Afatinib in Patients With Brain Metastases / Leptomeningeal Disease

Afatinib is approved in a number of markets, including the EU, Japan, Taiwan and Canada under the brand name GIOTRIF® and in the U.S. under the brand name GILOTRIF® for use in patients with distinct types of EGFR mutation-positive NSCLC. Registration conditions differ internationally, please refer to locally approved prescribing information. Afatinib is under regulatory review by health authorities in other countries worldwide.

Introduction

- The brain is a common site of metastatic spread in NSCLC, affecting 21%-64% of patients[1]
- These patients have a poor prognosis with a median survival of only 1 month from diagnosis if untreated, 2 months with glucocorticoid therapy and 2–5 months with WBRT[2-8]
- Intracranial responses and growth delay of CNS metastases with EGFR TKI treatment have been reported[9]
- Earlier studies of afatinib suggest that afatinib is effective in patients with NSCLC and brain metastases. Subgroup analysis of LUX-Lung 2 showed similar response rates independent of brain metastases[10]
- In a recent Compassionate Use Programme of afatinib, 35% of patients with brain metastases and a documented *EGFR* mutation had an intracranial response when treated with afatinib[5]
- These data substantiate preclinical and clinical observations that afatinib can penetrate the blood-brain barrier at sufficient concentrations to elicit anti-tumour activity[5,11]

TKI = tyrosine kinase inhibitor; WBRT = whole brain radiotherapy.

1. Nguyen and Deangelis. J Support Oncol. 2004;2:405; 2. Langer and Mehta. J Clin Oncol. 2005;23:6207; 3. Eichler and Loeffler. Oncologist. 2007;12:884; 4. Fan et al. Onco Targets Ther. 2013;6:1789; 5. Hoffknecht et al. J Thorac Oncol. 2015;10:156; 6. Khuntia et al. J Clin Oncol. 2006;24:1295; 7. Ruderman and Hall. Cancer. 1965;18:298; 8. Zimm et al. Cancer. 1981;48:384; 9. Heon et al. Clin Cancer Res. 2012;18:4406; 10. Yan et al. Lancet Oncol. 2012;13:539; 11. Campas et al. Drugs Future. 2008;33:649.

LUX-Lung 3 / 6: Patients With or Without Asymptomatic Brain Metastases (Common Mutations)

Characteristic	LUX-Lung 3				LUX-Lung 6			
	Afatinib		Cis/Pem		Afatinib		Cis/Gem	
	w/o BM (n=166)	With BM (n=20)	w/o BM (n=82)	With BM (n=15)	w/o BM (n=185)	With BM (n=28)	w/o BM (n=86)	With BM (n=18)
Median age	63.0	60.5	61.0	63.0	58.0	53.5	58.0	55.0
Female (%)	66.3	70.0	67.1	80.0	64.3	67.9	68.6	66.7
White (%)	28.3	15.0	29.3	20.0	0.0	0.0	0.0	0.0
Asian (%)	70.5	85.0	68.3	80.0	100.0	100.0	100.0	100.0
Never smoker	68.1	70.0	65.9	86.7	75.1	82.1	83.7	72.2
ECOG PS 1 (%)	56.6	80.0	63.4	53.3	78.9	85.7	65.1	72.2
Del19 (%)	53.6	55.0	56.1	53.3	56.8	60.7	60.5	38.9
L858R (%)	46.4	45.0	43.9	46.7	41.6	35.7	39.5	61.1
Prior WBRT (%)	1.2	35.0	0 .0	33.3	0 .0	21.4	0 .0	33.3

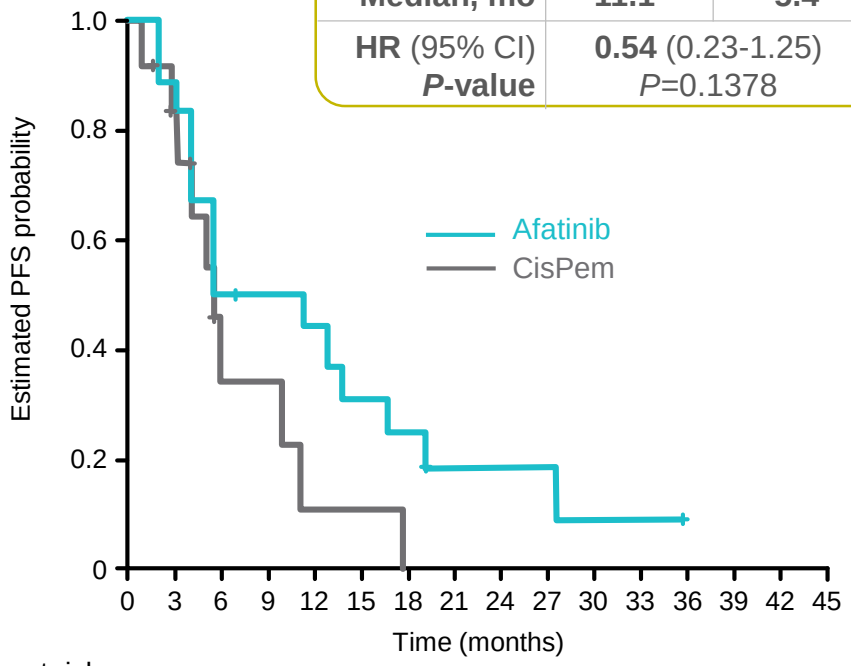
ECOG PS = Eastern Cooperative Oncology Group performance status.

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

LUX-Lung 3: PFS in Patients With and Without Brain Metastases (Common Mutations, Independent Review)

With brain metastases

	Afatinib	CisPem
Median, mo	**11.1**	**5.4**
HR (95% CI)	**0.54** (0.23-1.25)	
***P*-value**	*P*=0.1378	

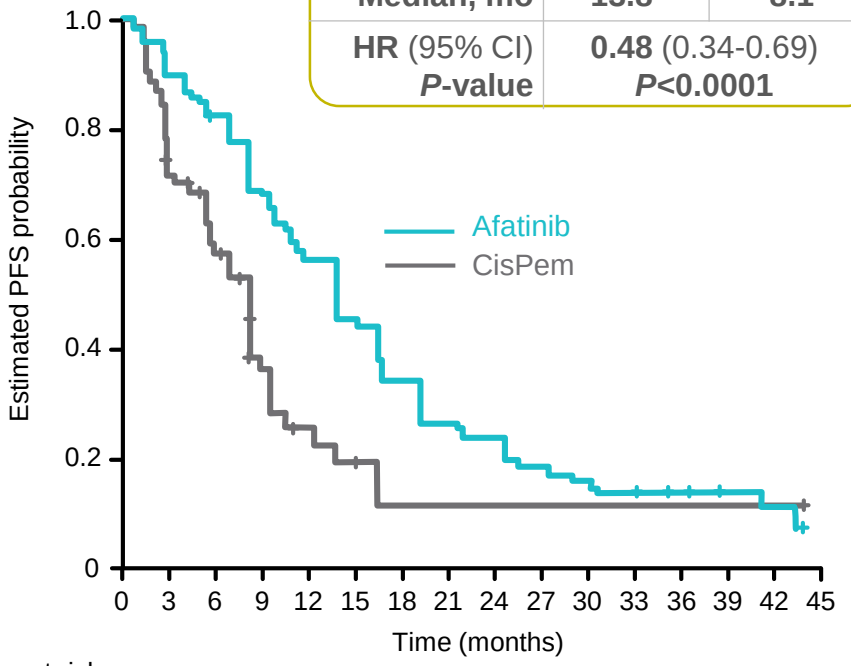


No. at risk

Afatinib	20	17	9	8	7	5	4	2	2	2	1	1	0	0	0	0
Cis/Pem	15	9	3	3	1	1	0	0	0	0	0	0	0	0	0	0

Without brain metastases

	Afatinib	CisPem
Median, mo	**13.8**	**8.1**
HR (95% CI)	**0.48** (0.34-0.69)	
***P*-value**	***P*<0.0001**	



No. at risk

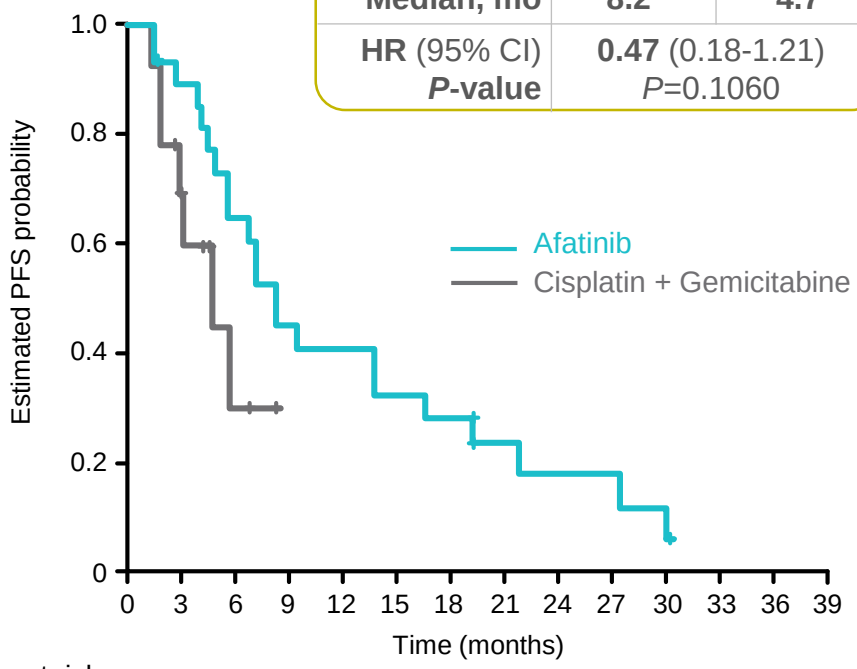
Afatinib	166	141	123	100	78	61	44	34	28	21	18	15	10	7	3	0
Cis/Pem	82	49	29	14	8	5	2	2	2	2	2	2	2	2	1	0

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

LUX-Lung 6: PFS in Patients With and Without Brain Metastases (Common Mutations, Independent Review)

With brain metastases

	Afatinib	CisGem
Median, mo	**8.2**	**4.7**
HR (95% CI)	**0.47** (0.18-1.21)	
***P*-value**	*P*=0.1060	

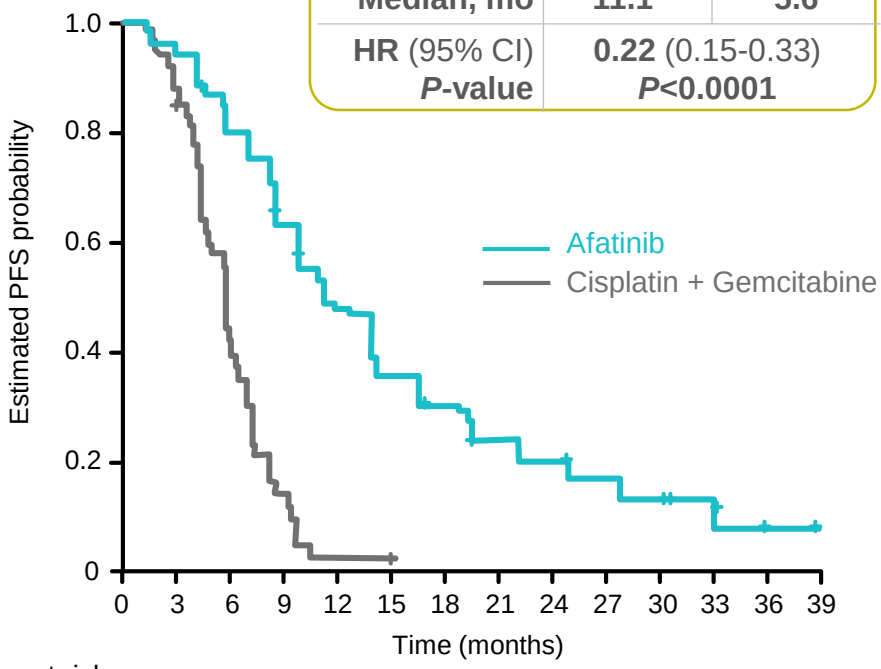


No. at risk

Afatinib	18	22	16	11	10	8	7	4	3	3	2	0	0	0
Cis/Gem	18	7	2	0	0	0	0	0	0	0	0	0	0	0

Without brain metastases

	Afatinib	CisGem
Median, mo	**11.1**	**5.6**
HR (95% CI)	**0.22** (0.15-0.33)	
***P*-value**	***P*<0.0001**	

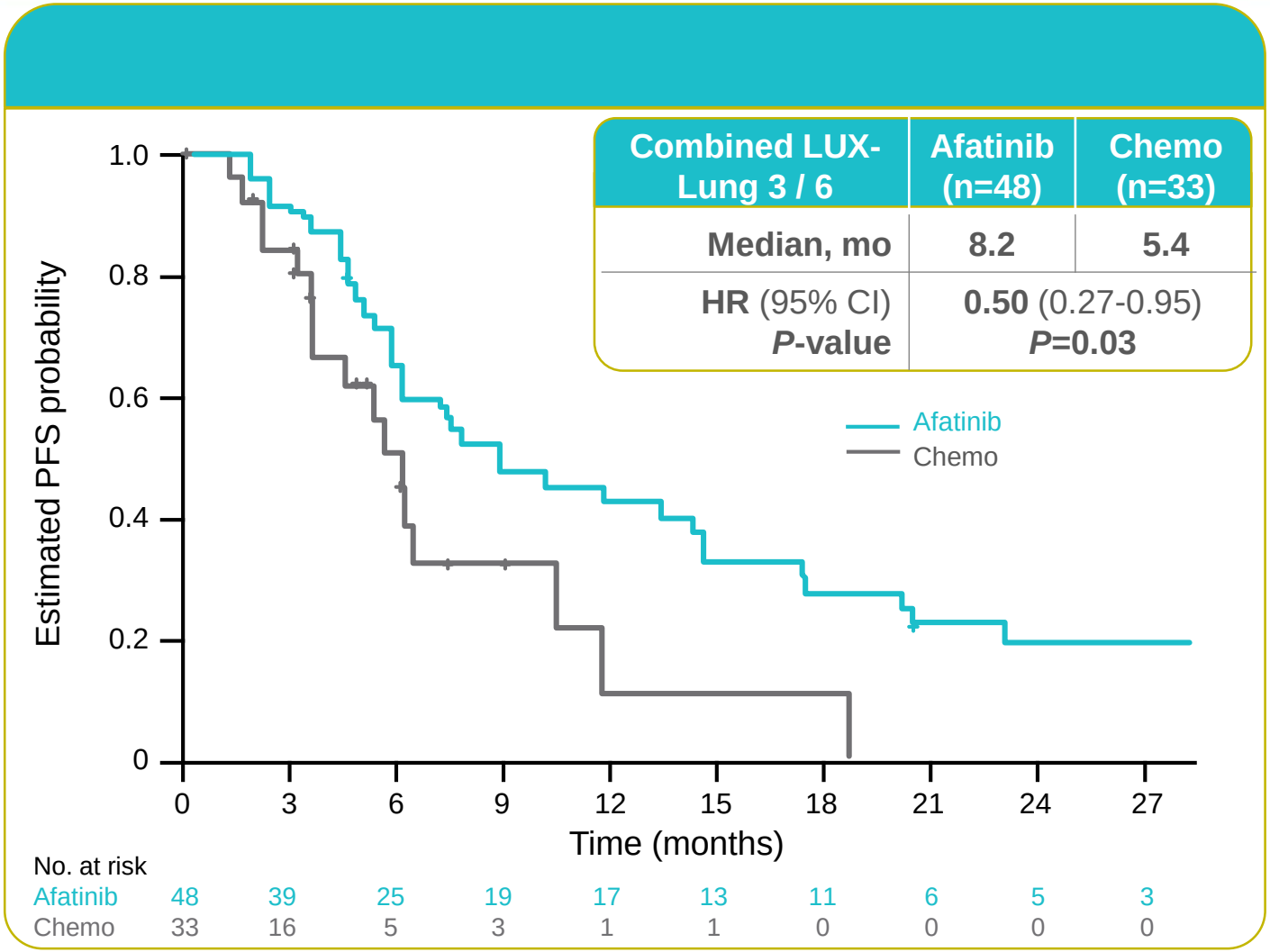


No. at risk

Afatinib	185	162	134	102	76	54	43	33	27	21	15	9	1	0
Cis/Gem	86	52	17	6	1	0	0	0	0	0	0	0	0	0

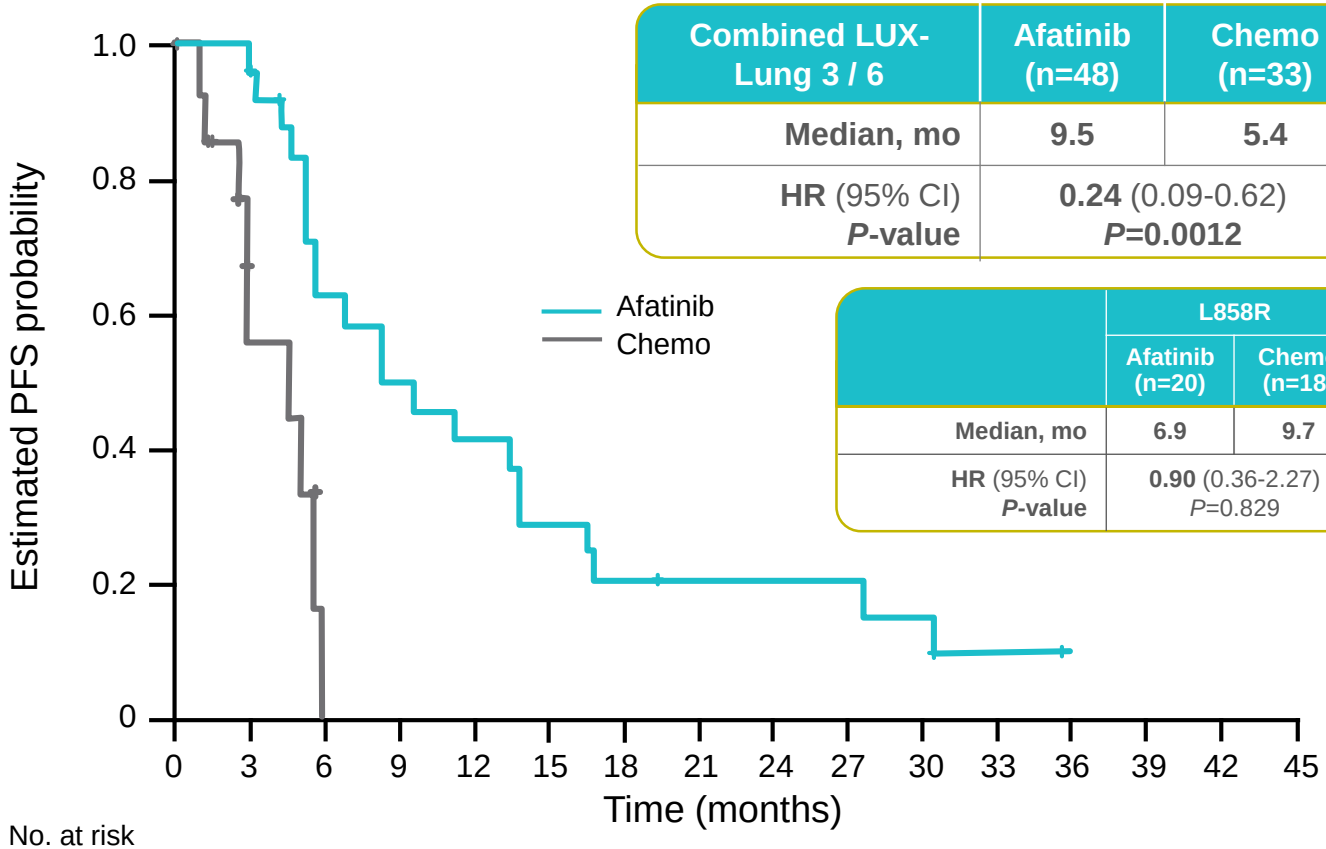
Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

PFS in Patients With Brain Metastases and Common *EGFR* Mutations (Combined Analyses from LUX-Lung 3/6)



Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

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	5.4
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	

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

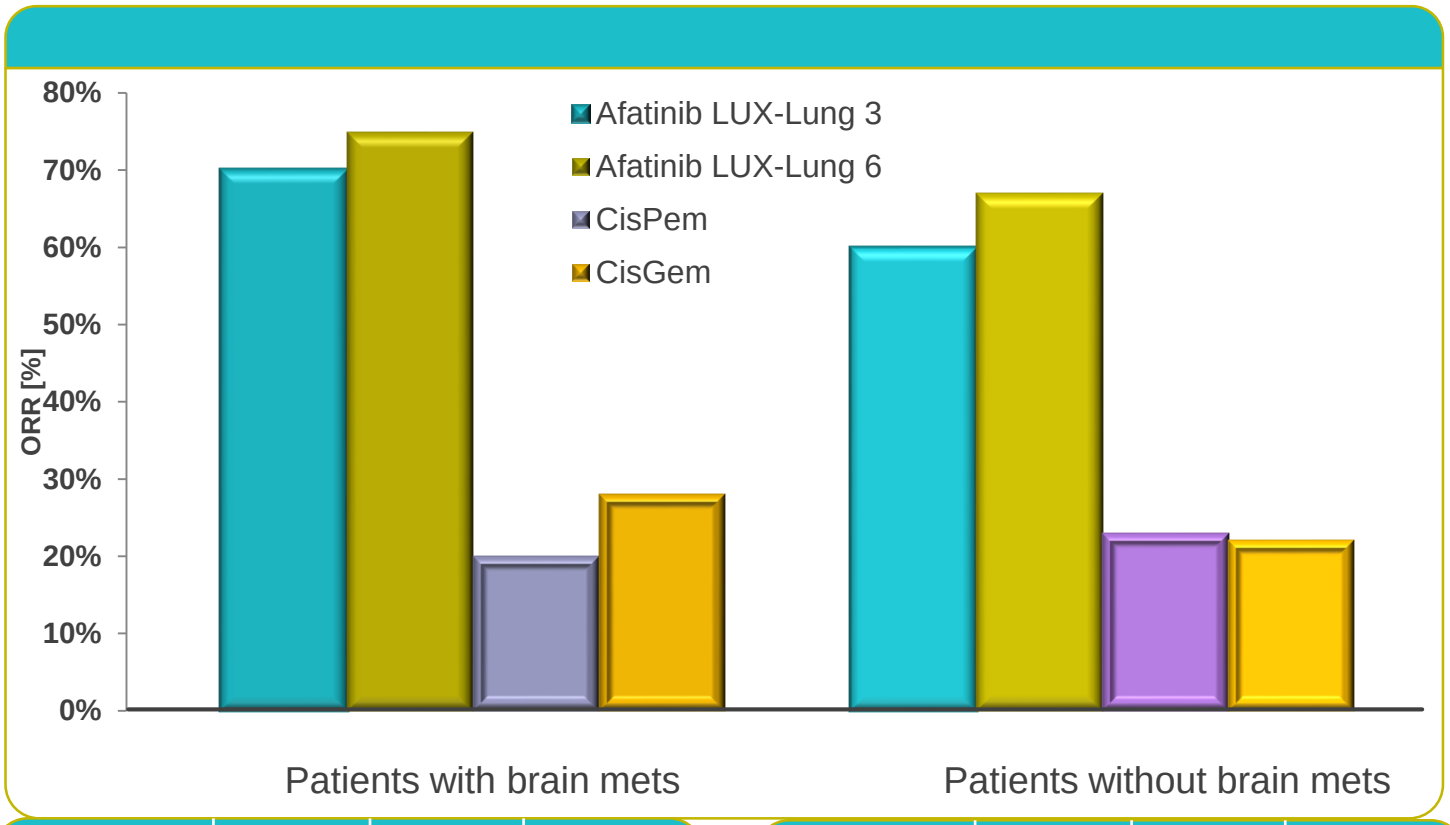
Time to CNS Progression

	LL3		LL6	
	Afatinib (n=9)	**Cis/Pem (n=5)**	**Afatinib (n=6)**	**Cis/Gem (n=5)**
Time to CNS progression, months (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)

- In the majority of patients with baseline BM who experienced PD on afatinib, the brain was not site of first disease progression.
- Rates of CNS progression were similar independent of treatment for both patients with or without baseline brain metastases.
- The median time to CNS progression was longer with afatinib versus chemotherapy for both patients with or without baseline brain metastases

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

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%	<0.0001

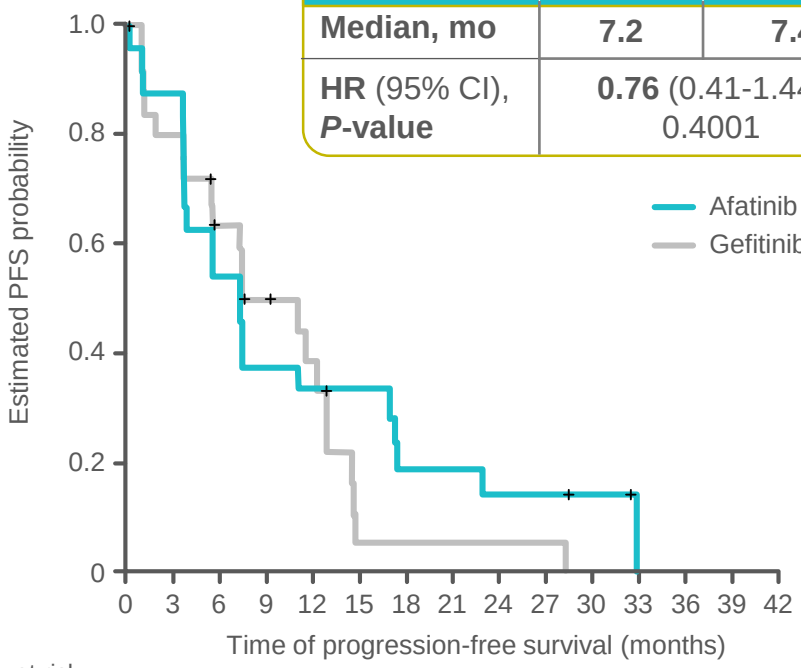
W/o brain mets	Afatinib	Chemo	P-value
LUX-Lung 3	60%	23%	0.0027
LUX-Lung 6	67%	22%	<0.0001

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

LUX-Lung 7: PFS in Patients With and Without Brain Metastases by Independent Review

With brain metastases

	Afatinib (n=26)	Gefitinib (n=25)
Median, mo	**7.2**	**7.4**
HR (95% CI), ***P*-value**	**0.76** (0.41-1.44) 0.4001	

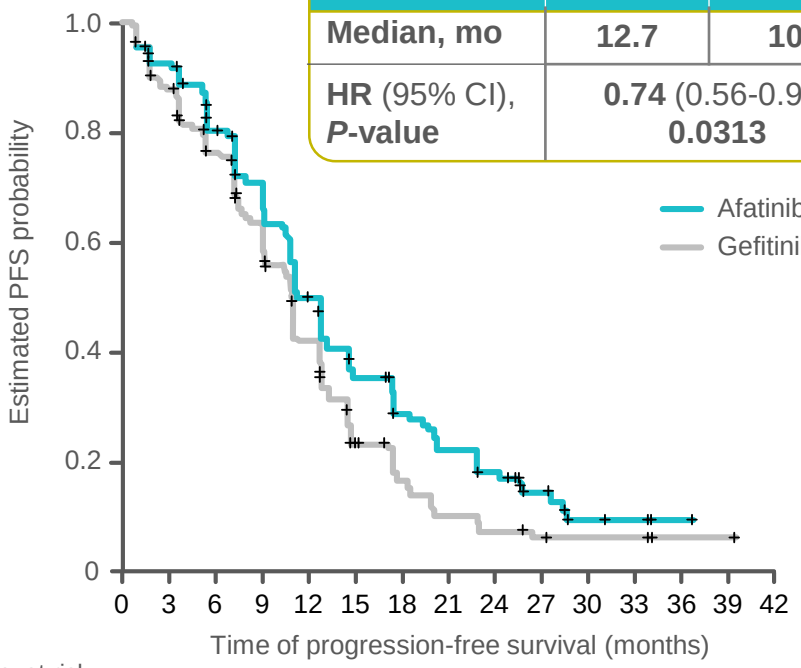


No. at risk:

Afatinib	26	21	13	9	8	7	4	4	3	3	2	0	0	0	0
Gefitinib	25	20	14	10	7	1	1	1	1	1	0	0	0	0	0

Without brain metastases

	Afatinib (n=134)	Gefitinib (n=134)
Median, mo	**12.7**	**10.9**
HR (95% CI), ***P*-value**	**0.74** (0.56-0.98) **0.0313**	



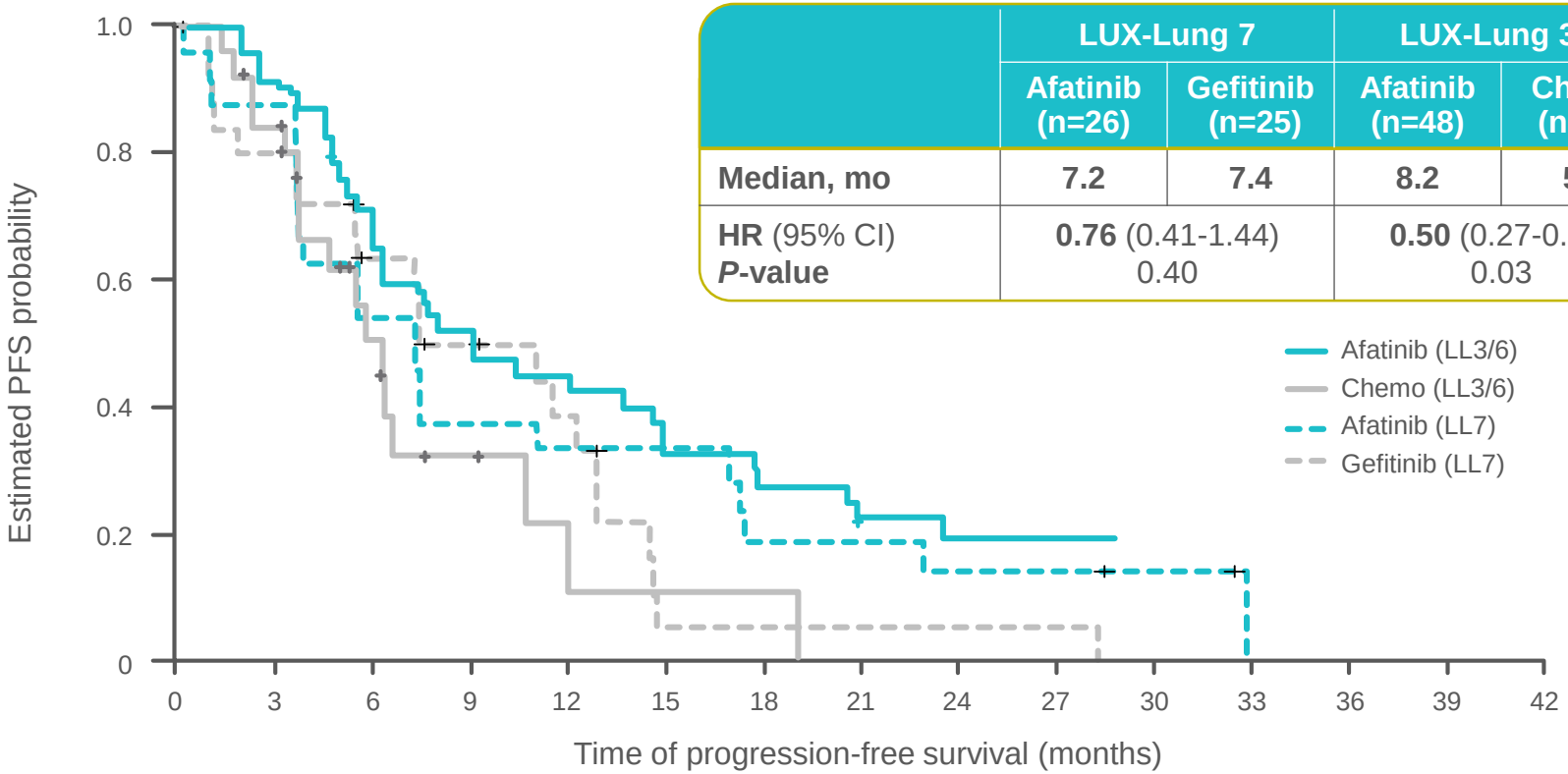
No. at risk:

Afatinib	134	121	99	85	59	40	30	23	18	10	4	3	1	0	0
Gefitinib	134	112	92	73	45	21	13	8	6	4	3	3	1	1	0

Park et al. *Ann Oncol*. 2015;26: (suppl 9; abstract LBA2).

PFS in Patients With Brain Mets – LUX-Lung 3/6 and -7

	LUX-Lung 7		LUX-Lung 3/6	
	Afatinib (n=26)	Gefitinib (n=25)	Afatinib (n=48)	Chemo (n=33)
Median, mo	**7.2**	**7.4**	**8.2**	**5.4**
HR (95% CI)	**0.76** (0.41-1.44)		**0.50** (0.27-0.95)	
***P*-value**	0.40		0.03	



No. at risk:

Afatinib	26	21	13	9	8	7	4	4	3	3	2	0	0	0	0
Gefitinib	25	20	14	10	7	1	1	1	1	1	0	0	0	0	0
Afatinib	134	121	99	85	59	40	30	23	18	10	4	3	1	0	0
Gefitinib	134	112	92	73	45	21	13	8	6	4	3	3	1	1	0

Park et al. *Ann Oncol*. 2015;26: (suppl 9; abstract LBA2).
Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

Summary

- In combined analysis of LUX-Lung 3 and -6, PFS was significantly improved with afatinib versus chemotherapy in patients with brain metastases with a trend in both independent trials; no OS benefit was observed
- The magnitude of PFS improvement with afatinib was similar to that observed in patients without brain metastases
- In the majority of patients with baseline BM who experienced PD on afatinib, the brain was not site of first disease progression
- Afatinib significantly improved ORR versus chemotherapy in patients with brain metastases
- Afatinib may delay onset of metastatic disease in the brain of patients without baseline metastases.

Schuler et al. *J Thorac Oncol.* 2016, 11(3):380-90.

TKI-Pretreated Patients

Experience from a Compassionate Use Programme

- Data from patients with brain metastases (n=31) treated in 3rd/4th line after reversible EGFR-TKI failure showed:
  - Partial Response: 42%, Stable Disease: 39% and 19% PD.
  - 35% had a cerebral response, 16% responded exclusively in brain.
  - Response duration was 120 (21–395) days.
  - 66% had cerebral disease control on afatinib.

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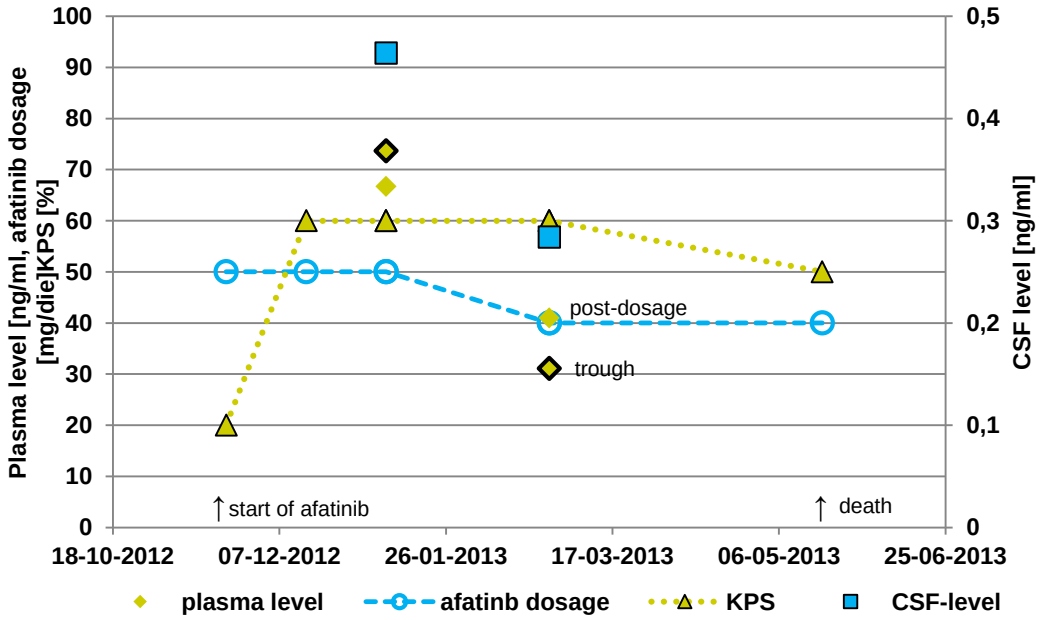
Hoffknecht et al. *J Thorac Oncol*. 2015;10:156.

CSF Level in a Patient with Leptomeningeal Disease

- Data from one patient with an impressive response showed an afatinib concentration in the cerebrospinal fluid of nearly 1 nMol.
- Calculating the molar concentration lead to a value of 0.95 nM, which is around the IC50 value for EGFR (0.5 nM) and for ErbB4 (1 nM) but below the value for HER2 (14 nM).



CSF = cerebrospinal fluid.
Hoffknecht et al. *J Thorac Oncol*. 2015;10:156.

SRPs

- “Is afatinib active in patients with brain metastasis?”
- “Does afatinib cross the blood-brain-barrier?”

Scientific Response Point: “Is afatinib active in patients with brain metastases?”

- *Afatinib is active in patients with brain metastases*
- *LUX-Lung 3 and LL6 included patients with asymptomatic brain metastases*
- *Median PFS for patients without brain metastases from LL3 and LUX-lung 6 (common mutations) was 13.8 vs. 8.1 months (LL3) and 11.1 vs 5.6 months (LL6) and in patients with brain metastases pooled from both trials 8.2 (n=48) vs 4.7 months (n=33), HR=0.50, being statistical significant (P=0.03).*
- *The subgroup of patients with Del19 and brain mets showed also a significant longer PFS (9.5 vs. 5.4 months).*
- *Time to CNS progression by investigator assessment was 15.2 months in both trials for afatinib (Chemo-arm 5.7 and 7.3 months, respectively).*

Scientific Response Point: “Does afatinib cross the blood-brain barrier?”

- *Penetration rate has not been investigated thoroughly. Data from a single case showed a CSF level of 1 nMol afatinib*
- *Calculating the molar concentration would lead to a value of 0.95 nM, which is around the IC50 value for EGFR (0.5 nM) and for ErbB4 (1 nM) but below the value for HER2 (14 nM).*
- *Afatinib is active in patients with brain mets.*

CSF = cerebrospinal fluid.

Osimertinib in Patients with Brain Metastases / Leptomeningeal Disease

AZD9291 activity in patients with EGFR-mutant advanced NSCLC and brain metastases: Data from Phase II studies

- Background: […]. In preclinical models, exposure of the brain to AZD9291 was greater than observed with gefitinib. In the AURA study Phase II extension cohort and the AURA2 Phase II study, **patients with asymptomatic, stable** (not requiring steroids for 4 weeks) **brain metastases were eligible for enrolment**; **exploratory/investigatory results relating to brain metastases are reported here.**
- Materials and Methods: […]. Patients received AZD9291 80 mg once daily until disease progression; **brain metastases were assessed as non-target lesions and/or new lesions by RECIST 1.1 scheduled assessments, so non-central nervous system (CNS) response is reported here.** The definition of brain metastases at entry was patients with current or past medical history of brain metastases. […].
- Results: From 411 patients dosed, a total of 162 (39%) patients fulfilled brain metastases criteria at entry in AURAext and AURA2 combined. In both studies a higher proportion of third-line patients had brain metastases compared with second-line patients (44% vs 29%). The **systemic objective response rate** (ORR; by independent central review) in the overall population evaluable for response was 61% (242/397; 95% confidence interval [CI] 56, 67). ORR in patients with brain metastases at entry was 56% (88/158; 95% CI 48, 64), and was 64% (154/239; 95% CI 58, 71) in patients without brain metastases. **There is anecdotal evidence of shrinkage of brain metastases in some patients. Cerebrospinal fluid concentration (CSF) data from one patient showed AZD9291 CSF concentration of 3.44 nM.** […].
- Conclusions: Non-CNS objective response to AZD9291 is observed in patients with and without brain metastases. AZD9291 is being further investigated in patients with CNS metastases in a Phase I study.

Ahn et al., Eur. J. Cancer, 51 (2015) Abstract #3083

Osimertinib in in Patients With Brain Metastases / Leptomeningeal Disease

- Objective: […] Preclinical data have shown that AZD9291 crosses the blood-brain barrier, with anecdotal reports of response in patients with brain metastases. Here we investigate the use of AZD9291 in the difficult-to-treat setting of leptomeningeal disease.
- Methods: 13 patients with EGFR-mutant NSCLC who had progressed on prior EGFR-TKI therapy and had confirmed diagnosis of leptomeningeal disease by positive cerebrospinal fluid (CSF) cytology (detectable tumor cells) were enrolled onto the Phase I BLOOM study (NCT02228369). Patients were treated with **AZD9291 160 mg**, once daily. Response was assessed based on symptoms, neurological examination, MRI, and measurement of CSF cytology. In addition, EGFR-mutant DNA was quantified in CSF. Pharmacokinetics of AZD9291 and its key metabolites in CSF were also investigated.
- Results: All patients were heavily pre-treated; 10 patients had received an EGFR-TKI as their last prior systemic treatment, six patients had prior intrathecal chemotherapy, and seven patients had prior brain radiotherapy. Two patients had T790M positive disease as detected by DNA in CSF, and four patients had T790M positive disease by circulating tumor DNA testing in plasma at baseline. Of the 13 patients enrolled, one patient did not have tumor cells detectable in baseline CSF samples and was therefore ineligible for response assessment. As of data cut-off , 11/12 patients were evaluable for response assessment, the longest duration on study treatment was 21 weeks and ongoing. **Of the 11 evaluable patients, eight had imaging improvement as assessed by the investigator**; six patients have reached a 12-week assessment, with all six showing continued improvement by imaging. Nine patients had neurological symptoms at baseline, with five showing symptomatic improvements as assessed by the investigator. Two patients had complete clearance of tumor cells from CSF on two consecutive visits. Among nine patients with pre- and post-dose CSF samples (cycle 2 Day 1, 3 weeks post-dose), seven patients had a decrease in EGFR-mutant DNA, with a >50% decrease in five patients. Three patients discontinued therapy (one extracranial progression, one dysphagia, and one non-drug-related serious adverse event [AE] leading to death) and nine patients are ongoing. […]
- Conclusion: Early data suggest that AZD9291 shows encouraging efficacy in heavily pre-treated patients with leptomeningeal disease from EGFR-mutant NSCLC.

Lee DH et al., AACR-NCI-EORTC 2015, abstract PR07

Putting Into Perspective

		Afatinib	Osimertinib
TKI-naive	Brain mets	In LUX-Lung 3/6 ORR is 70-75%. In the majority of patients with baseline BM who experienced PD on afatinib, the brain was not site of first disease progression. The median time to CNS progression was longer with afatinib versus CT for both patients with or without baseline BM	NA
	LMD	Preclinical data indicate similar activity of afatinib and osimertinib in the TKI-naive setting[1]	
TKI-pretreated	Brain mets	CUP-data: PR 42%, SD: 39% and 19% PD. 35% had a cerebral response, 16% responded exclusively in brain. Response duration was 120 (21–395) days. 66% had cerebral disease control on afatinib.	Data from single-arm AURA study Phase II extension cohort and the AURA2 Phase II are exploratory and a non-central nervous system response of 56% is reported.
	LMD	CSF data from 1 patient was 0.95 nM, which is around the IC50 value for EGFR (0.5 nM). Anecdotal data from patients treated with afatinib with standard dose (or even less) indicate efficacy in this setting as well [2,3]. An IIS addressing this prospectively is ongoing	CSF data from 1 patient treated with 80mg showed a concentration of 3.44 nM which is lower than the IC50 for EGFR (9-12 nM) Data from the BLOOM trial with doubled dosage (160mg) are interesting with 8/11 patients showing a response by MRI.

1.Nanjo S et al., Oncotarget 7 :4:3847-3856 2. Hoffknecht et al. *J Thorac Oncol*. 2015;10:156. 3. Sekine A,, et al. Presentation at the Conference of the 55 Japan Lung Cancer Society, Tokyo, 14 May 2015

Summary

- **There are no data for osimertinib in first-line TKI-naive setting whereas afatinib has convincing data for patients with brain mets from LUX-Lung 3, 6 and -7** (systemic ORR 70-75%, brain mostly not site of first disease progression, delayed time to CNS progressionvs chemotherapy)
- Data for patients with brain mets after EGFR-TKI failure for osimertinib are hard to interprete with only systemic response rate being reported (56%).
- Data from BLOOM trial for patients with LMD are interesting, however, these limited data were achieved by doubling the approved dose of osimertinib. Single-case CSF data indicate that 80mg do not lead to a sufficient high level.