Are EGFR TKIs Treatment Options for NSCLC With Brain Metastases?

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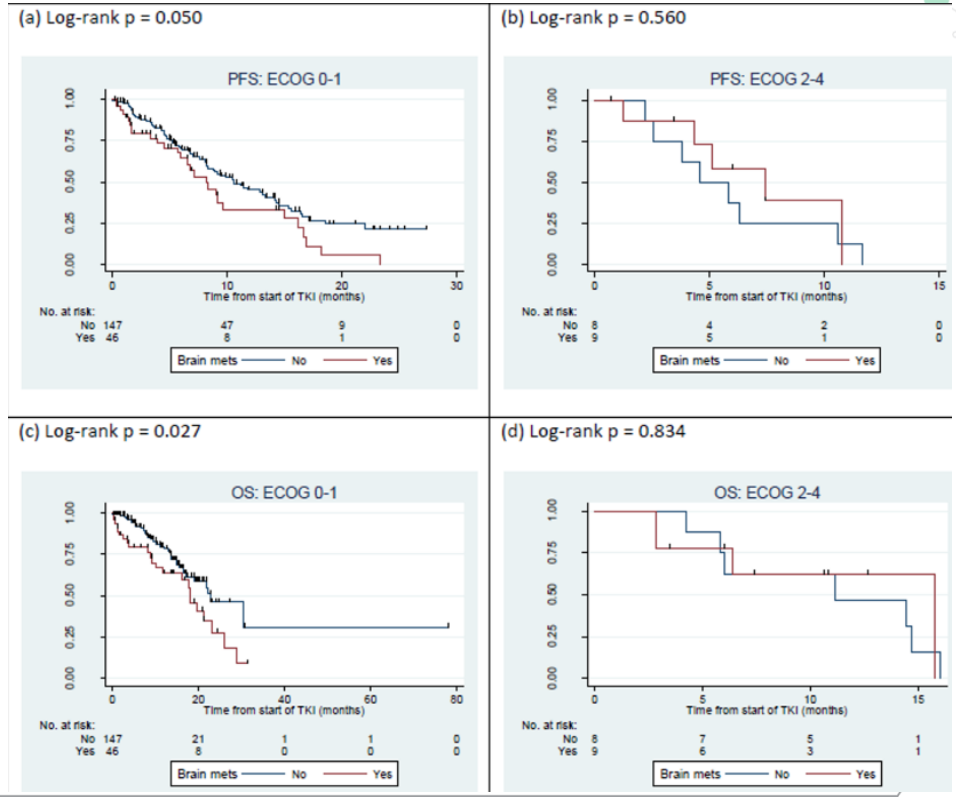
Disclosures

- Honoraria – Merck Sharp & Dohme, Bristol-Myers Squibb, Roche, Pfizer
- Advisories – Boehringer Ingelheim, Bristo-Myers Squibb, Merck Sharp & Dohme, Novartis

Impact of Brain Metastases

- Brain metastases can be devastating
- Common sanctuary site for metastatic disease
  - ≈10% of newly diagnosed stage IV NSCLCs have brain metastases[1]
- Life-limiting, as treatment options were limited to radiation



Kaplan-Meier plots of cohort of 211 patients treated with 1st-line EGFR TKI[2]

(a) PFS by brain metastasis in ECOG 0-1 patients

(b) PFS by brain metastasis in ECOG 2-4 patients

(c) OS by brain metastasis in ECOG 0-1 patients

(d) OS by brain metastasis in ECOG 2-4 patients

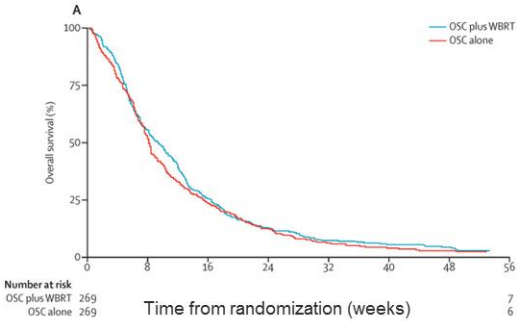
ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-gree survival.

1. Schouten et al. *Cancer*. 2002;94:2698; 2.Jain et al. *PLOS One.* 2015;10:e0123587.

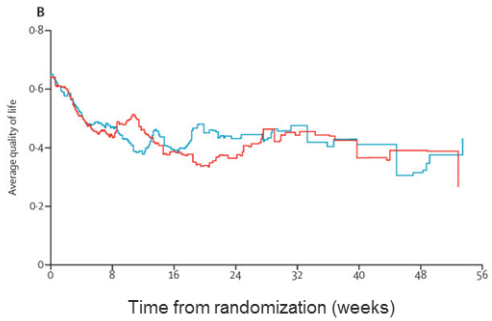
WBRT for Patients With Brain Metastases

- WBRT is routinely used to treat patients with NSCLC with brain metastases
- Despite the widespread use of WBRT, there is a paucity of studies assessing its benefit over optimal supportive care (OSC)
- Data also indicate that WBRT is inferior to stereotactic radiosurgey[1]
- Only one adequately powered randomised clinical trial has assessed the use of WBRT in patients with brain metastases from NSCLC; **the findings indicate that WBRT provides limited clinical benefit[2]**

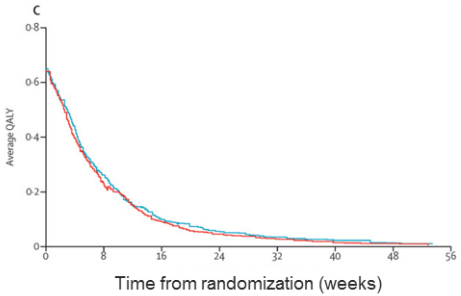
No between-group difference in overall survival (hazard ratio 1.06, 95% CI 0.90–1.26)



Quality of life (EQ-5D 3L) remained similar over time



Limited improvement in QALY with WBRT
OSC + WBRT vs OSC:
46.4 days (3.66) vs 41.7 (3.23) days



- Therefore, alternate treatments should be considered for these patients

CI = confidence interval; EQ-5D 3L = three-level EQ-5D; NSCLC = non-small cell lung cancer; OSC = optimal supportive care; QALY = quality-adjusted life year; WBRT = whole brain radiotherapy.

1. Magnuson et al. *J Clin Oncol*. 2017;35:1070; 2. Mulvenna et al. *Lancet*. 2016;388:2004.

CSF Levels and Penetration of EGFR TKIs[a]

Drug	Study	CSF Levels (Concentration, nM)	CSF Penetration Rate (Mean ± SD)
Gefitinib[1]	Comparison of the 2 TKIs in 15 Japanese patients	8.2±4.3 nM	1.13%±0.36%
Erlotinib[1]		66.9±39.0 nM	2.77%±0.45%
Afatinib[2-4]	Prospective multicentre trial of 11 Japanese patients[2] 1 patient from CUP treated with afatinib in the 4th line[3] Afatinib is also being studied as high-dose intermittent monotherapy[4b]	2.9 nM 1 nM	2.5%±2.9%
Osimertinib[5-7]	1 patient AURA-1 extension 1 patient from AURA 16 patients from BLOOM	0.77 nM[5] 3.44 nM[6] 7.51 nM (range 2.19-21.1 nM)[7]	NA (only data from preclinical models available)

[a]NOTE: In each of the above studies, CSF concentrations were determined using different methods of analysis, but CSF penetration rate was determined using the same method. Therefore, only the CSF penetration rate of different EGFR TKIs can be directly compared

[b]A phase Ib study found that high-dose intermittent afatinib dosing (maximum tolerated dose:160 mg for 3 days every 14 days) achieved higher peak plasma concentration than continuous standard dosing (40 mg/day) and preserved afatinib's tolerability[4]

CSF = cerebrospinal fluid; CUP = compassionate use program; EGFR = epidermal growth factor; NA = not available; SD = standard deviation; TKI = tyrosine kinase inhibitor.

1. Togashi et al. *Cancer Chemother Pharmacol.* 2012;70:399; 2. Tamiya et al. *Anticancer Res.* 2017;37:4177; 3. Hoffknecht et al. *J Thorac Oncol*. 2015;10:156; 4. Camidge et al. *Clin Lung* Cancer. 2018;19:e655; 5. Pareek et al. *J Thorac Oncol.* 2016;11:e135; 6. Ahn et al. *Eur J Cancer.* 2015;51:3083; 7. Yang et al. ASCO 2017. Abstract 2020.

First-Generation EGFR TKIs Prospective Data Limited

Phase 2 Study With Either Erlotinib or Gefitinib[1]

- N=28
- Systemic PR=83%; SD=11%; mPFS, 6.6 mo; mOS, 15.9 mo
- No significant differences
- **No information was provided on intracranial activity**

Phase 2 CTONG-0803 Study of Erlotinib as Second-Line Treatment[2]

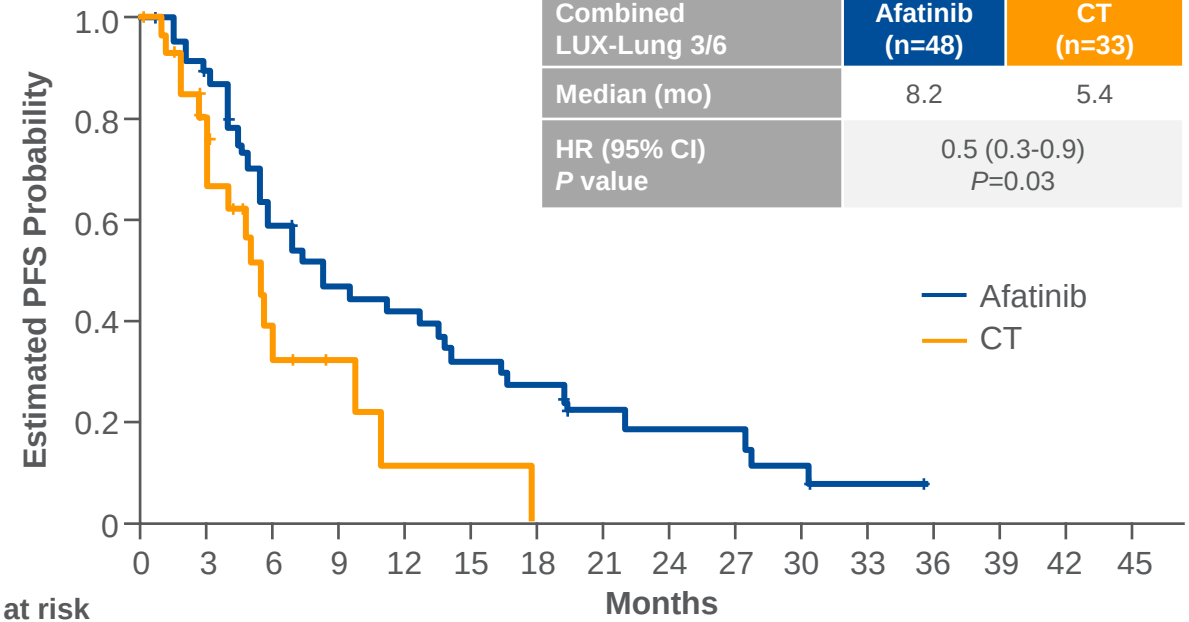
- N=48 with asymptomatic brain metastases after first-line CT[2]
- Intracranial mPFS, 10.1 mo; overall mPFS, 9.7 months
- **8 patients** with EGFRm+ disease
  - **No intracranial efficacy was reported**

CT = chemotherapy; EGFR = epidermal growth factor; mPFS = median progression-free survival; mOS = median overall survival; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.

1. Park et al. *Lung Cancer*. 2012;77:556; 2. Wu et al. *Ann Oncol*. 2013;24:993.

Second-Generation EGFR TKI Prospective Data for Afatinib: LUX-Lung 3/6

Combined LUX-Lung 3/6	Afatinib (n=48)	CT (n=33)
Median (mo)	8.2	5.4
HR (95% CI) *P* value	0.5 (0.3-0.9) *P*=0.03	

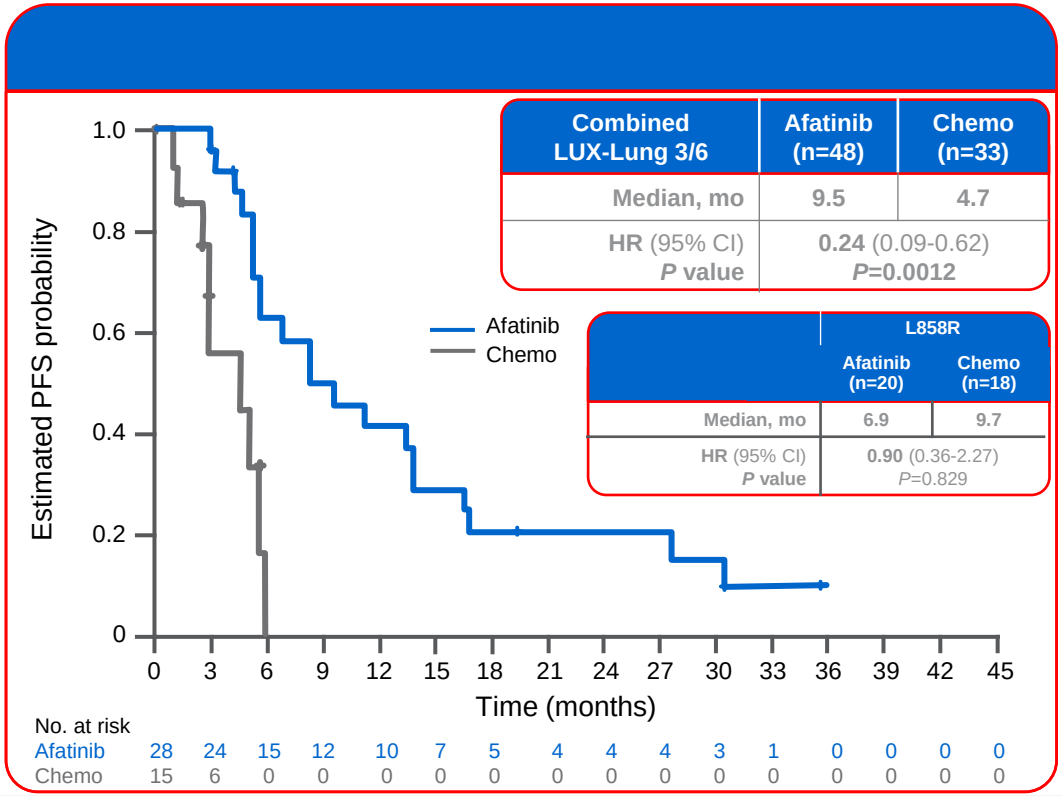


No. at risk																
Afatinib	48	39	25	19	17	13	11	6	5	5	3	1	0	0	0	0
CT	33	16	5	3	1	1	0	0	0	0	0	0	0	0	0	0

CT = chemotherapy; EGFR = epidermal growth factor; HR = hazard ratio; TKI = tyrosine kinase inhibitor.

Schuler et al. *J Thorac Oncol*. 2016;11:380.

PFS in Patients With Brain Metastases and Del19 Mutation (From LUX-Lung 3/6)



Combined LUX-Lung 3/6	Afatinib (n=48)	Chemo (n=33)
Median, mo	9.5	4.7
HR (95% CI) *P* value	**0.24** (0.09-0.62) ***P*=0.0012**	

	L858R	
	Afatinib (n=20)	Chemo (n=18)
Median, mo	6.9	9.7
HR (95% CI) *P* value	**0.90** (0.36-2.27) *P*=0.829	

HR = hazard ratio; PFS = progression-free survival.

Schuler et al. *J Thorac Oncol.* 2016;11:380.

Time to CNS Progression

	LUX-Lung 3		LUX-Lung 6	
	Afatinib (n=9)	Cis/Pem (n=5)	Afatinib (n=6)	Cis/Gem (n=5)
Time to CNS progression, mo (95% CI)	15.2 (7.7-29.0)	5.7 (2.6-8.2)	15.2 (3.8-23.7)	7.3 (3.7-10.9)

Patients with or without baseline brain metastases:

- Median time to CNS progression was longer with afatinib vs chemotherapy

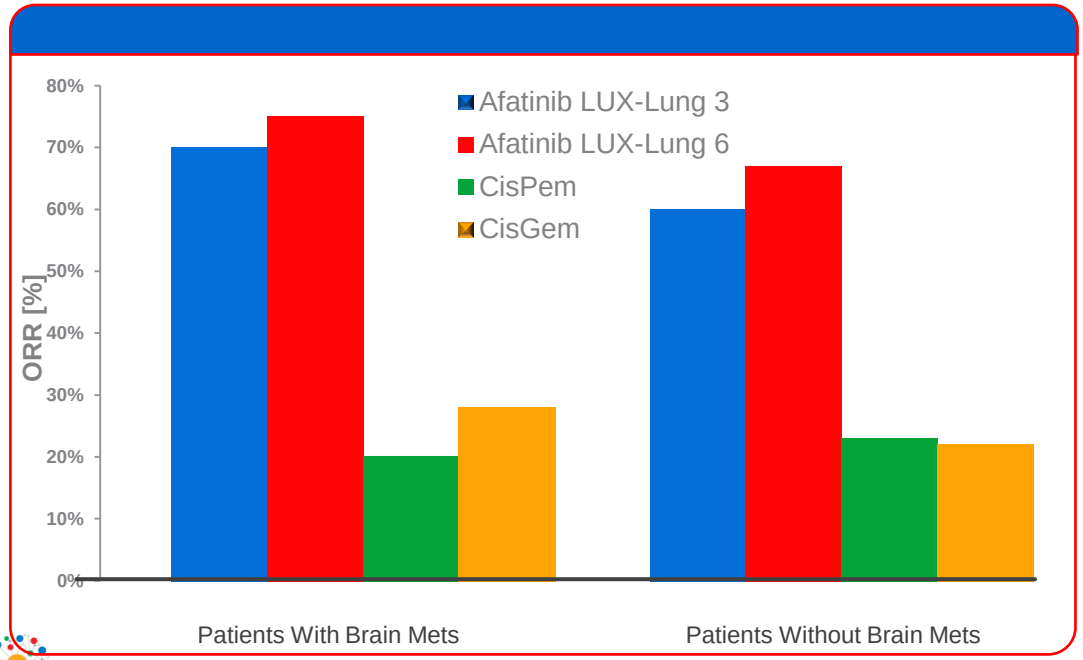
Patients with baseline brain metastases:

- In the majority of patients who experienced PD on afatinib, the brain was not the site of first disease progression

CI = confidence interval; CNS = central nervous system; PD = progressive disease.

Schuler et al. *J Thorac Oncol.* 2016;11:380.

ORR in Patients With and Without Brain Metastases and Common EGFR Mutations in LUX-Lung 3 and 6



With Brain Mets	Afatinib	Chemo	*P* value
LUX-Lung 3	70%	20%	0.0058
LUX-Lung 6	75%	28%	0.0027

Without Brain Mets	Afatinib	Chemo	*P* value
LUX-Lung 3	60%	23%	<0.0001
LUX-Lung 6	67%	22%	<0.0001

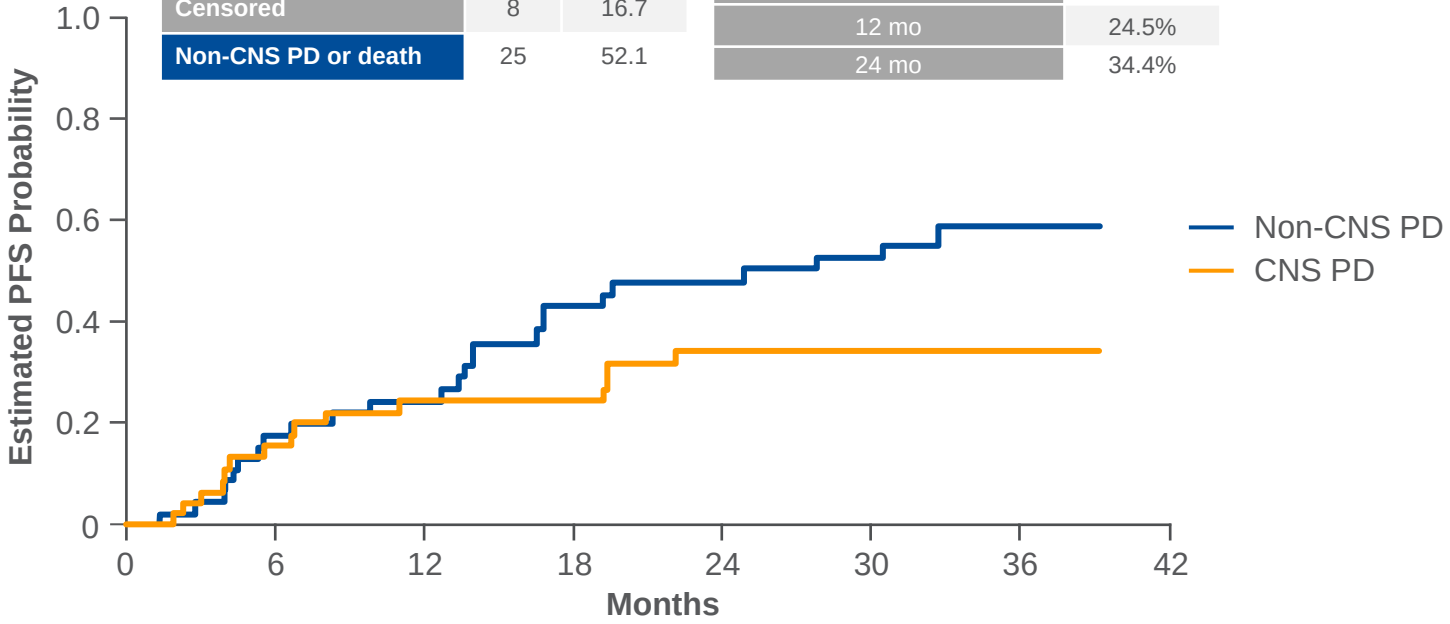
EGFR = epidermal growth factor receptor; ORR = objective response rate.

Schuler et al. *J Thorac Oncol.* 2016;11:380.

Prospective Data for Afatinib: LUX-Lung 3/6—Competing Risk for Progression in Patients With Baseline BM

LUX-Lung 3/6[1]	n	%
CNS PD	15	31.3
Censored	8	16.7
Non-CNS PD or death	25	52.1

Risk for CNS Progression (LUX-Lung 3/6, Common Mutation)[2]	With Baseline BM
6 mo	15.5%
12 mo	24.5%
24 mo	34.4%



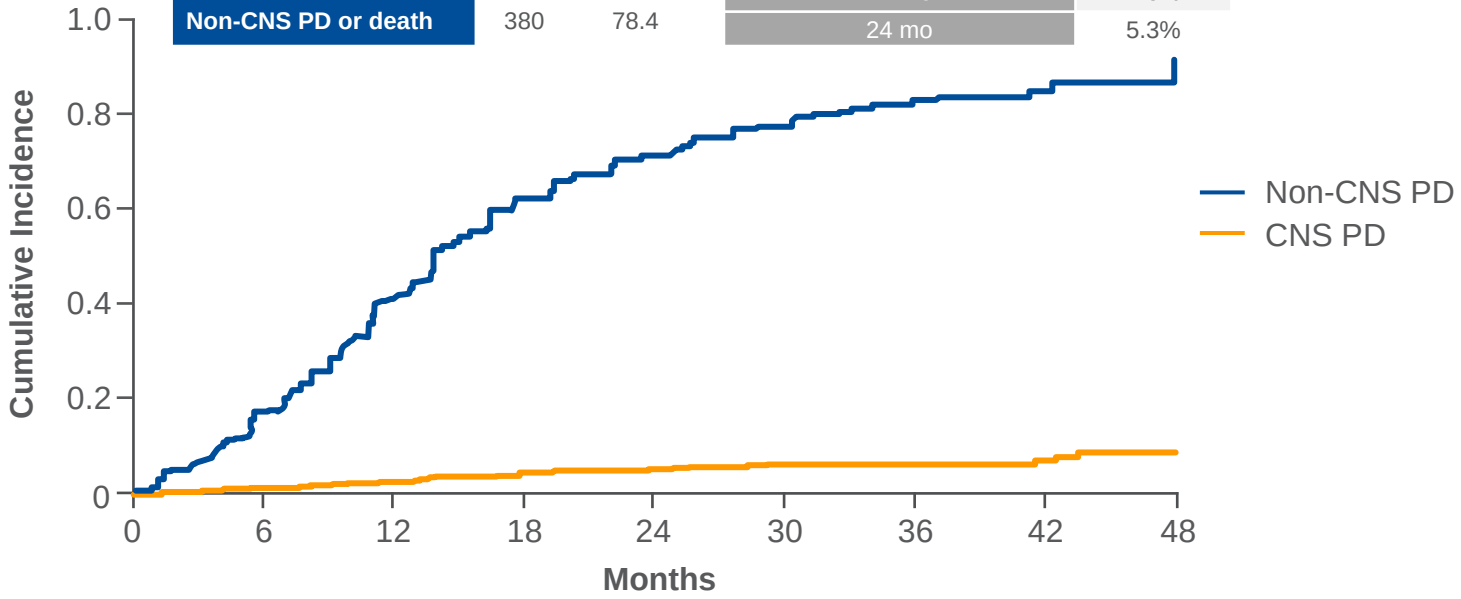
BM = brain metastasis; CNS = central nervous system; PD = progressive disease.

1. Girard. *Future Oncol.* 2018;14:1117; 2. Data on file, Boehringer Ingelheim.

Prospective Data for Afatinib: LUX-Lung 3/6/7— Competing Risk for Progression in Patients Without Baseline BM

LUX-Lung 3/6/7[1]	n	%
CNS PD	31	6.4
Censored	74	15.3
Non-CNS PD or death	380	78.4

Risk for CNS Progression (LUX-Lung 3/6/7, Common Mutation)[2]	Without Baseline BM
6 mo	1.3%
12 mo	2.6%
24 mo	5.3%



BM = brain metastasis; CNS = central nervous system; PD = progressive disease.

1. Girard. *Future Oncol.* 2018;14:1117; 2. Data on file, Boehringer Ingelheim.

First-Line Afatinib in EGFR-M+ NSCLC Patients With Brain Metastases: Significance of Starting Dose

- Retrospective analysis of 125 patients treated with first-line afatinib for advanced EGFR-M+ NSCLC diagnosed at the National Cancer Centre Singapore between April 2005 and January 2017
- Afatinib was started between January 2012 and February 2017

Amongst patients who had brain metastasis at start of afatinib (n=42):	No. of events / patients	Median PFS, months (95% CI)	Hazard ratio (95% CI)	Log-rank p-value
Starting dose of afatinib OD				0.040
30 mg	13 / 23	5.3 (3.1, 10.7)	1	
40 mg	7 / 17	13.3 (6.5, UD)	0.39 (0.15, 0.99)	

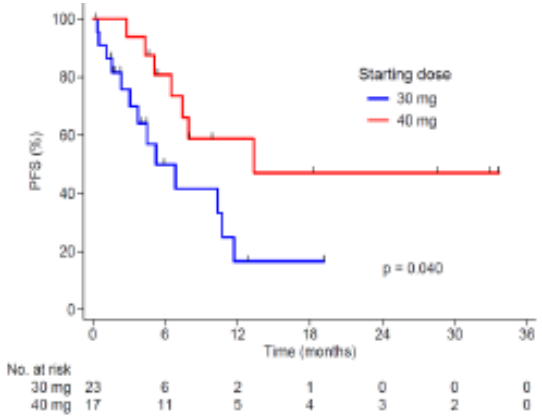


Fig. 3. Kaplan-Meier plot of PFS by afatinib starting dose in BM+ patients

Table 5: Multivariable cox model for brain metastases and afatinib starting dose on PFS

	No. of events / patients	Median PFS, months (95% CI)	Hazard ratio (95% CI)	p-value
No brain mets; 30mg starting dose	10 / 35	Not reached	1	
No brain mets; 40mg starting dose	30 / 44	15.0 (10.8, 22.1)	1.07 (0.51, 2.26)	0.852
Brain mets; 30mg starting dose	13 / 23	5.3 (3.1, 10.7)	3.10 (1.35, 7.08)	0.007
Brain mets; 40mg starting dose	7 / 17	13.3 (6.5, UD)	0.83 (0.31, 2.23)	0.020*

* This is the p-value for the interaction between brain mets and starting dose.
UD, undefined.

BM = brain metastases; CI = confidence interval; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; OD = once a day; PFS = progression-free survival.
Tan et al. CSCO 2017. Poster B0129; BMC Cancer 2018 (accepted).

Afatinib in Patients with EGFR M+ NSCLC with Leptomeningeal Carcinomatosis

Patient no.	Concentration (nM)		Penetration rate (%)	Best response	PFS (days)	OS (days)
	Plasma	CSF				
1	202.1	1.9	0.9	PD	45	57
2	141.1	2.5	1.7	PD	32	32
3	156.6	3.3	2.1	PD	44	115
4	235.8	3.9	1.6	PD	19	512[b]
5	257.2	NE	NE	PD	67	67
6	146.9	NE	NE	PR	309	396
7	62.6	5.8	9.3	SD	176	410
8	192.0	6.0	3.1	PD	61	212
9	NE	NE	NE	PD	17	31
10	767.6	0.8	0.1	PR	171[a]	171[b]
11	170.8	1.2	0.8	PR	105	105
Mean±SD	233.3±195.4	3.2±1.9				
Median (95% CI)	181.4	2.9	1.7 (2.5±2.9)	–	61 (18-174)	115 (32-410)

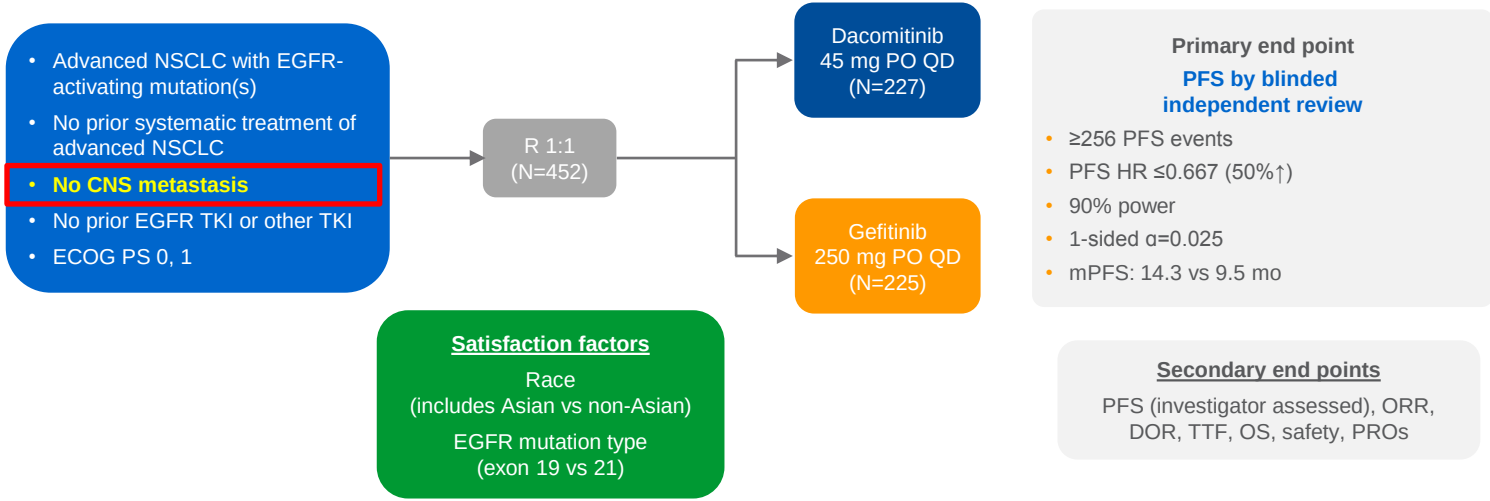
Median PFS: 2.0 months

Median OS: 3.8 months

EGFR = epidermal growth factor receptor; NE = not evaluated; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; SD = stable disease / standard deviation.
Tamiya et al. *Anticancer Res.* 2017;37:4177.

Second-Generation EGFR TKI
No Prospective Data for Dacomitinib

- A phase 2 study of dacomitinib in patients with progressive BM was terminated because of slow enrollment[1]
- In the phase 3 ARCHER 1050 trial, dacomitinib demonstrated superior benefit over gefitinib (mPFS 14.7 vs 9.2 mo; *P*<0.0001), **but patients with CNS metastases were excluded**[2,3]



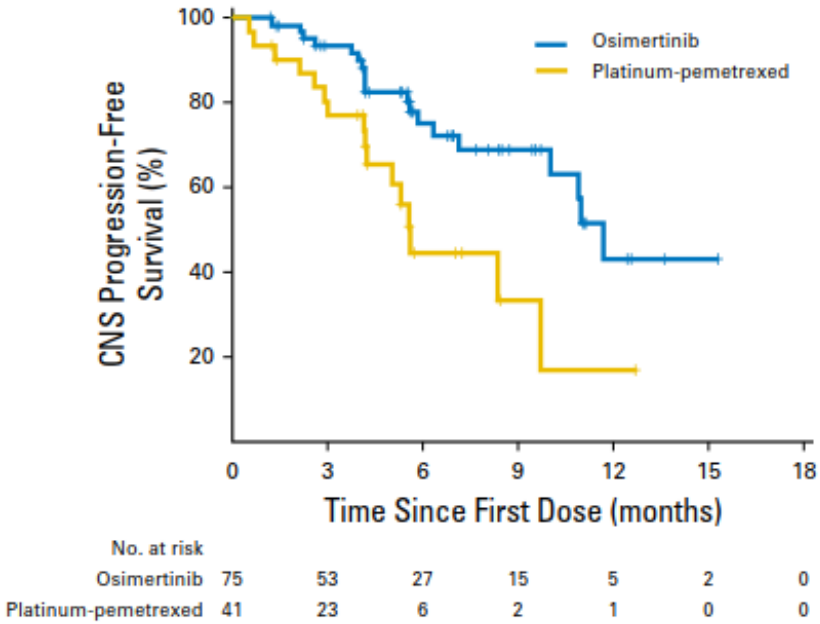
DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PO = by mouth; PRO = patient-reported outcome; R = randomisation; TTF = time to treatment failure.

1. https://clinicaltrials.gov/ct2/show/results/NCT02047747; 2. Mok et al. ASCO 2018. Abstract 9004; 3. Wu et al. *Lancet Oncol*. 2017;18:1454.

Third-Generation EGFR TKI Osimertinib Data: AURA 3 CNS Full Analysis Set

	OSI (n=75)	CT (n=41)
Prior brain RT	28 (37%)	20 (49%)
CNS ORR	30 (40%)	7 (17%)
Median CNS PFS	11.7 mo	5.6 mo
Median time to response onset	9.1 wk	6.1 wk

- Prior RT ≤6 mo of randomization
  - OSI: 9/14 (64%) had a response
  - CT: 2/9 (22%) had a response
- No prior RT or >6 mo before randomization
  - OSI: 21/61 (34%) had a response
  - CT: 5/32 (16%) had a response

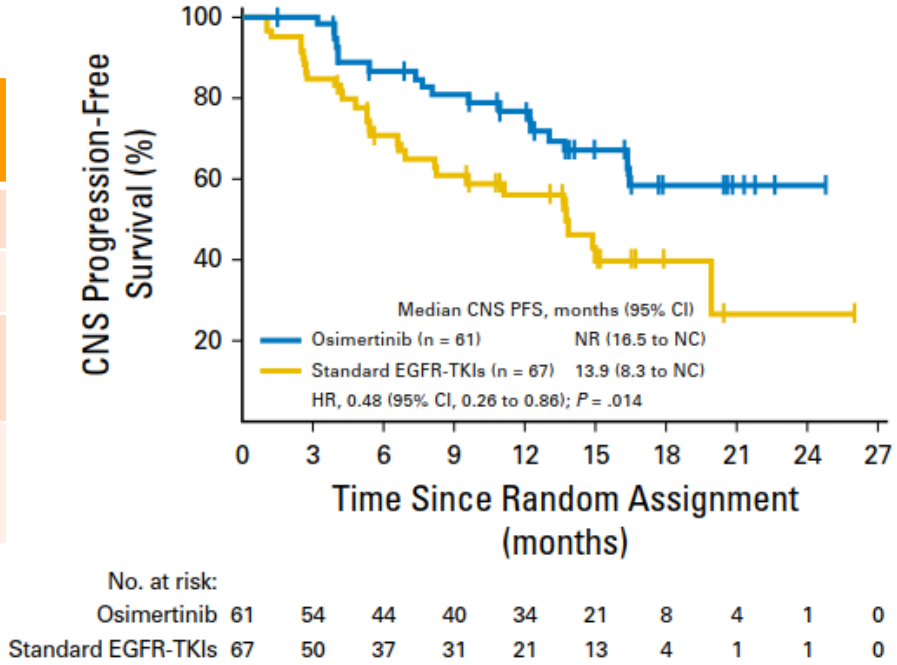


CNS = central nervous system; CT = chemotherapy; EGFR = epidermal growth factor receptor; OSI = osimertinib; RT = radiotherapy; TKI = tyrosine kinase inhibitor.

Wu et al. *J Clin Oncol*. 2018;36:2702.

Osimertinib Data: FLAURA CNS Full Analysis Set

	Osimertinib (n=61)	Gefitinib or Erlotinib (n=67)
Prior brain RT	15 (25%)	16 (24%)
CNS ORR	40 (66%)	29 (43%)
Median CNS PFS	Not Reached	13.9 mo
Median time to response onset	6 wk	12 wk

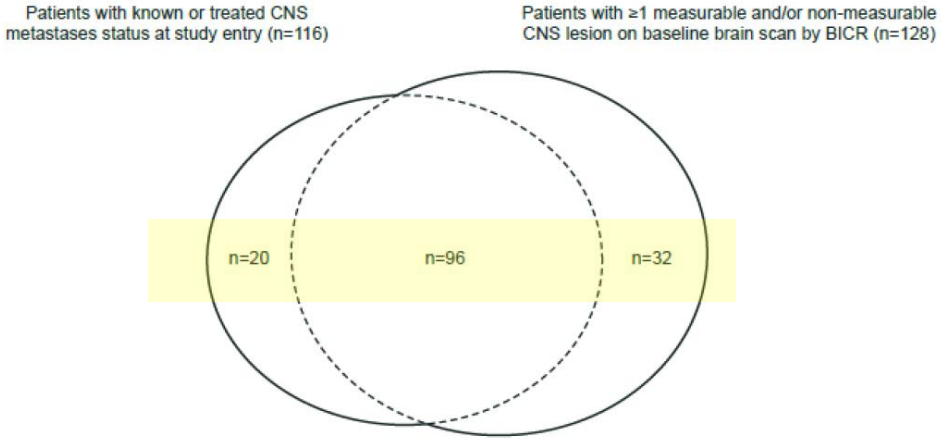


CNS = central nervous system; NR = not reached; NC = not calculable; ORR = objective response rate; PFS = progression-free survival; RT = radiotherapy.

Reungwetwattana et al. *J Clin Oncol*. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. [Epub ahead of print].

Osimertinib Data: ORR of Patients With Known or Treated CNS Metastases at Trial Entry in FLAURA

Overlap between patients with known or treated metastases at study entry and CNS full analysis set in FLAURA[1]



ORR and Duration of Response in patients with known or treated metastases at study entry in FLAURA[2]

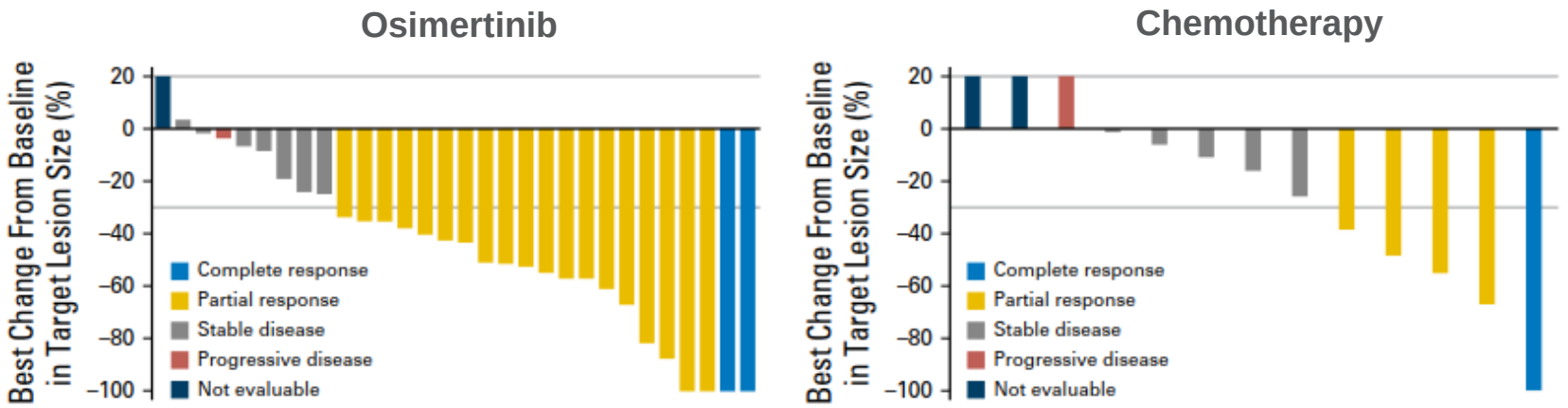
	Osimertinib (n=53)	Gefitinib or Erlotinib (n=63)
ORR	75%	86%
Median Duration of Response	13.8 mo	8.3 mo

BICR = blinded independent central review; CNS = central nervous system; ORR = objective response rate.

1. Supplement to Reungwetwattana et al. *J Clin Oncol*. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. [Epub ahead of print];
2. Supplement to Soria et al. *N Engl J Med*. 2018;378:113.

Osimertinib Data: AURA 3 CNS Evaluable-for-Response Set

	OSI (n=30)	CT (n=16)
CNS ORR	21 (70%)	5 (31%)
Median time to response onset	6.1 weeks	6.1 weeks
Median best percentage change from baseline in the sum of CNS target lesion size	- 43%	- 16%

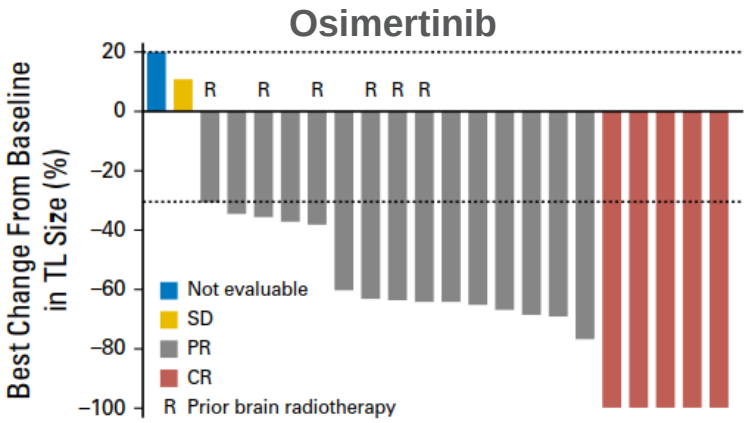


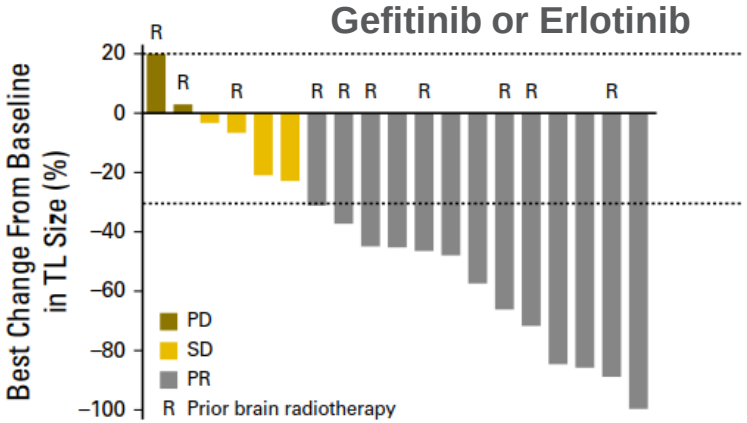
CNS = central nervous system; CT = chemotherapy; ORR = objective response rate; OSI = osimertinib.

Wu et al. *J Clin Oncol*. 2018;36:2702.

Osimertinib Data: FLAURA CNS Evaluable-for-Response Set

	OSI (n=22)	Gefitinib or Erlotinib (n=19)
CNS ORR	20 (91%)	13 (68%)
Median time to response onset	6 weeks	6 weeks
Median best percentage change from baseline in the sum of CNS target lesion size	- 64%	- 45%





CNS = central nervous system; ORR = objective response rate; OSI = osimertinib.

Reungwetwattana et al. *J Clin Oncol*. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. [Epub ahead of print].

Osimertinib: AURA 3 Leptomeningeal Disease

- 7 patients with retrospectively identified LMD (all were in the OSI arm):
  - 2 had complete radiographic response
  - 2 had partial radiographic response

Prior Brain Radiotherapy	Best Objective Response		
	LM	CNS	Systemic
No	CR	CR	PR
No	CR	PR	PR
No	PR	SD	SD
No	PR	SD	SD
No	SD	Non-CR, non-PD	PR
Yes	SD	SD	SD
Yes	SD	Non-CR, non-PD	SD

CR = complete response; LMD = leptomeningeal disease; LM = leptomeningeal; OSI = osimertinib; PD = progressive disease; PR = partial response; SD = stable disease.

Wu et al. *J Clin Oncol*. 2018;36:2702.

Osimertinib: FLAURA Leptomeningeal Disease

Treatment Arm	Highest Response in LMD	Highest Response in Target Lesion	Best Objective Response – CNS	Best Objective Response – Systemic
Osimertinib	CR	PR	PR	PR
Osimertinib	Non-CR, non-PD	No TL	SD	PR
Osimertinib	CR	No TL	CR	PR
Osimertinib	CR	No TL	SD	PR
Osimertinib	CR	CR	CR	PR
Gefitinib or erlotinib	Non-CR, non-PD	No TL	SD	PR
Gefitinib or erlotinib	Baseline only	No TL	NE	PR

BLOOM study is ongoing comparing 160 mg OD vs 80 mg OD for LMD

CNS = central nervous system; CR = complete response; LMD = leptomeningeal diseaseNE = nonevaluable; OD = once a day; PD = progressive diseasePR = partial response; SD = stable disease; TL = target lesion.

Reungwetwattana et al. *J Clin Oncol*. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. [Epub ahead of print].

BLOOM: Osimertinib LMD

First patient dosed: April 14, 2015

Osimertinib LM arm

Metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- **T790M positive cohort only**: patients must have central confirmation of T790M positive status from a sample taken after documented progression on the last treatment administered prior to enrolling in the study
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- **T790M unselected cohort only**: stable extracranial disease
- **T790M positive cohort only**: no restriction on stable extracranial disease
- At least one LM lesion by MRI scan

Osimertinib 160 mg QD

Data cut-off: February 03, 2017

Assessments

- Adverse events
- Efficacy assessment:
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - Overall survival
  - CNS symptoms*
- PK in CSF
- Quantification of EGFR-mutant DNA

T790M unselected cohort (n=21)	
Gender, n (%): male/female	6 (29)/15 (71)
Age: median (range), years	59.0 (44-75)
Neurological status, n (%): normal/abnormal	11 (52)/10(48)
ECOG performance status, n (%): 0/1/2/3	1 (5)/11 (52)/9 (43)/0
History of WBRT, n (%)	12 (57)
Number of previous CT regimens, median (range)	2 (1-6)
EGFR mutation type‡, n (%): L858R/Del19/T790M	13 (62)/9 (43)/2 (10)

*As assessed by study investigator; †Modified RECIST for CNS disease; RECIST 1.1 for extracranial disease. CT/MRI, CSF cytology and neurological exam frequency every 6 weeks. 1 cycle = 21 days of continuous dosing; ‡Patients could have more than one mutation.

CSF = cerebrospinal fluid; CNS = central nervous system; CT = computer-guided tomography; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; LMD = leptomeningeal disease; MRI = magnetic resonance imaging; PK = pharmacokinetics; TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

Yang et al. ASCO 2017. Abstract 2020.

BLOOM: Osimertinib

- Overall LM response by investigator assessment was 43%, including 1 CR
- Median duration of response was 18.9 mo (range, 5.6-19.3 mo; 95% CI, 11.1-NC)
- Of the 11 patients with “normal” baseline neurologic assessment, 10 patients (91%) had no change in neurologic assessment, and 1 patient worsened (change from "normal” to “mildly abnormal”)
- Of the 10 patients with “abnormal” baseline neurologic assessment, 7 patients (70%) had an improvement in neurologic assessment
- 6/20 (30%; 95% CI 12-54) had a confirmed CSF response
- Osimertinib mean concentration in CSF was 7.5 nM (range, 2.2-26.4 nM) at steady state (n=21) [IC_{50} is 9-12 nM]

CSF = cerebrospinal fluid; CI = confidence interval; CR = complete response; LM = leptomeningeal; NC = not calculable.
Yang et al. ASCO 2017. Abstract 2020.

Summary

- Brain-penetrant EGFR TKIs are an effective treatment for brain metastases
  - Both afatinib and osimertinib have shown brain penetration and clinical activity in patients with BM and LMD
- Patient selection is important
  - Parenchymal vs leptomeningeal disease
  - Asymptomatic vs symptomatic patients
- EGFR TKI dosage may influence CNS exposure and outcome
- An ongoing study in National Cancer Centre Singapore is examining increased dosage and pulsed dosing of afatinib:
  - A Dose Finding Study of Continuous and Intermittent High-dose (HDI) Afatinib (EGFR TKI) on CNS Metastases and Leptomeningeal Disease (LMD) in Patients With Advanced Refractory EGFR Mutation Positive Non-small Cell Lung Cancer [ClinicalTrials.gov ID: NCT03711422]

BM = brain metastases; CNS = central nervous system; EGFR = epidermal growth factor receptor; LMD = leptomeningeal diseae; TKI = tyrosine kinase inhibitor.