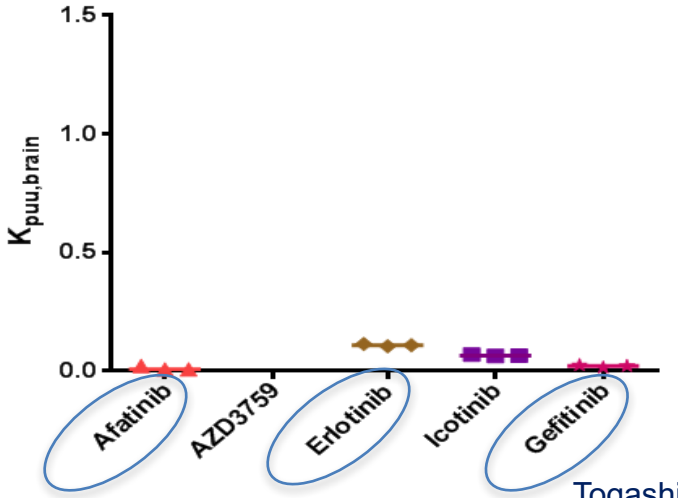


Kpuu, CSF (ratio of cerebral spinal fluid concentration/free plasma concentration)

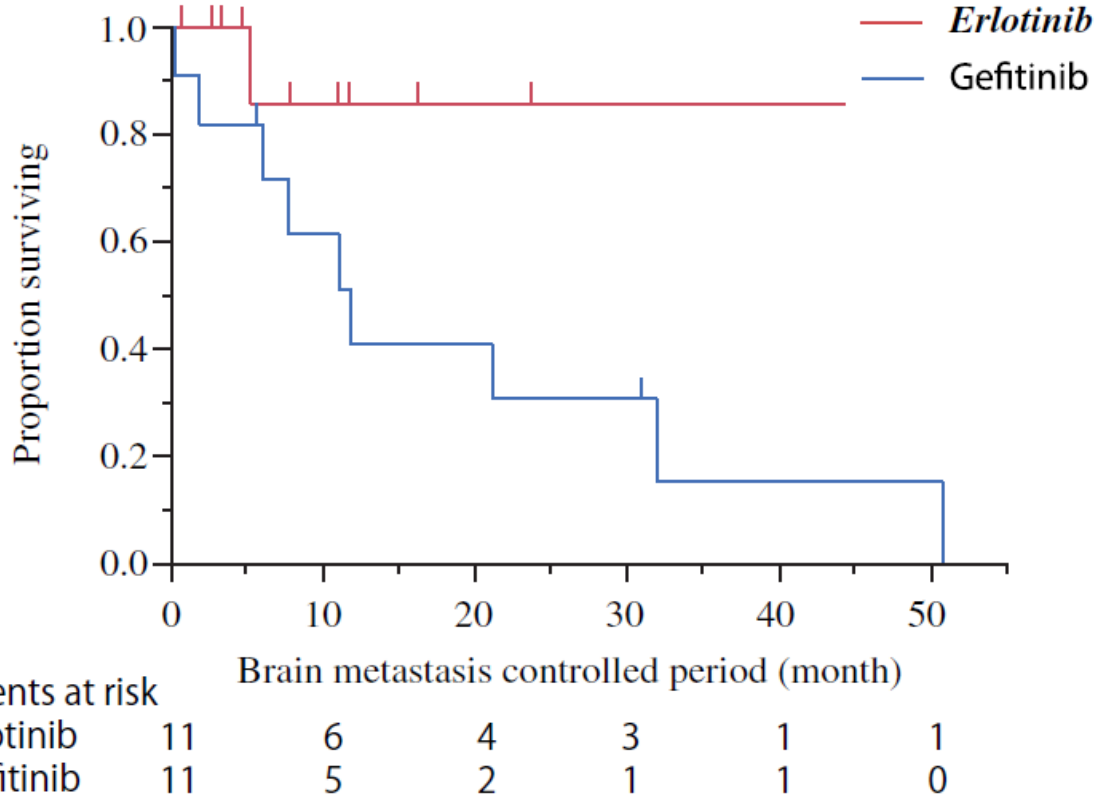
Kpuu,brain is well established as a good predictor of BBB permeability, with values greater than 0.3 indicative of good diffusion across the BBB

T.Mok, ESMO 2017

Togashi et al Can Chemother Pharmacology 2012; Ballad et al CCR 2016

Erlotinib was deemed more effective than gefitinib in preventing intracranial lesions and prolonging survival

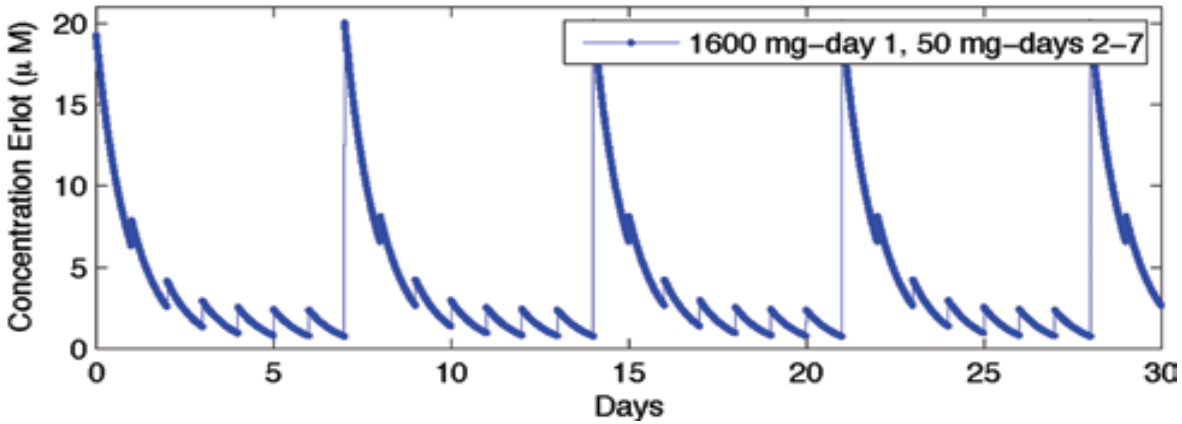
Retrospective analysis
Single institution

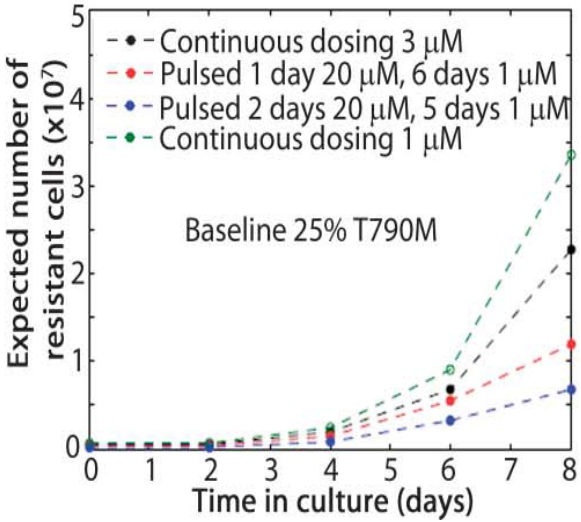


Jumpei Kashima et al, Med Oncol 2016

EGFR TKI Pulse administration?

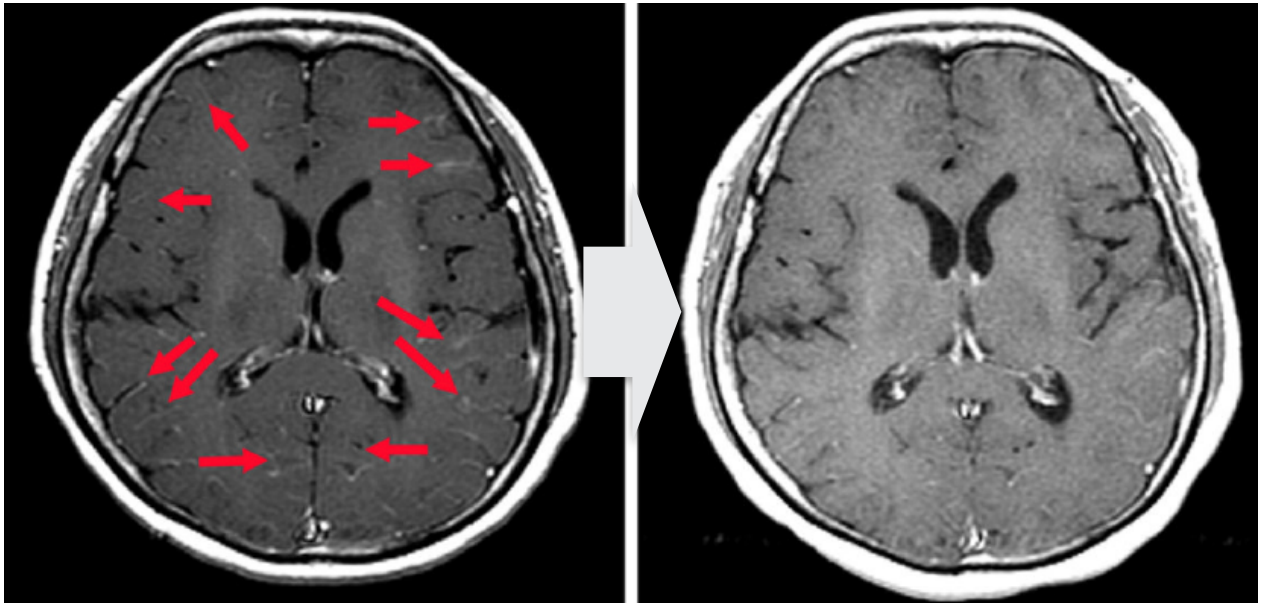
Up to 10-fold increases of approved doses of gefitinib or erlotinib transiently reach the predicted efficacious concentration in CSF and demonstrate modest palliative effect





Pulse administration: modest palliative effect

- But patients could not tolerate long term treatment due to serious adverse effects
- In addition, the response duration very short

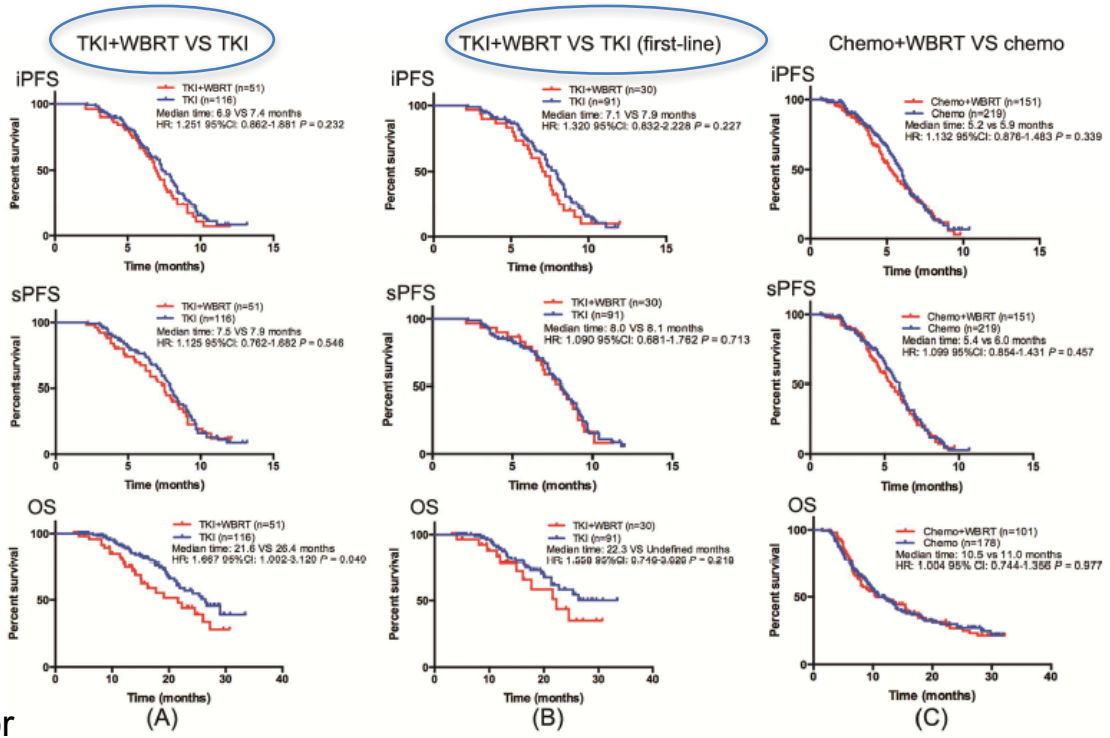


EGFR TKIs plus WBRT demonstrated no survival benefit than TKIs alone in NSCLC patients with EGFR mutation and brain metastases

- 230 patients were retrospectively collected
- Chinese population

- Addition of WBRT to EGFR TKIs **did not appear to** have survival benefit superior to that of EGFR TKIs alone in with EGFR-mutant NSCLC with BM.

- WBRT also did not bring additional benefit to chemotherapy in patients with BM and EGFR of wild-type or unknown status.

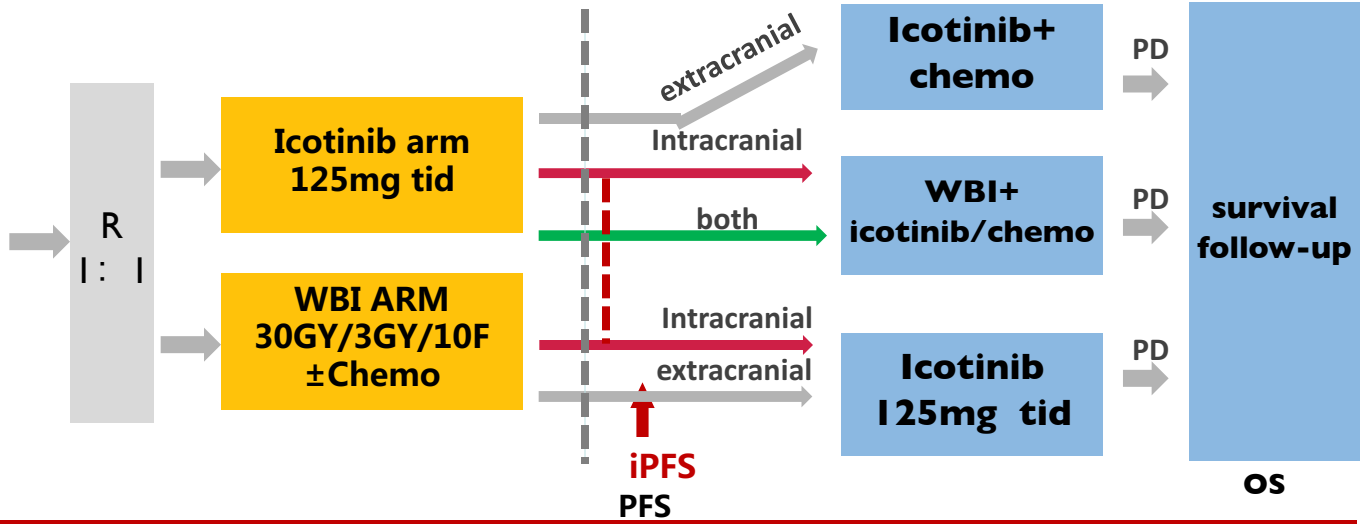


Tao Jiang, et al. J Thorac Oncol 2016

Study Design (NCT01724801)

Phase Ⅲ Trial Comparing WBI and Chemotherapy with Icotinib

- Advanced NSCLC with BM
- *EGFR* mutation & EGFR TKIs naive
- Brain metastatic sites≧3
- 18-75 years
- Life expectancy ≧12 weeks
- ECOG PS score 0-1

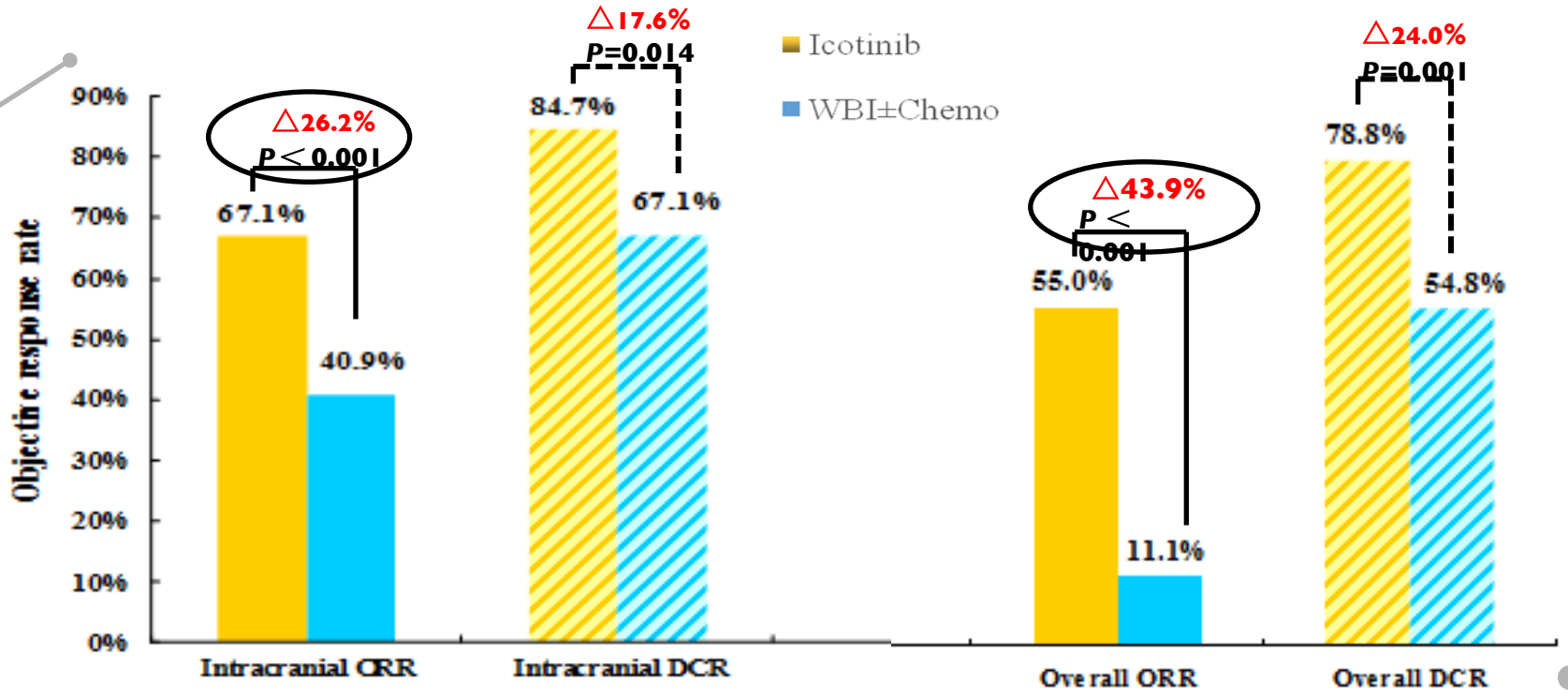


Primary endpoint:
Intracranial progression-free survival (iPFS)

Secondary endpoints:
Progression –free survival(PFS)
Intracranial Objective response rate (iORR) ; Overall survival(OS)
Safety and tolerability

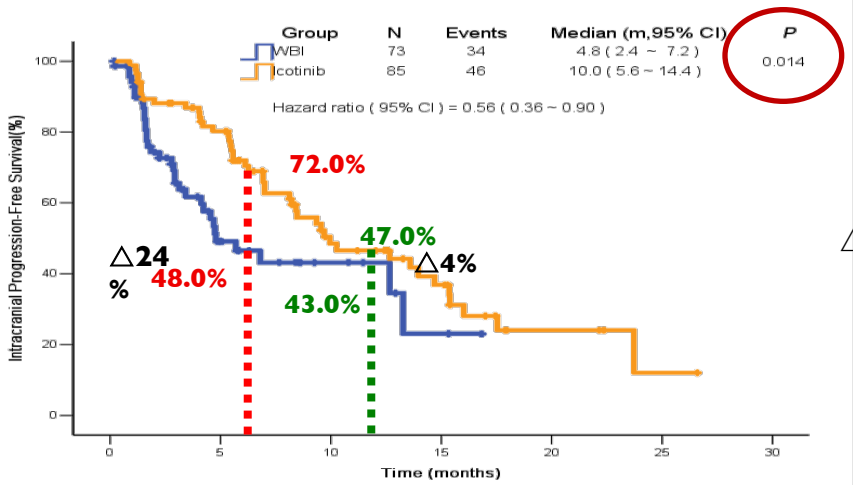
Yan JJ et al, Lancet Respir Med 2017

Intracranial RR and overall RR



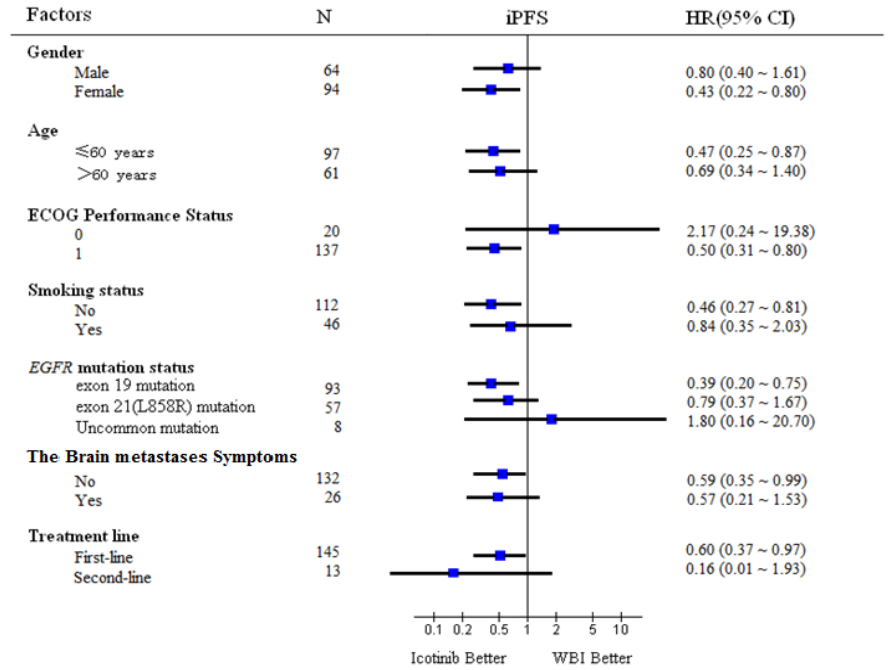
Yan JJ et al, Lancet Respir Med 2017

Primary endpoint: iPFS



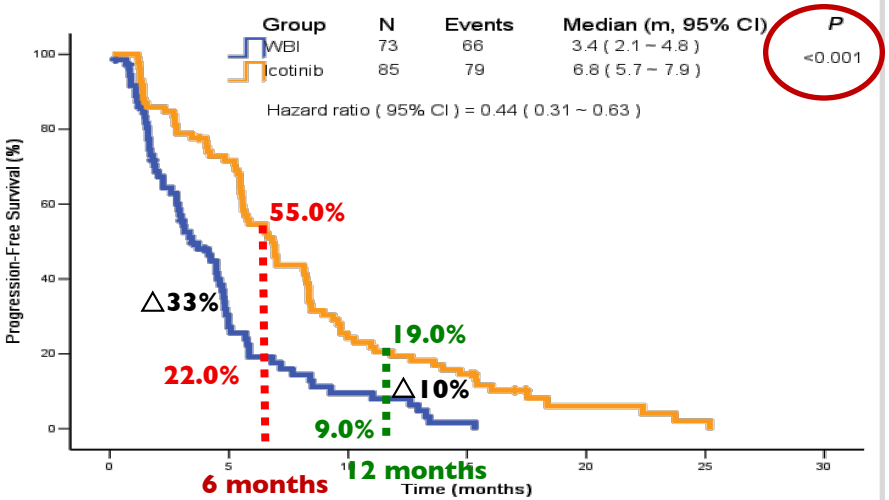
NO. at Risk

WBI	73	43	41	39	39	39	39
Icotinib	85	69	49	44	40	39	39



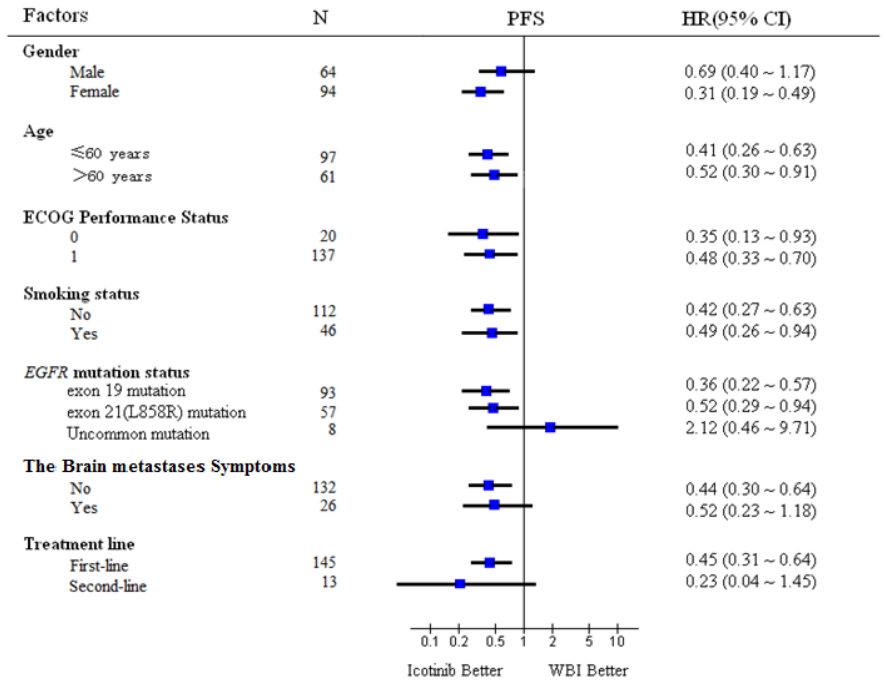
Yan JJ et al, Lancet Respir Med 2017

Secondary endpoint: PFS



NO. at Risk

WBI	73	24	13	8	7	7	7
Icotinib	85	61	22	14	9	7	6

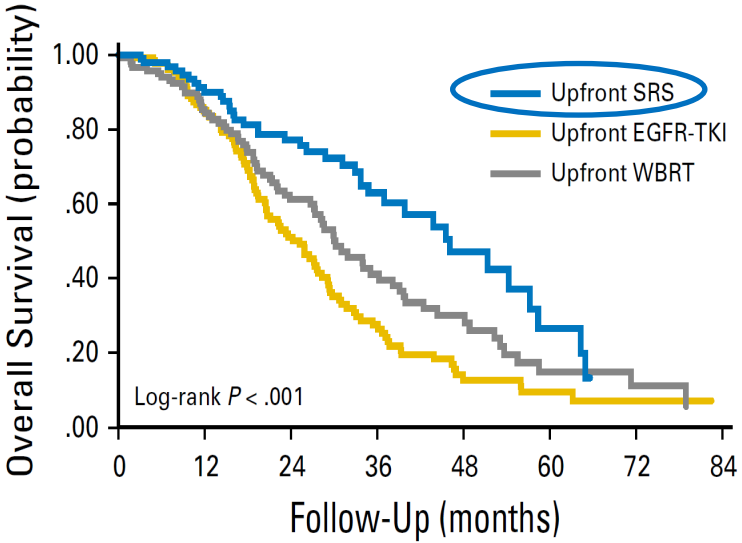


Yan JJ et al, Lancet Respir Med 2017

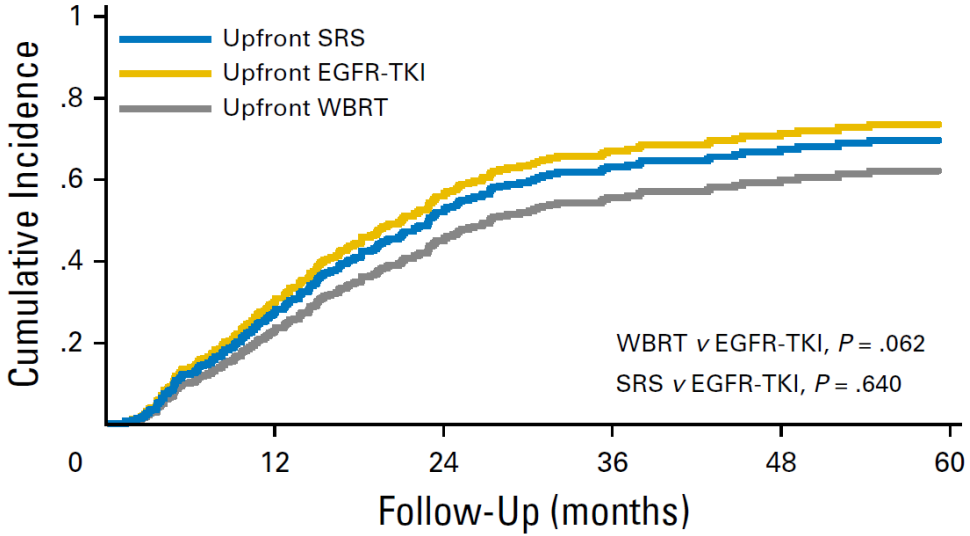
Ongoing phase III studies of upfront EGFR TKI vs. WBRT in BM from *EGFR*-mutated NSCLC

Study	Comparator	Primary endpoint	Secondary endpoints
NCT02714010 EGFR-TKI Concurrent With/Without WBRT in Brain Metastasis From NSCLC	Erlotinib, Gefitinib or Icotinib	iPFS	OS, ORR, cognitive QoL, toxicity
NCT02338011 Compare the effect and safety of gefitinib alone with gefitinib plus concomitant WBRT	Gefitinib	iPFS, sPFS	OS, QoL, mental status

Brain Metastases in TKI–Naive EGFR NSCLC:
A Retrospective Multi-Institutional Analysis



No. at risk								
Upfront SRS	100	76	51	29	13	5	1	1
Upfront WBRT	120	97	52	27	15	6	3	1
Upfront EGFR-TKI	131	103	54	24	8	4	2	0



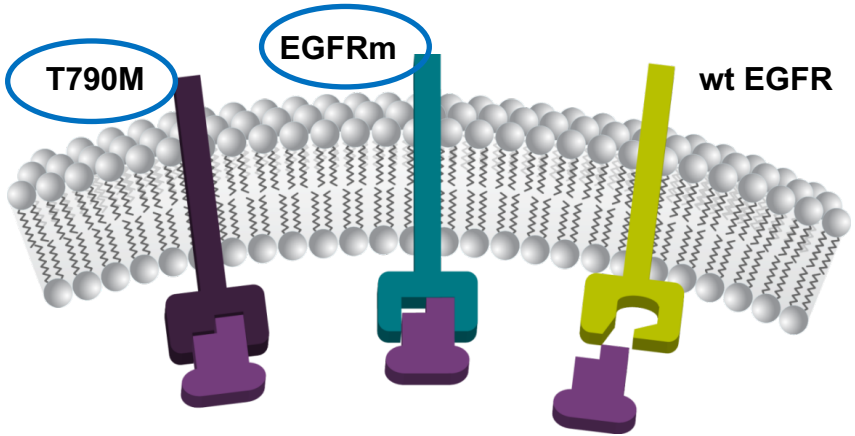
Cumulative incidence of intracranial progression

SRS followed by EGFR-TKI resulted in the longest OS

prospective, multi-institutional randomized trial of SRS followed by EGFR-TKI versus EGFR-TKI followed by SRS at intracranial progression is urgently needed

William J. Magnuson et al, JCO 2017

Novel agents are an area of need:
Osimertinib is selective for EGFR sensitising mutations (L858R and exon19del) and T790M mutations



Inhibition of T790M[1,3]

Inhibition of EGFRm (exon 19 deletion and L858R)[1,3]

Low affinity for wt EGFR[1,3]

del, deletion; IGFR; insulin-like growth factor receptor; IR, insulin receptor; wt, wild type.

1. TAGRISSO Prescribing Information. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.3.2017. © 2016 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed October 14, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc. 3. Cross DA, et al. *Cancer Discov*. 2014;4(9):1046-1061.

Osimertinib a new standard – EGFR+

1st line vs EGFR-TKI and 2nd line vs chemoT (T790M+)

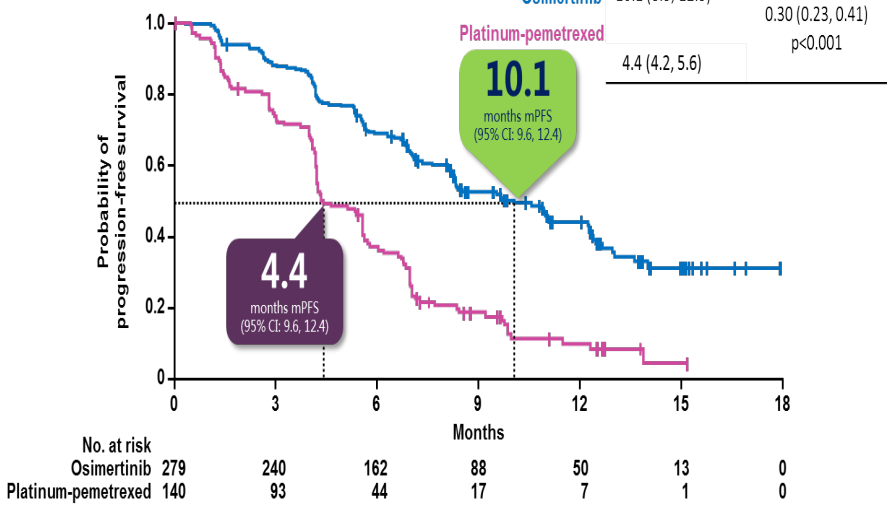
At resistence (EGFR- T790M+)

First line EGFRm+

EGFR T790M+

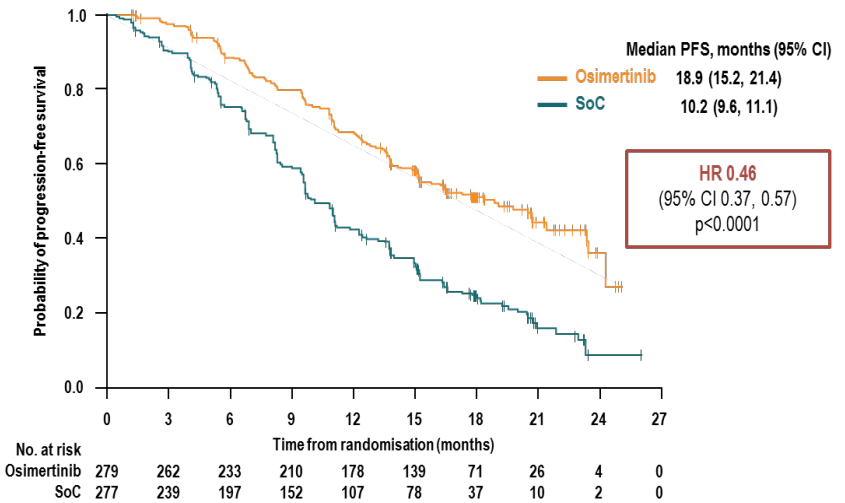
AURA3 trial (Osimertinib vs ChemoT)

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



OSIMERTINIB FIRST LINE VS GEFTINIB OR ERLOTINIB FLAURA TRIAL

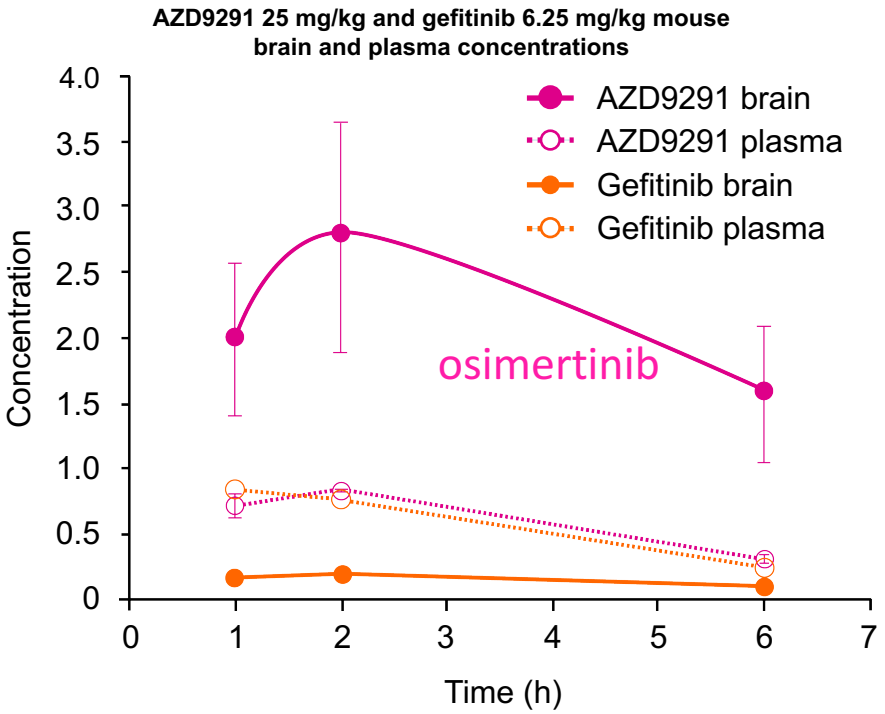
342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



T.Mok et al, NEJM 2017

AZD9291 (osimertinib) is distributed to mouse brain to a greater extent than gefitinib, CO-1686, or afatinib

AZD9291 and gefitinib p.o.



AZD9291, gefitinib, CO-1686, and afatinib p.o. plasma and brain C_{max}

	AZD9291	Gefitinib	CO-1686	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (μM)	0.82	0.82	3.3	0.14
Brain C_{max} (μM)	2.8	0.17	BLQ	BLQ
Brain/plasma ratio	3.4	0.21	NC	NC

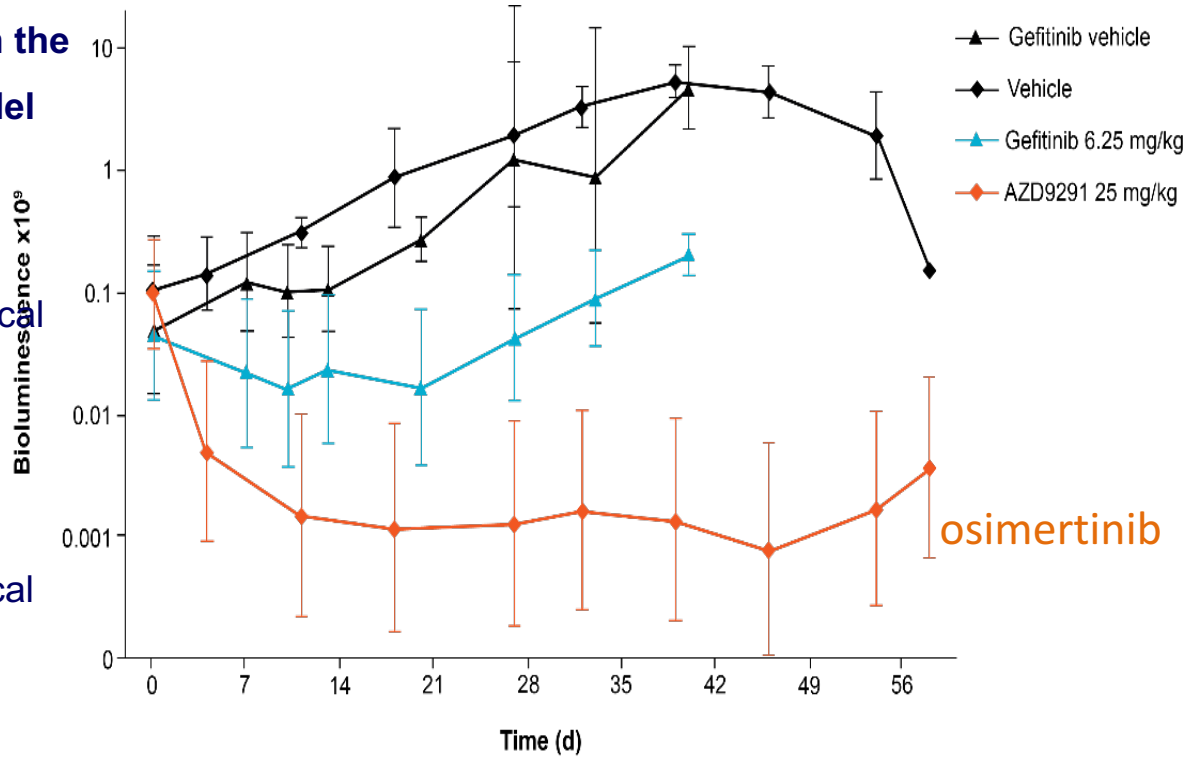
BLQ, below limit of quantification (CO-1686 0.25 μM, afatinib 0.05 μM); C_{max}, maximum concentration; NC, not calculated; p.o., orally. Doses are equivalent to clinical doses or reported previously for preclinical studies.

Osimertinib shown to have a good Kpuu,brain value (0.39) compared with other currently available TKIs and rociletinib, suggesting it has the potential to achieve good brain exposure

Presented by P Ballard at the World Conference on Lung Cancer 2015. ***Journal of Thoracic Oncology*** **2015; 10(9, Suppl 2): S300, abstract Mini 10.12**

Anti-tumour efficacy of AZD9291 (osimertinib) and gefitinib (bioluminescence) in PC9 mouse brain mets model

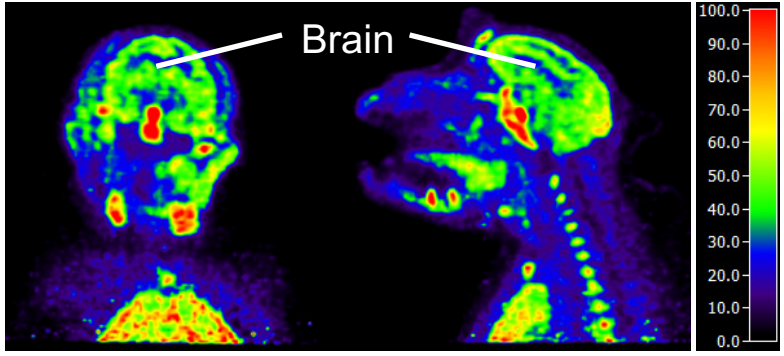
- **AZD9291 (osimertinib) is efficacious in the PC9 (EGFRm+) mouse brain mets model**
  - **AZD9291** at 25 mg/kg in mouse approximates 80 mg once daily clinical exposure
  - **Gefitinib** at 6.25 mg/kg in mouse approximates 250 mg once daily clinical exposure



Kim et al. Ann Oncol 2014;25(Suppl 4): Poster 456P

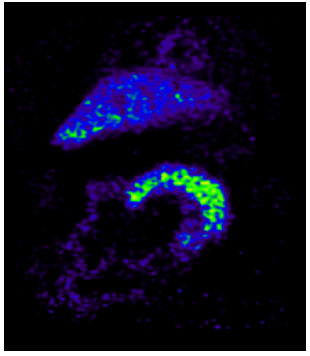
[^{11}C]AZD9291 (osimertinib) showed marked exposure in the cynomolgus monkey brain in contrast toother EGFR-TKIs

[^{11}C]AZD9291 Head/neck

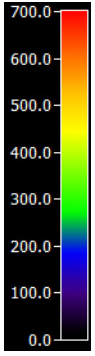


Radioactivity (kBq/cc)

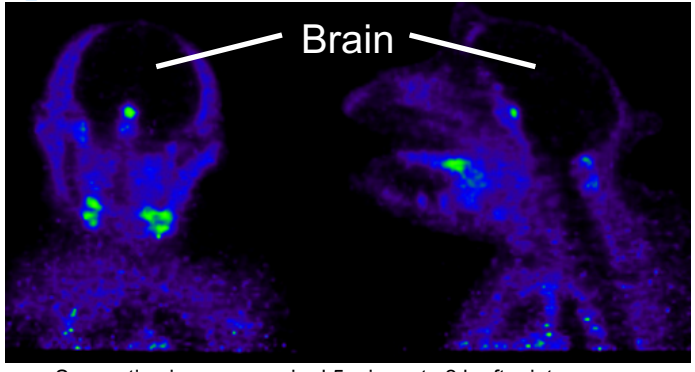
Abdomen



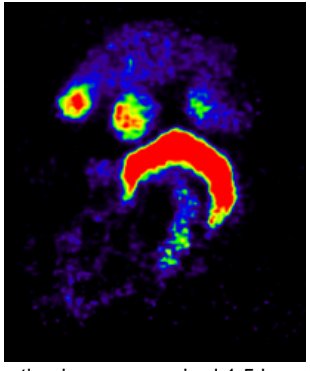
Radioactivity (kBq/cc)



[^{11}C]CO-1686



Summation images acquired 5 min up to 2 h after intravenous microdose (<3 µg) injection

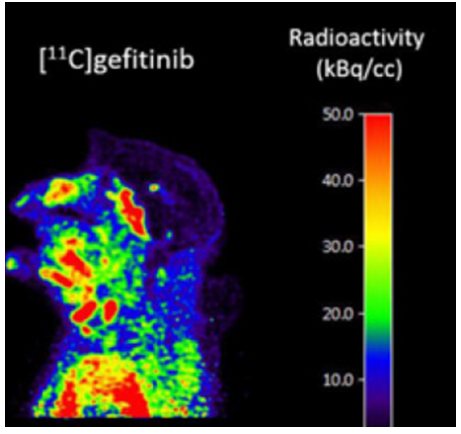


Summation images acquired 1.5 h up to 2 h after intravenous microdose (<3 µg) injection

Radiolabeled imaging

	Brain to blood ratio $AUC_{0–90\ min}$
[^{11}C]AZD9291	2.6 ± 1.4*
[^{11}C]CO-1686	0.025†

[^{11}C]gefitinib

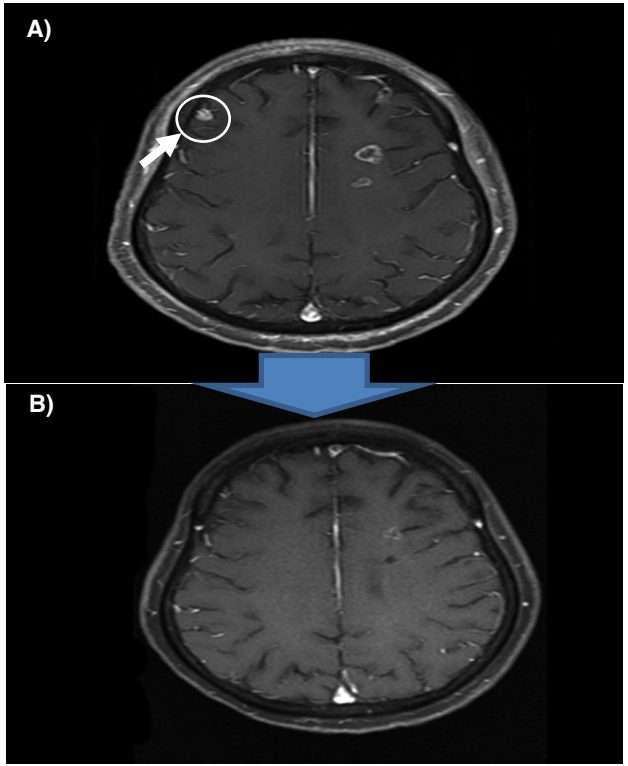


Presented by P Ballard at the World Conference on Lung Cancer 2015. ***Journal of Thoracic Oncology*** **2015; 10(9, Suppl 2): S300, abstract Mini 10.12**

Brain metastases – Case Study 1

- **Sixty-three-year-old Korean female diagnosed with advanced NSCLC (exon 19 deletion) in December 2010**
- Prior therapy: gemcitabine/cisplatin four cycles (SD), gefitinib June 2011–October 2012 (PR), pemetrexed 10 cycles (SD) October 2012–June 2013 with whole-brain radiotherapy December 2012–January 2013. T790M detected
- AZD9291 40 mg daily started 7 August 2013 in T790M+ expansion cohort, best response PR, with non-CR/non-PD reported in NTLs (including evidence of shrinkage in brain mets) from 18 August 2013 and is still ongoing at 40 mg (11 months NTL response)

Brain MRI
A) Baseline on 23 July 2013. B) 2 July 2014

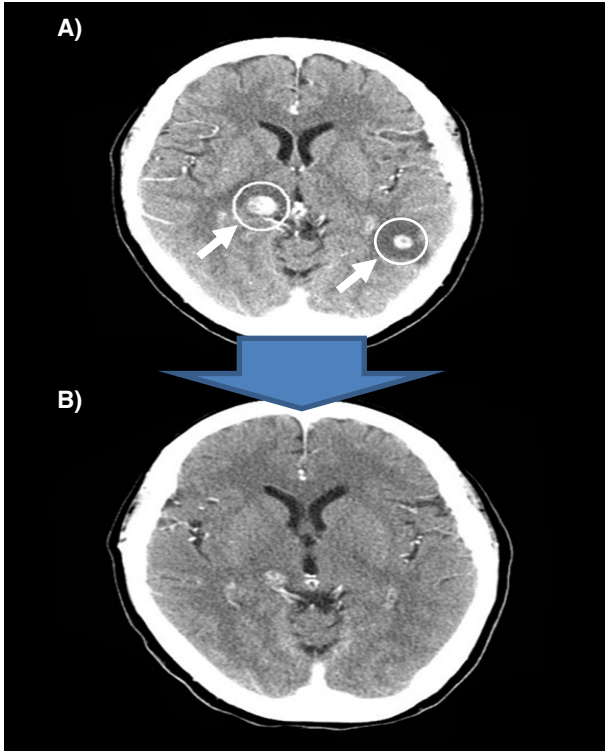


Kim et al. Ann Oncol 2014;25(Suppl 4): Poster 456P
MRI, magnetic resonance imaging; NTL, non-target lesion

Brain metastases – Case Study 2

- **Sixty-year-old Taiwanese female diagnosed with advanced NSCLC (L858R) in January 2011**
- Prior therapy: erlotinib January 2011–October 2012 (PR), pemetrexed/cisplatin/ carboplatin October 2012–January 2013 (SD), erlotinib January 2013–March 2013 (NE), docetaxel April 2013–June 2013 (SD), gemcitabine June 2013–July 2013 (NE). T790M detected in August 2013
- AZD9291 80 mg daily started 2 September 2013 in expansion cohort, best response PR. A single brain met target lesion decreased from 13 mm at baseline to 12 mm at Week 6, 8 mm at Week 12–18 (38% shrinkage). NTLs including brain mets had non-CR/non-PD reported for 4 months between 8 October 2013 to 2 January 2014, but progressed in the brain met NTLs on
  13 February 2014

Brain MRI
A) Baseline on 9 August 2013. B) 8 October 2013



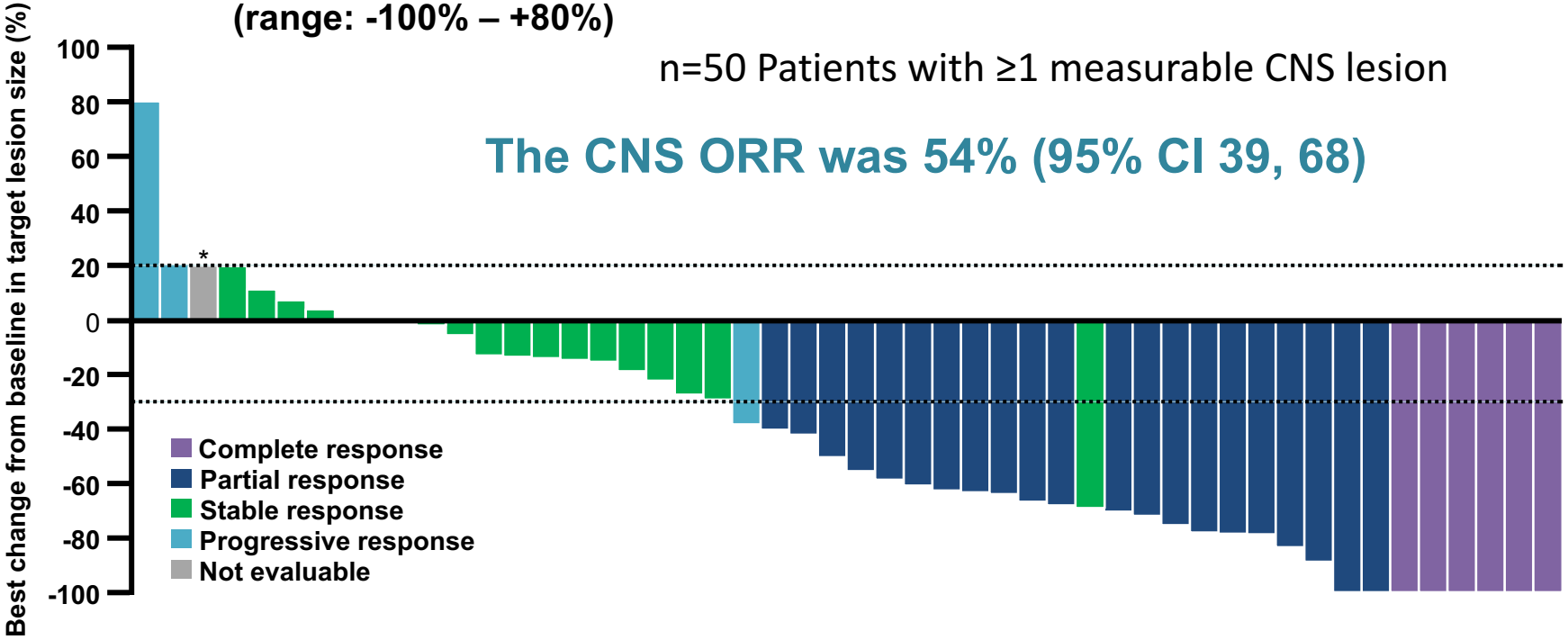
Kim et al. Ann Oncol 2014;25(Suppl 4): Poster 456P
NE, not evaluable

Pooled analysis of two Phase II studies (AURA extension and AURA2), CNS target lesions show shrinkage from baseline

- **Median best percentage change from baseline in CNS target lesion size was -53% (range: -100% – +80%)**

n=50 Patients with ≥1 measurable CNS lesion

The CNS ORR was 54% (95% CI 39, 68)



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

CNS overall response rate was encouraging

- 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

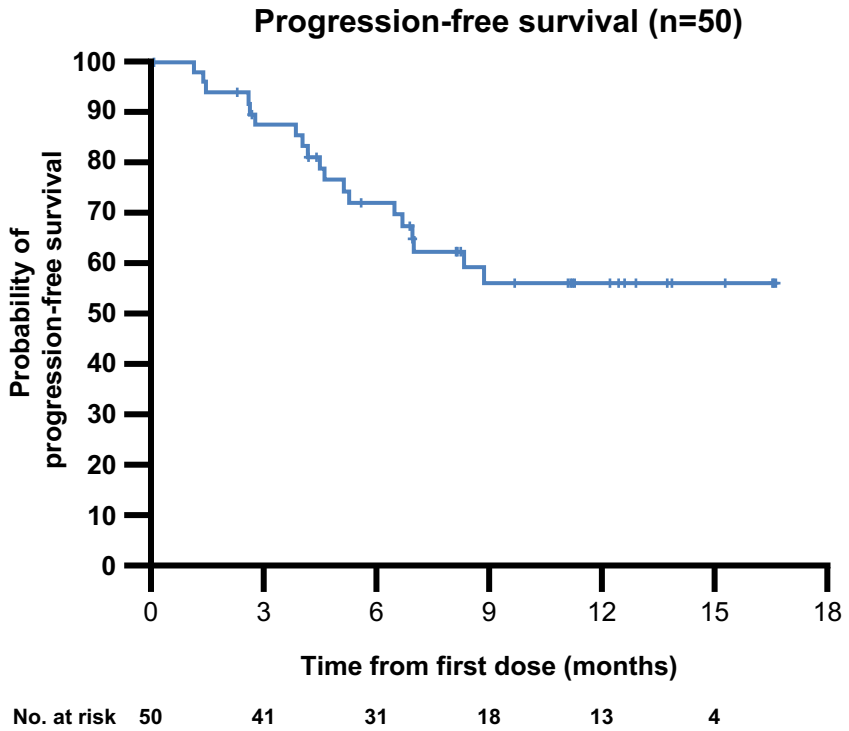
Patients evaluable for CNS response (n=50)	
CNS ORR*, %	**54 (95% CI 39, 68)**
Complete response, n (%)	6 (12)
Partial response, n (%)	21 (42)
Stable disease ≥6 weeks, n (%)	19 (38)
Progressive disease, n (%)	3 (6)
Not evaluable, n (%)	1 (2)
CNS DCR, %	**92 (95% CI 81, 98)**

CNS response based on prior brain RT status*	
Prior RT ≤6 months before first dose, n	19 / 50
CNS ORR, %	32% (95% CI 13, 57)
Complete response / partial response, %	11 / 21
No prior RT or RT >6 months before first dose, n	31 / 50
CNS ORR, %	68% (95% CI 48, 83)
Complete response / partial response, %	13 / 55

Population: evaluable for response
Scans were performed at baseline and every 6 weeks thereafter until RECIST disease progression
RT, radiation therapy

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

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#	19 / 50
Maturity	38%
Median CNS PFS#, months	**NC (95% CI 7, NC)**
Progression-free	
at 6 months§	**72% (95% CI 57, 83)**
at 12 months§	**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

AURA3 study design

Progression following 1st line, T790M+

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:

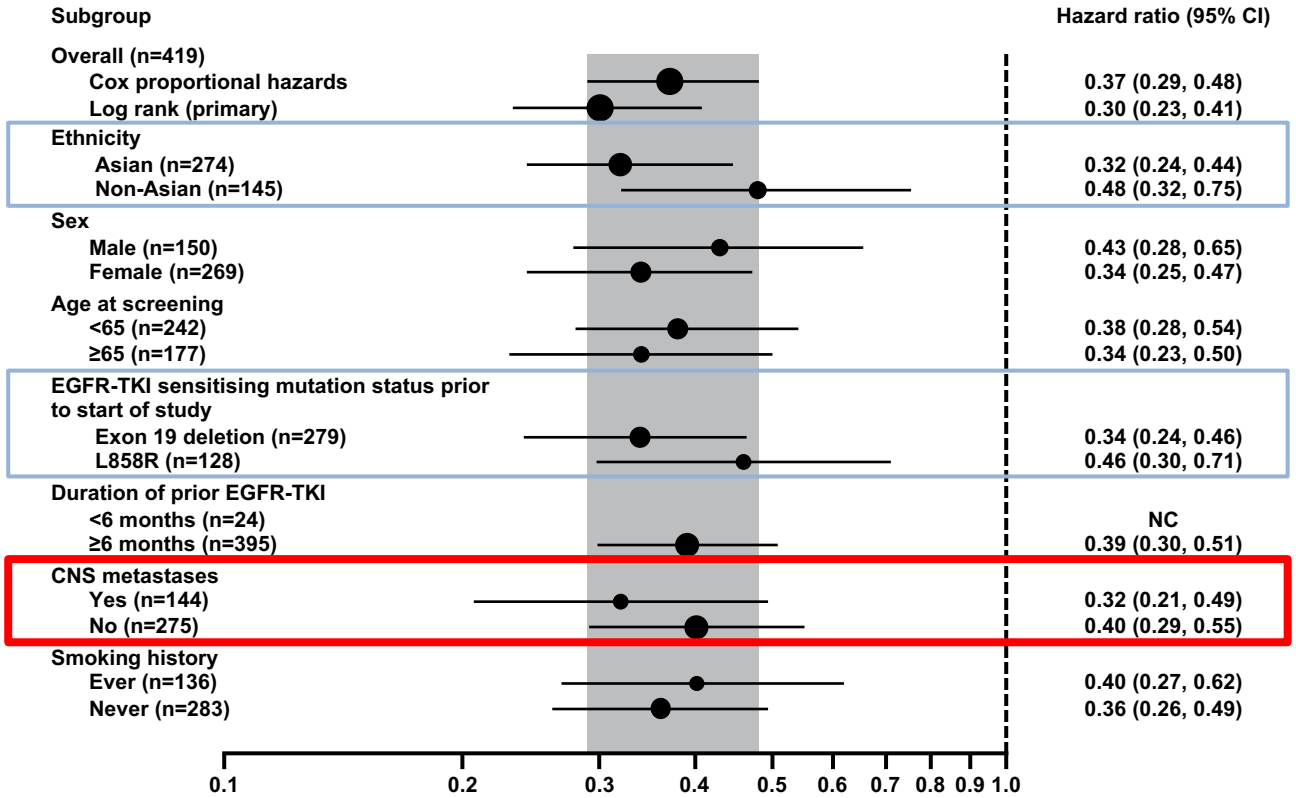
- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

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

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

CNS overall response

Evaluable for response set

	Osimertinib 80 mg n=30	Chemotherapy n=16
CNS ORR (95% CI)	**70% (51, 85)**	**31% (11, 59)**
Odds ratio (95% CI)	5.13 (1.44, 20.64); p=0.015	
Median time to response, weeks	6.1	6.1
Median DoR, months (95% CI)	**8.9 (4.3, NC)**	**5.7 (NC, NC)**
DCR (95% CI)	**93% (78, 99)**	**63% (35, 85)**

- CNS ORR in patients who had brain RT within 6 months of randomization vs no prior brain RT or RT ≥6 months before randomization (full analysis set) were:
  - Osimertinib: 64% (9/14) (95% CI 35, 87) and 34% (21/61) (95% CI 23, 48)
  - Chemotherapy: 22% (2/9) (95% CI 2, 60) and 16% (5/32) (95% CI 5, 33)

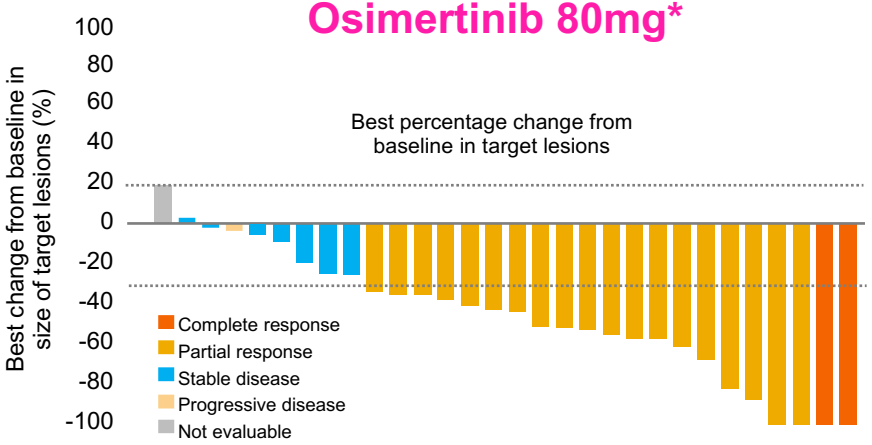
Populations: CNS evaluable for response set: patients with ≥1 measureable CNS metastases on baseline brain scan by BICR. CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR

Data cut-off: April 15, 2016. CR, complete response; DoR; duration of response; NE, not evaluable; NC, not calculable; ORR, objective response rate; PD, progressive disease; PR, partial response; RT, radiotherapy; SD, stable disease; *response did not require confirmation

Tumor response in CNS

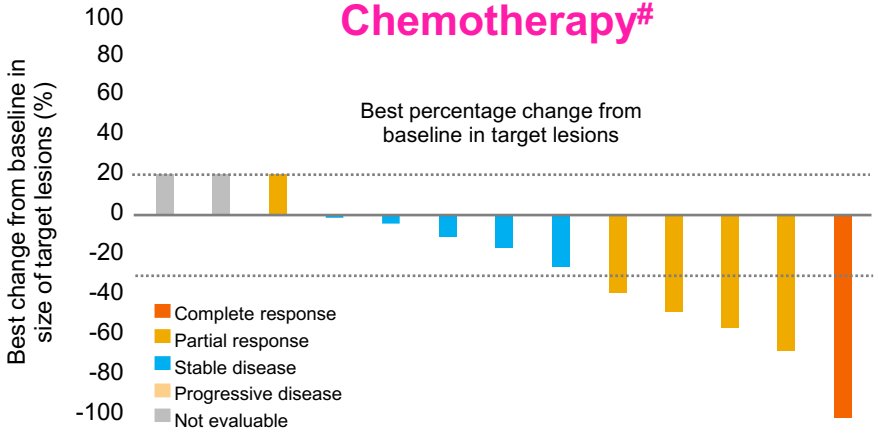
Evaluable for response set

Osimertinib 80mg*



- Median baseline CNS target lesion size:
  - 16.3 mm (range 10–60 mm)
- Median best percentage change from baseline in CNS target lesion size:
  - -43% (range -100% to +20%)

Chemotherapy#



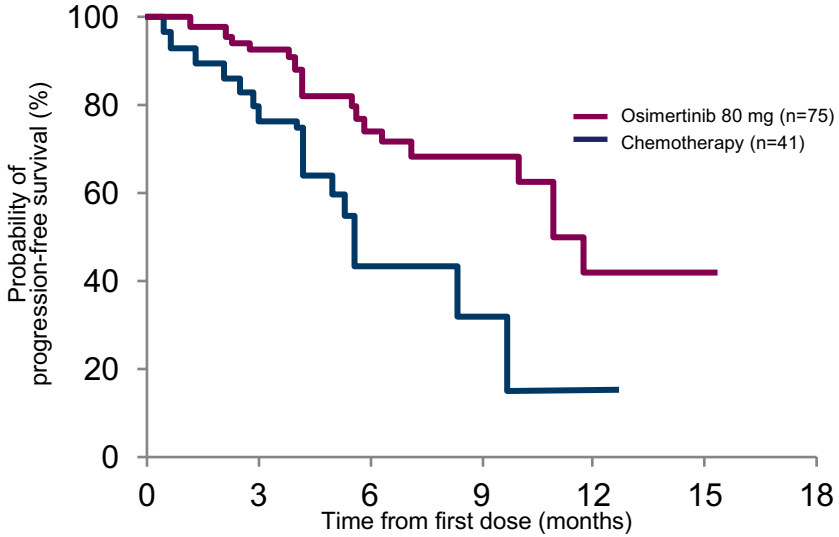
- Median baseline CNS target lesion size:
  - 16.2 mm (range 11–56 mm)
- Median best percentage change from baseline in CNS target lesion size:
  - -16% (range -100% to +20%)

Population: CNS evaluable for response set : patients with ≥1 measurable CNS metastases on baseline brain scan by BICR

Data cut-off: April 15, 2016. *1patient was not evaluable due to no evaluable follow-up assessments. #Best % change in CNS target lesions for 3 patients with stable disease could not be imputed as the patients did not meet any of the three imputation criteria, 2 patients were not evaluable due to death (n=1) and study withdrawal due to progressive disease (n=1)

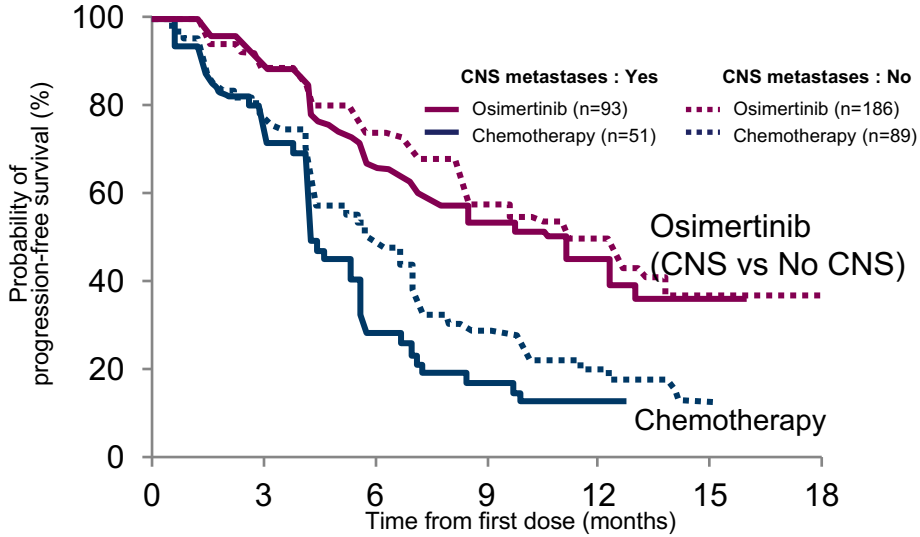
CNS PFS in AURA3

CNS full analysis set



Median CNS PFS, months	n	CNS PFS	HR (95%, CI)
Osimertinib 80mg	75	**11.7**	**0,32** (0.15-0.69); p=0.004
Chemotherapy	41	**4,2**	

Overall population



Median PFS, months	CNS metastases : Yes			CNS metastases : No		
	n	PFS	HR (95%, CI)	n	PFS	HR (95%, CI)
Osimertinib 80mg	93	**8.5**	**0.32** (0.21-0.49) p<0.001	186	**10.8**	**0.40** (0.29-0.55) p<0.001
Chemotherapy	51	**4.2**		51	**4.2**	

Population: CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR

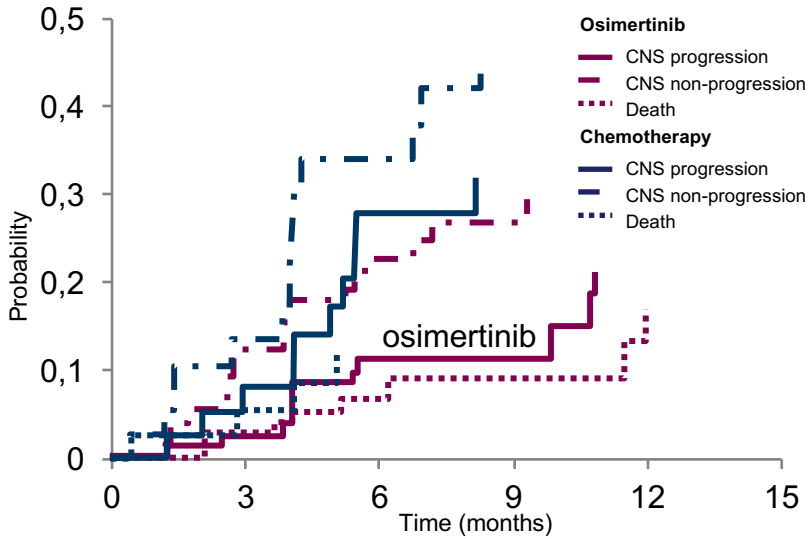
Data cut-off: April 15, 2016

*Censored patients only; #Only includes progression events that occurred within 19 weeks of the last evaluable assessment; §Estimated by Kaplan-Meier technique,

Probability of experiencing a CNS progression event lower for osimertinib

Full analysis set

	Osimertinib 80mg n=75	Chemotherapy n=41
Type of event, n %		
- CNS progression	**11 (15)**	**10 (24)**
- Non-CNS progression	19 (25)	15 (37)
- Death	8 (11)	4 (10)
- Censored	37 (49)	12 (29)
CNS conditional probability		
- At 3 months, % (95% CI)	**2.7** (0.8, 9.6)	8.2 (2.3, 28.7)
- At 6 months, % (95% CI)	**11.5** (5.9, 22.4)	28.2 (16.6, 48.0)



- The probability of experiencing a CNS progression event (conditional on the patient not experiencing a competing risk at that time) was lower for osimertinib than for chemotherapy at both 3 and 6 months
- There is **clear separation of the cumulative incidence curves** in favour of osimertinib, for both CNS and non-CNS progression, for the duration of the follow-up period

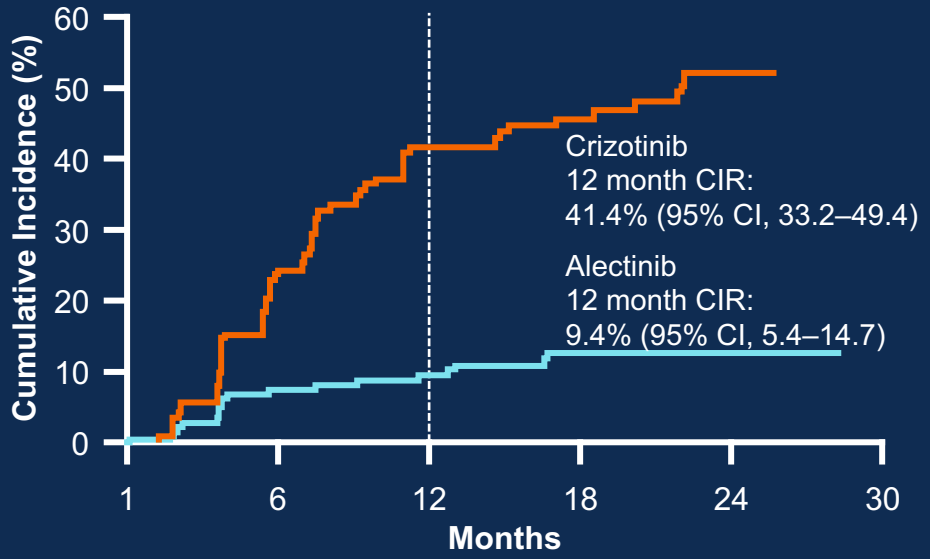
Population: CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR
Data cut-off: April 15, 2016

Exemple in ALK+ (crizotinib vs alectinib)
Time to CNS progression (by IRC, ITT)

- A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted
- For each patient, the first event of CNS progression, non-CNS progression or death was counted

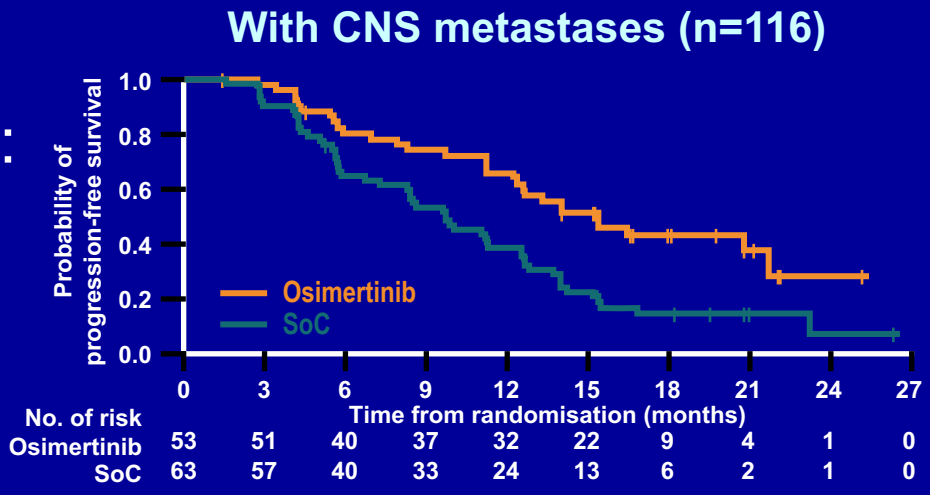
	Crizotinib (N=151)	Alectinib (N=152)
Patients with events, n (%)	68 (45)	18 (12)
Cause-specific HR (95% CI) P-value (log-rank test)	**0.16** (0.10–0.28) P<0.0001	

Cumulative incidence of CNS progression



1st line EGFR+ CNS efficacy in FLAURA

- CNS progression in patient **with** CNS met at presentation:
  - Osimertinib: 10/53 (18.9%)
  - SoC: 27/63 (42.7%)
- CNS progression in patients **without** CNS met at presentation:
  - Osimertinib: 5 patients
  - SoC: 17 patients



Systemic PFS (not CNS progression)

T.Mok, ESMO 2017

So what does this mean ?

▲ **Osimertinib is highly active in the brain**

- Rapid, durable responses
- Active against LM disease

▲ **Osimertinib is protective aganist CNS metastases**

- Without compromising PFS
- An early switch to osimertinib on PD: preferred
- Questions « treatment beyond PD » on 1st line TKI and role of CNS RT ?

New drug…AZD3759

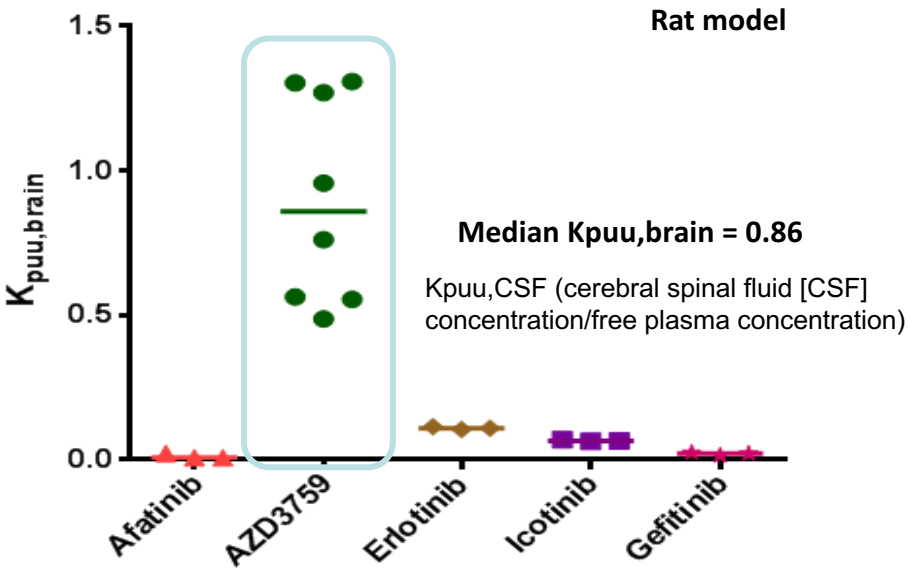
- AZD3759 is an oral, CNS penetrable, reversible inhibitor of EGFR activating mutations, designed to achieve high free-drug exposure in brain, CSF and plasma

- AZD3759 shows profound anti-tumor efficacy in pre-clinical BM and LM models[6,7], and promising anti-tumor activity in TKI relapsed patients with CNS metastases in dose escalation cohorts of BLOOM study

6. Zeng Q et al *J Med Chem* 2015; 58;8200-15. 7. Yang et al *Sci Transl Med.* 2016;8:368ra172. 8. Ahn et al *ASCO 2016.*

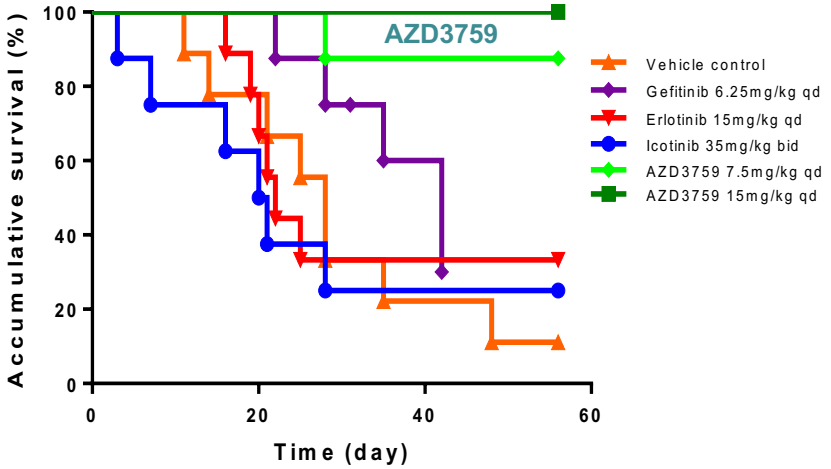
First and second generation EGFR-TKIs modestly penetrate Blood Brain Barrier (BBB)

AZD3759 outstanding BBB characteristics



Median Kpuu,brain = 0.86

Kpuu,CSF (cerebral spinal fluid [CSF] concentration/free plasma concentration)



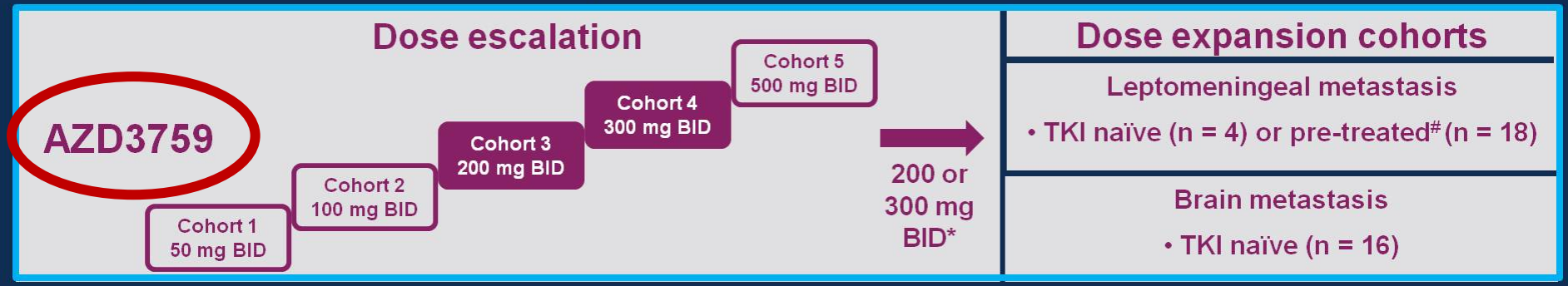
AZD3759 is not a substrate
- **of PGP**
- **or BCRP efflux transporters**

Significantly prolonged animal survival in PC-9 BM model, compared with gefitinib, erlotinib, icotinib

Kim DW, et al. ASCO 2015

BLOOM study design overview

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

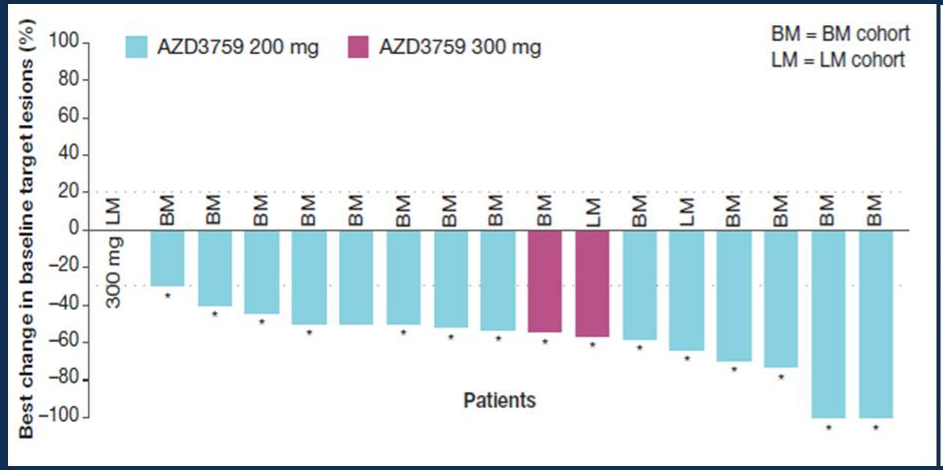


*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy; #Requires stable extracranial disease if EGFR TKI pre-treated; BID, twice daily; QD, once daily

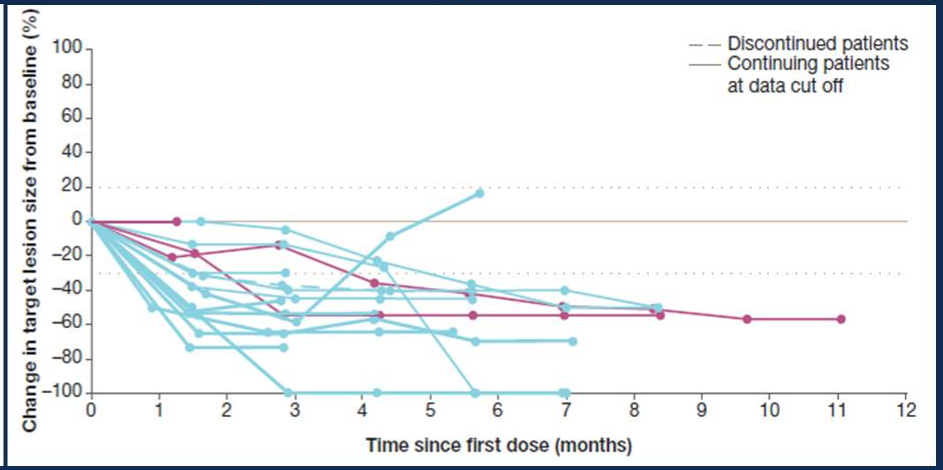
This presentation only covers AZD3759 TKI naïve BM (n = 16) and LM (n = 4) cohorts

Promising intracranial anti-tumor efficacy

Best % change of BM target lesions



% change of BM target lesion size with time



Patients with BM target lesions at baseline and at least one mRECIST assessment were included. *: confirmed response

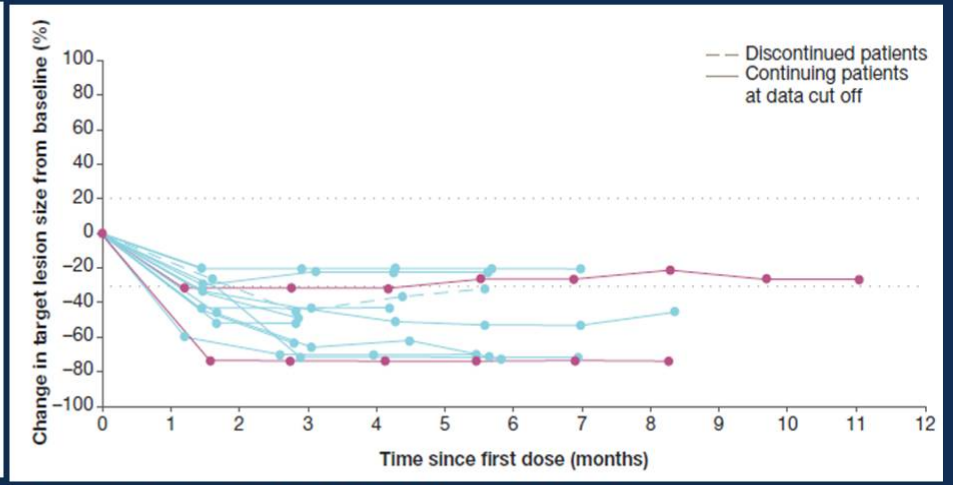
Investigator Assessed

- 15 out of 18 (83%) patients with measurable BM lesions at baseline had confirmed objective response, 14 PRs and 1 CR.
- Median best % change of intracranial target lesions was -54% (ranging -100% to 0)
- 16 patients were still on AZD3759 treatment at data cut-off on December 12th, 2016.

Promising extracranial anti-tumor efficacy

Best % change of extracranial target lesions

% change of extracranial target lesion size with time



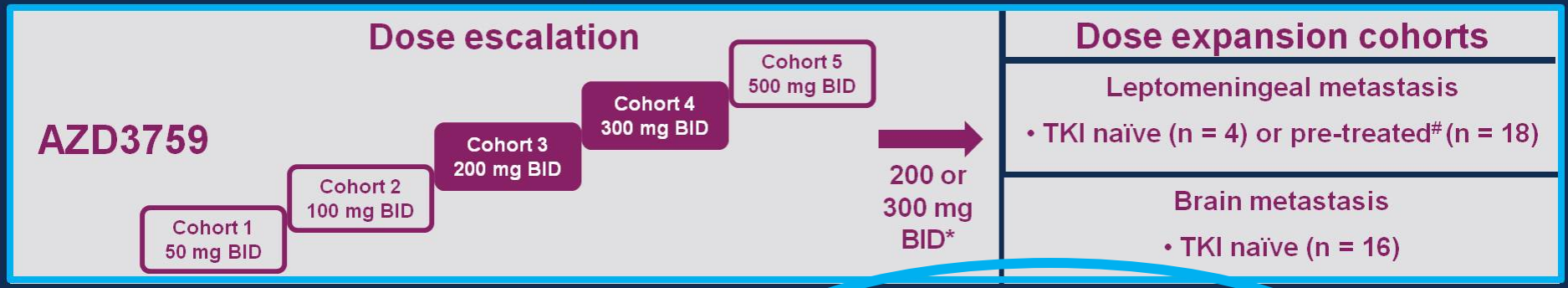
Patients with extracranial target lesions at baseline and at least one RECIST assessment were included. *: confirmed response

- 13 out of 18 (72%) patients with extracranial lesions had confirmed objective response, 11 PRs and 2 CRs (these two patients had non-target lesions at baseline).
- Median best % change of extracranial target lesions was -50% (ranging -74% to -20%)
- 12 patients were still responding at data cut-off on December 12th, 2016

Investigator Assessed

BLOOM study design overview

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



*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy; #Requires stable extracranial disease if EGFR TKI pre-treated; BID, twice daily; QD, once daily

This presentation only covers AZD3759 TKI naïve BM (n = 16) and LM (n = 4) cohorts

BLOOM study: duration of exposure (*T790M unselected cohort, n=21*)

- Median duration of exposure:12.4 months (range: 0–22 months)
- 5 patients (24%): dose reduction ➔ 4 patients (19%): dose reduction due to an AE

ae, discontinued treatment due to an AE; D, died; dc, discontinued treatment; dcD,discontinued and died; QD, once daily.

James Chih-Hsin Yang et al, ASCO 2017

BLOOM study: osimertinib activity across LM assessments

Overall LM response by investigator assessment in the evaluable for LM response analysis set *(T790M unselected cohort, n=21)*

	T790M unselected cohort (n=21)
LM response*, % (95% CI)	43% (22, 66)
Best LM response, n (%)	
• Complete response*	1 (5%)
• Responding*	8 (38%)
• Stable disease (≥ 6 weeks)	9 (43%)
• Progression	1 (5%)
• Not evaluable	2 (10%)

Median duration of response

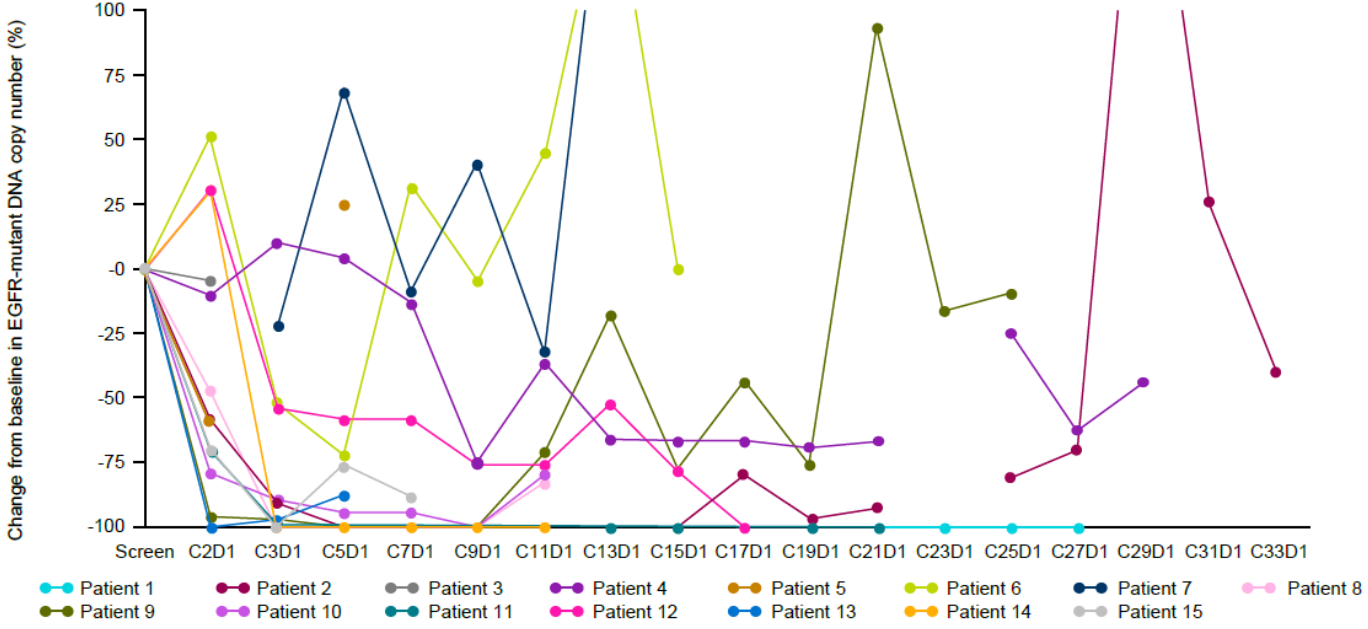
18.9 months
(range: 5.6–19.3 months; 95% CI 11.1, NC)

*Response for LM is defined as at least one confirmed response of Complete Response or Responding (as defined by investigator's assessment), requires confirmation after 4 weeks.
LM, leptomeningeal metastases.

James Chih-Hsin Yang et al, ASCO 2017

BLOOM study: dynamic changes in EGFR-mutant DNA copy number in T790M unselected cohort *(mutant DNA copies / mL; n=15)*

From screening to Cycle 2 Day 1, **mean decrease in EGFR-mutant DNA copy: 39% in 15/21**



C, cycle; D, day.

James Chih-Hsin Yang et al, ASCO 2017

CNS responses in pts with leptomeningeal metastases at baseline (AURA 3: Progression following 1st line, T790M+)

Full analysis set

- Patients with leptomeningeal metastases (LM) were not excluded from the trial
- Retrospective independent radiological review based on RANO-LM[1] identified LM in 7/116 patients with CNS metastases at baseline in the osimertinib arm
- **4 out of 7 patients had a LM response**
  - 2 patients had a complete LM response
  - 2 patients had a partial LM response
- In patients with an LM response, clinical activity was also seen in the CNS and systemically

Treatment	Prior brain radiotherapy	Best objective response		
		LANO RANO-LM score	CNS RECIST v1.1	Systemic RECIST v1.1
Osimertinib 80 mg	No	CR	CR	PR
	No	CR	PR	PR
	No	PR	SD	SD
	No	PR	SD	SD
	No	SD	SD	PR
	Yes	SD	SD	SD
	Yes	SD	SD	SD

Data cut-off: April 15, 2016 Population: CNS full analysis set: patients with ≥1 measureable and/or non-measurable CNS metastases on baseline brain scan by BICR

1. Chamberlain et al. Neuro Oncol2017 Apr1;19(4):484-492. LANO, Leptomeningeal Assessment in Neuro-Oncology; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumors

In conclusion

- **In EGFRm NSCLC, brain increasingly become a sanctuary site where the BBB may offer protection from pharmacological agents**

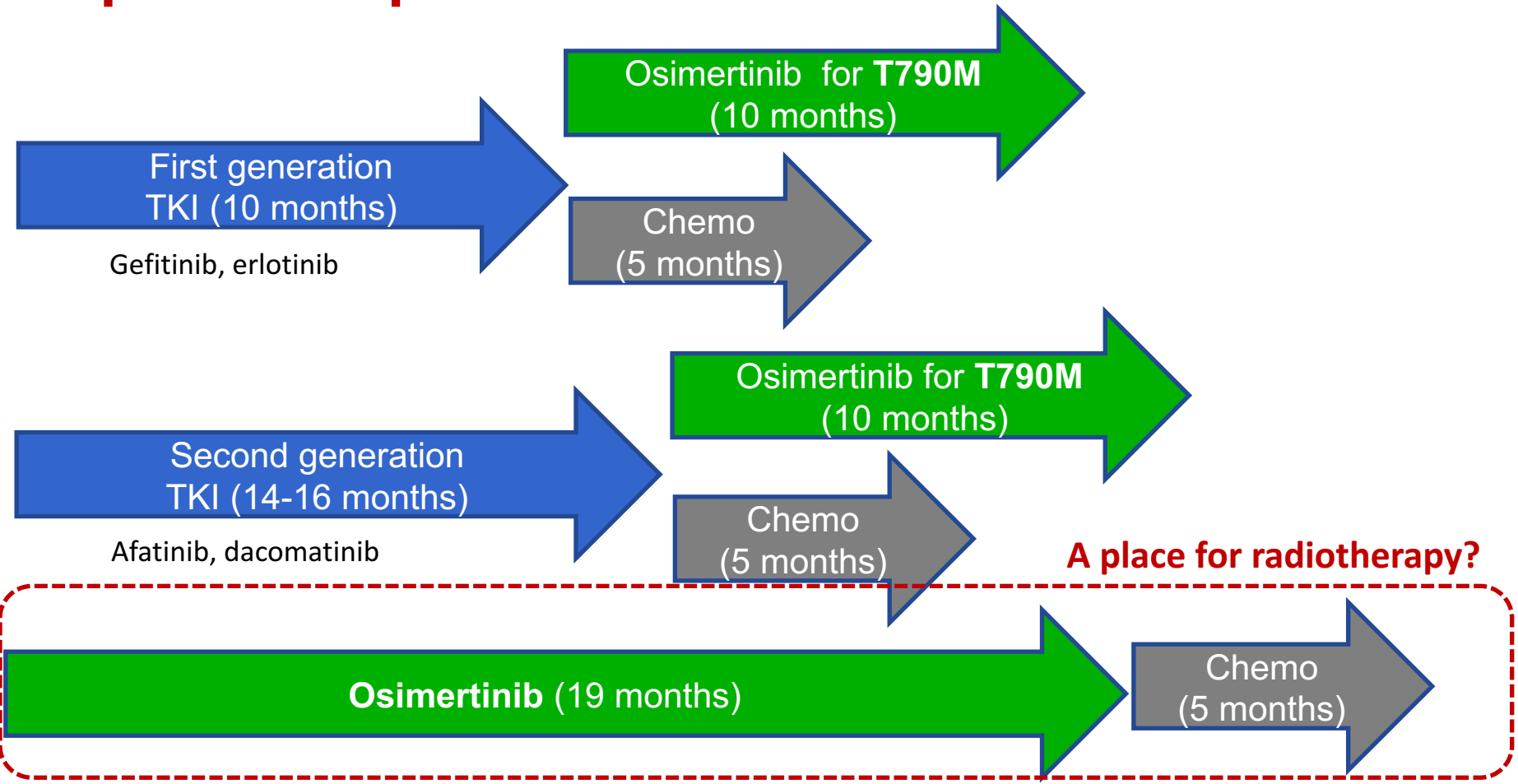
- Poor penetration rates of 1st /2nd generation EGFR-TKIs across the BBB
- Role of systemic chemotherapy is controversial

- **3nd EGFR TKI like osimertinib** is particularly promising in BM or LM population:
  - Osimertinib approved by the FDA/EMA for treatment of patients with NSCLC harboring a T790M mutation
  - Moving in 1st line … FLAURA trial

- **AZD3759** outstanding BBB characteristics

- **Further evaluation of in larger clinical studies is required alone and in combination with brain irradiation**

Optimal sequence for EGFR mutation?



THANK YOU !

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