# Clinical Considerations in *EGFR* Mutation-Positive NSCLC: the Challenge of Preventing and Managing Brain Metastases

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# Disclosures

- Has been a consultant or advisor to Boehringer Ingelheim, Bristol-Myers Squibb, Guardant Health, Merck Sharp & Dohme, Pfizer, Roche
- Has received trial funding from Novartis, Pfizer, Roche

# Introduction

- The brain is a common site of metastasis in NSCLC, affecting 18%-64% of patients[1]
- Patients with NSCLC defined by specific oncogenic drivers (eg, EGFR and ALK) have a particularly high prevalence of BM at primary diagnosis and progression[2,3]
  - ≈24% at diagnosis
  - ≈30%-70% at progression
- Intracranial responses and growth delay of CNS metastases with EGFR TKI treatment have been reported[4]
- Intracranially active TKI may defer the need for brain irradiation, which is associated with substantial morbidity[5]



ALK = anaplastic lymphoma kinase; BM = brain metastases; CNS = central nervous system; EGFR = epidermal growth factor receptor; NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor.

1. Nguyen and Deangelis. *J Support Oncol*. 2004;2:405; 2. Rangachari et al. *Lung Cancer*. 2015;88:108; 3. Khalifa et al. *J Thorac Oncol*. 2016;11:1627; 4. Heon et al. *Clin Cancer Res*. 2012;18:4406; 5. Zhou et al. *J Clin Oncol*. 2017;35:1033.

# Prospective Data for First-Generation EGFR TKIs in Patients With BM Are Limited

## Phase 2 Study With Either Erlotinib or Gefitinib[1]

- N=28
- Systemic PR=83%; SD=11%; mPFS 6.6 months; mOS 15.9 months
- 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 metastasis after first-line CT[2]
- Intracranial mPFS 10.1 months; overall mPFS 9.7 months
- **Eight patients** with *EGFR*m+ disease
  - **No intracranial efficacy was reported**



CT = chemotherapy; *EGFR*m = epidermal growth factor receptor mutation; mPFS = median progression-free survival; mOS = median overall survival; PR = partial response; SD = stable disease.

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

# Prospective Data for CSF-Permeant TKI: AZD3759—the BLOOM Study

## BLOOM Study Design Overview

Phase 1 study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumour efficacy of AZD3759 or osimertinib in patients with *EGFR*m+-advanced NSCLC

**AZD3759**

**Dose Escalation**

- Cohort 1: 50 mg BID
- Cohort 2: 100 mg BID
- Cohort 3: 200 mg BID
- Cohort 4: 300 mg BID
- Cohort 5: 500 mg BID

200 or 300 mg BID[a]

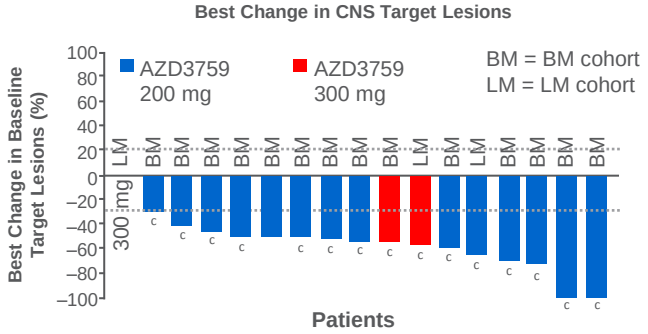
**Dose Expansion Cohorts**

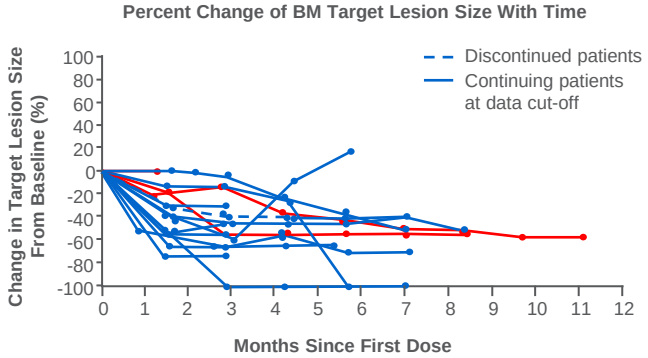
- LM: TKI-naive (n=4) or pretreated[b] (n=18)
- BM: TKI-naive (n=16)

**Osimertinib 160 mg QD**

TKI-pretreated LM

- Cohort 1: T790M unselected LM (n=21)
- Cohort 2: T790M + LM (n=20)




- 20 TKI-naive patients with advanced *EGFR*m+ NSCLC were enrolled (16 with BM and 4 with LM)
- **83%** (15/18) patients with measurable CNS target lesions at baseline had confirmed objective response (14 PRs and one CR)

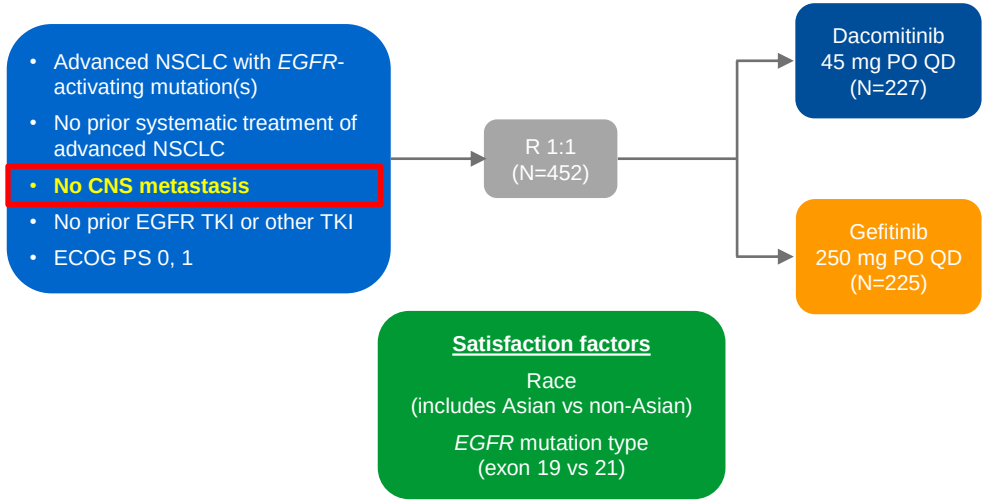


[a]Both AZD3759 200 and 300 mg BID were explored to evaluate long-term tolerability and efficacy; [b]Requires stable extracranial disease if EGFR TKI pretreated; [c]Confirmed response. BID = twice daily; CR = complete response; CSF = cerebrospinal fluid; LM = leptomeningeal metastasis; QD = once daily.

Ahn et al. *J Clin Oncol*. 2017;35(suppl): Abstract 2006; Ahn et al. *Lancet Respir Med*. 2017;5:891.

# Prospective Data for Second-Generation TKI: Dacomitinib

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




**Primary end point**

**PFS by blinded independent review**

- ≥256 PFS events
- PFS HR ≤0.667 (50%↑)
- 90% power
- 1-sided α=0.025
- mPFS: 14.3 vs 9.5 mo

**Secondary end points**

PFS (investigator assessed), ORR, DOR, TTF, OS, safety, PROs

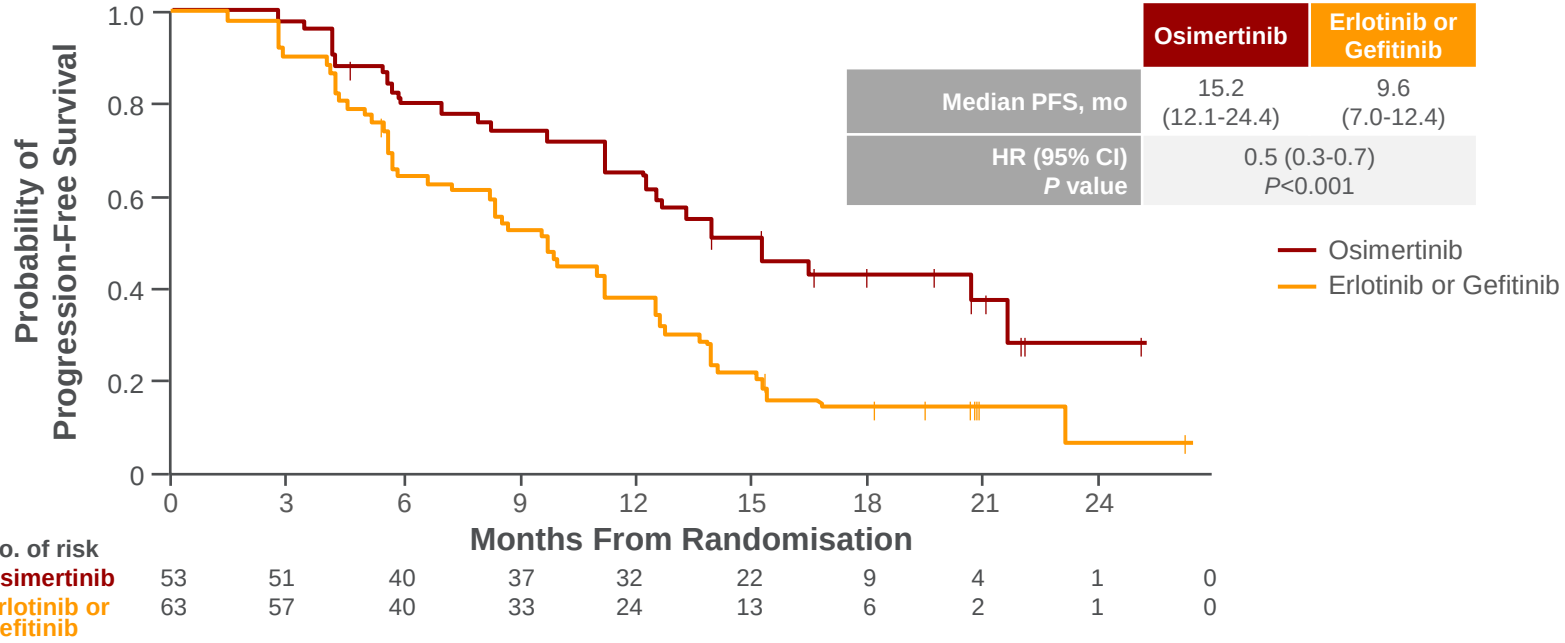


DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PO = by mouth; PRO = patient-reported outcome; R = randomisation; TTF = time to treatment failure.

1. https://clinicaltrials.gov/ct2/show/results/NCT02047747; 2. Mok et al. *J Clin Oncol*. 2018;36(suppl): Abstract 9004; 3. Wu et al. *Lancet Oncol*. 2017;18:1454.

# FLAURA: PFS by Investigator Review in Patients With CNS Metastases at Study Entry

With CNS Metastases (n=116)




| | Osimertinib | Erlotinib or Gefitinib |
|---|---|---|
| Median PFS, mo | 15.2 (12.1-24.4) | 9.6 (7.0-12.4) |
| HR (95% CI) *P* value | 0.5 (0.3-0.7) *P*<0.001 | |

| No. of risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Osimertinib | 53 | 51 | 40 | 37 | 32 | 22 | 9 | 4 | 1 | 0 |
| Erlotinib or Gefitinib | 63 | 57 | 40 | 33 | 24 | 13 | 6 | 2 | 1 | 0 |

- CNS progression events occurred in 17 (6%) and 42 (15%) patients receiving osimertinib or 1st-gen TKI, respectively



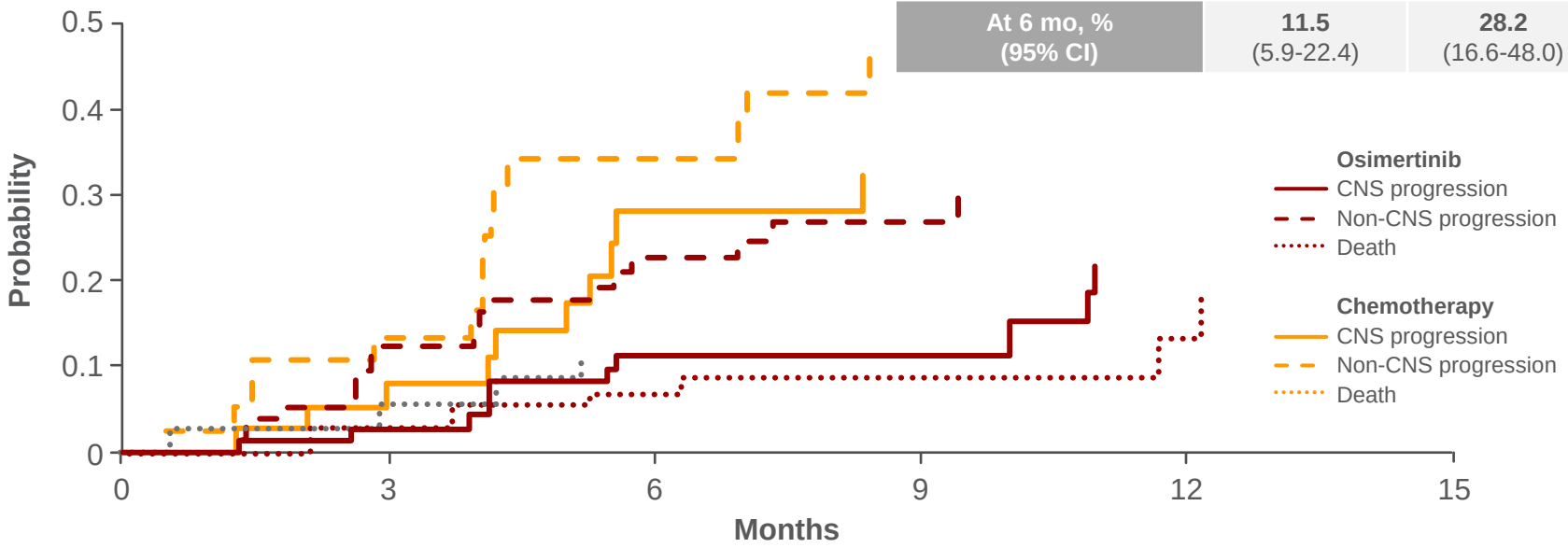
Data cut-off: 12 June 2017.

Soria et al. *N Engl J Med*. 2018;378:113.

# AURA3: Competing Risk Analysis—Full Analysis Set

The probability of experiencing a CNS progression event was lower for osimertinib than for chemotherapy at both 3 and 6 months[a]

| CNS Conditional Probability | Osimertinib 80 mg (n=75) | Chemotherapy (n=41) |
|---|---|---|
| At 3 mo, % (95% CI) | **2.7** (0.8-9.6) | **8.2** (2.3-28.7) |
| At 6 mo, % (95% CI) | **11.5** (5.9-22.4) | **28.2** (16.6-48.0) |

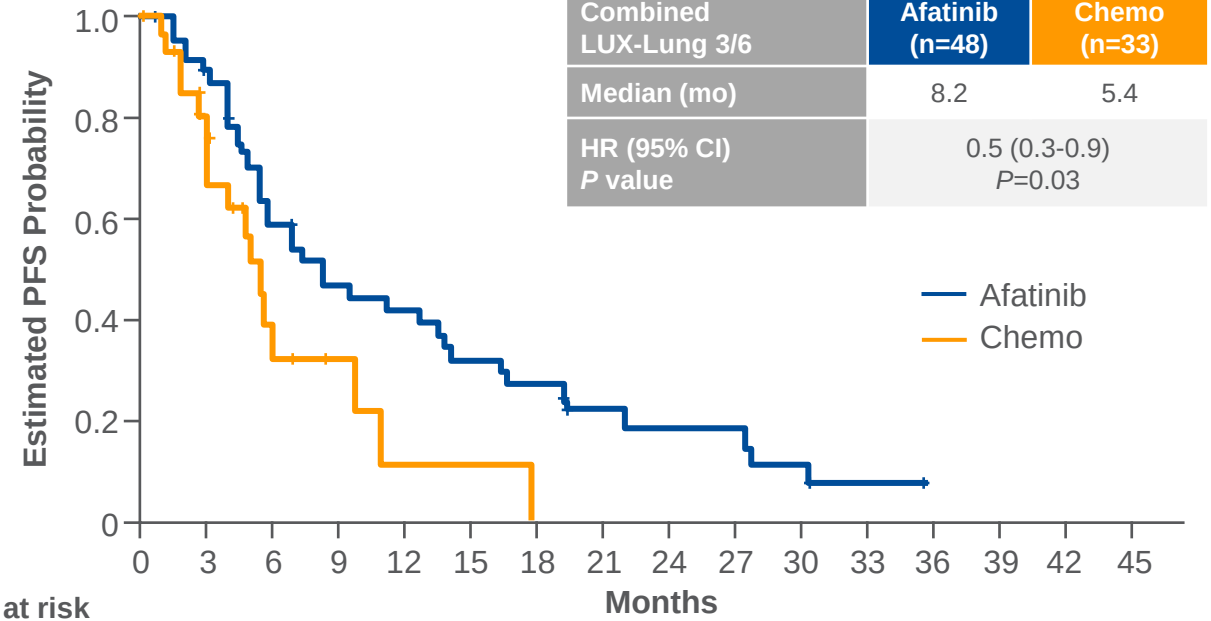





[a]Conditional on the patient not experiencing a competing risk at that time. Types of event, osimertinib/chemotherapy; CNS progression, 15% (n=11)/24% (n=10); Non-CNS progression, 25% (n=19)/37% (n=15); Death, 11% (n=8)/10% (n=4): Censored, 49% (n=37)/29% (n=12).
Population: CNS full analysis set: patients with ≥1 measureable and/or nonmeasurable CNS metastases on baseline brain scan by blinded independent central review. Data cut-off: 15 April 2016.
Wu et al. *J Clin Oncol*. 2018;36:2702.

# Prospective Data for Second-Generation TKI: LUX-Lung 3/6— PFS in Patients With BM and Common *EGFR*m

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




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

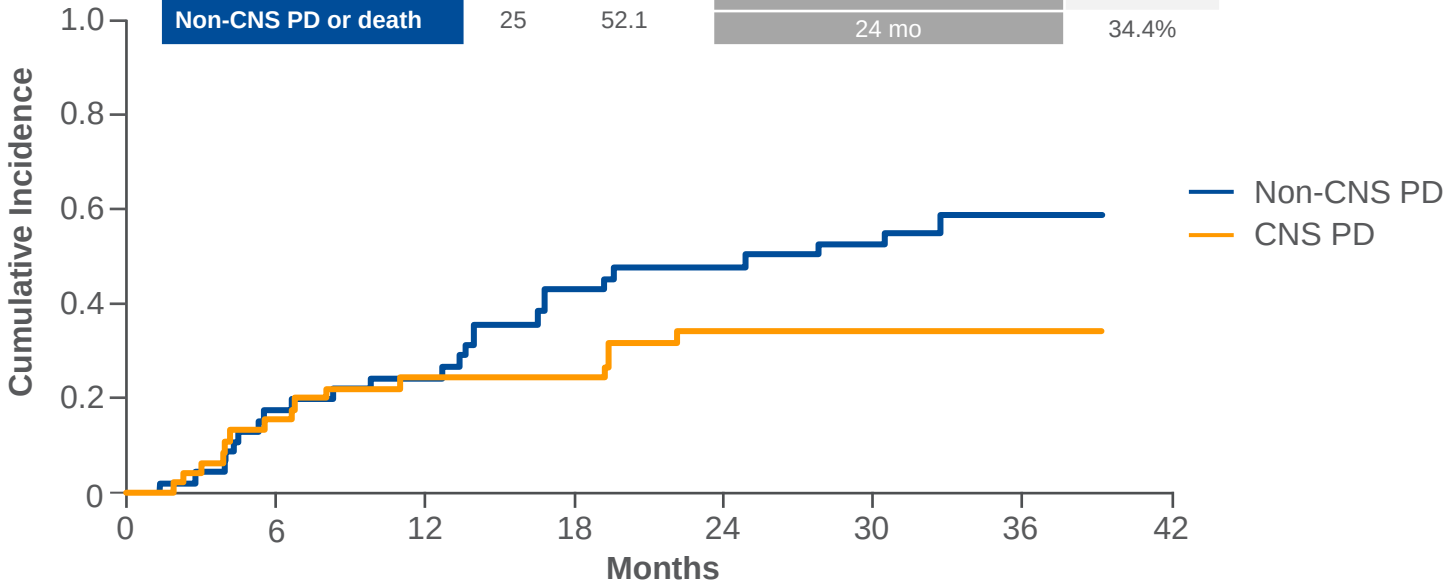


CI = confidence interval; HR = hazard ratio.
Schuler et al. *J Thorac Oncol*. 2016;11:380.

# Prospective Data for Second-Generation TKI: 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% |





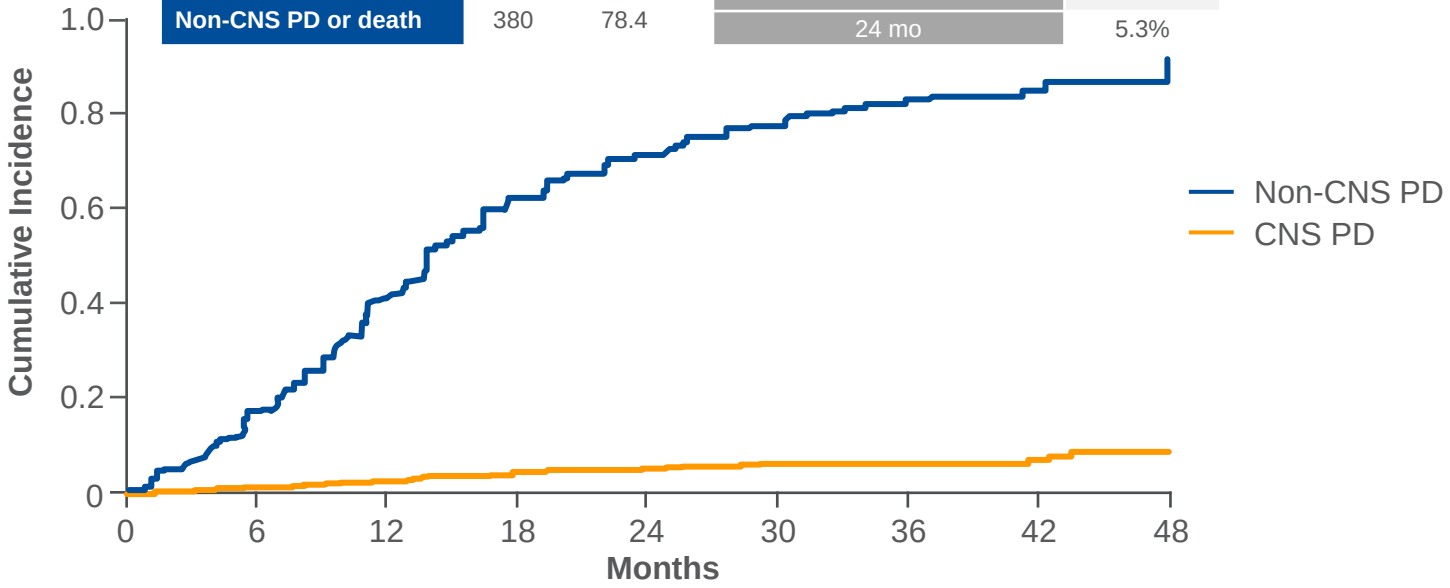

PD = progressive disease.

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

# Prospective Data for Second-Generation TKI: 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% |

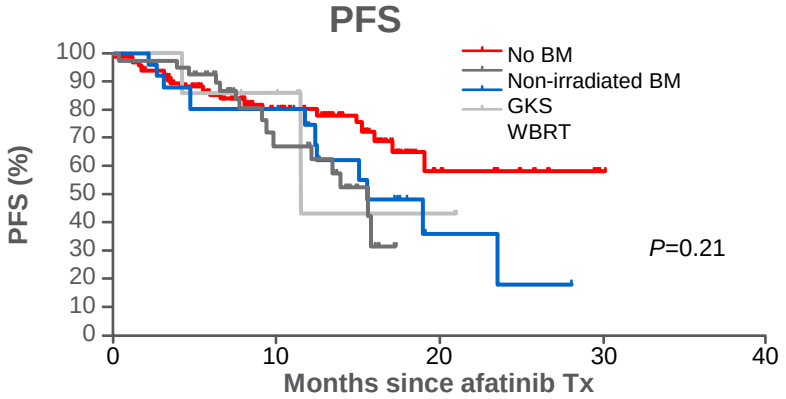





1. Girard. *Future Oncol.* 2018;14:1117; 2. Data on file, Boehringer Ingelheim.

# Real-World Experience in Korea in Patients With BM Receiving First-Line Afatinib

A retrospective population-based study in 165 adult patients receiving first-line afatinib at Samsung Medical Center in S. Korea




| N=165 | n (%) | PFS (mo) |
|---|---|---|
| No BM | 94 (57.0) | Not reached |
| BM before starting afatinib | 71 (43.0) | |
| No irradiation to brain tumour | 39 (23.6) | 15.7 |
| GKS | 25 (15.2%) | 15.6 |
| WBRT | 7 (4.2%) | 11.5 |

| Brain Tumour Response to Afatinib | n (%) |
|---|---|
| BM without irradiation | 39 |
| No follow-up brain MRI | 10 |
| Non-irradiated BM with follow-up MRI data | 29 (100%) |
| Disappeared | 6 (20.7%) |
| Significantly decreased | 16 (55.2%) |
| No significant change | 5 (17.2%) |
| Progression | 2 (6.9%) |
| Response rate to BM with afatinib | 22 (75.9%) |

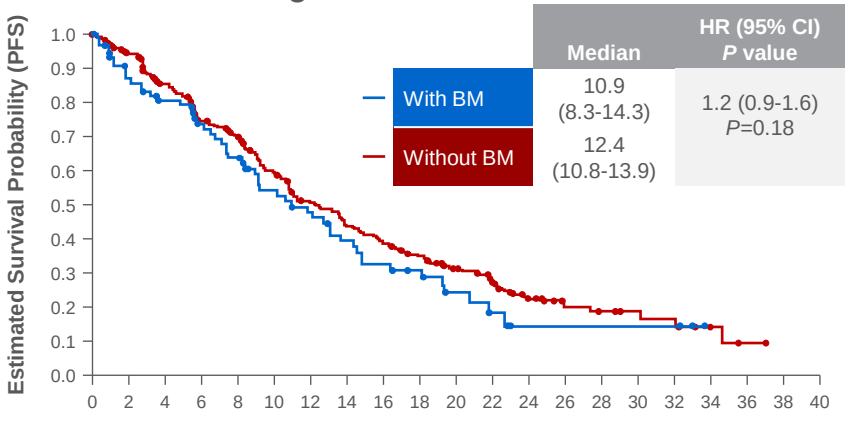
GKS = gamma knife surgery; WBRT = whole brain radiotherapy

Kim Y, et al. *J Thorac Oncol*. 2017;12:S2209

# Real-World Experience With Afatinib: Phase 3b Study

- Phase 3b open-label study of afatinib in a broad Asian* population (N=479) of EGFR TKI-naive patients
- 92 (19.2%) patients had BM at baseline

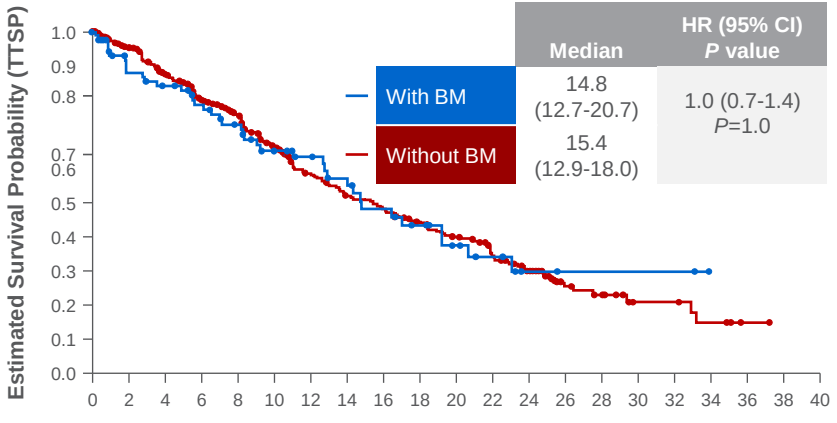
## Progression-Free Survival




No. at risk:

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| With BM | 92 | 69 | 59 | 51 | 44 | 34 | 29 | 23 | 19 | 15 | 8 | 5 | 2 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 |
| Without BM | 387 | 322 | 276 | 227 | 208 | 168 | 140 | 121 | 107 | 94 | 74 | 59 | 34 | 14 | 11 | 8 | 6 | 3 | 1 | 0 | 0 |

## Time to Symptomatic Progression




No. at risk:

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| With BM | 92 | 70 | 64 | 56 | 49 | 41 | 32 | 26 | 21 | 17 | 12 | 9 | 3 | 2 | 2 | 2 | 2 | 0 | 0 | 0 | 0 |
| Without BM | 387 | 335 | 288 | 252 | 222 | 186 | 155 | 135 | 126 | 110 | 99 | 77 | 55 | 21 | 17 | 8 | 8 | 5 | 2 | 0 | 0 |

**This study provides additional evidence for the efficacy of afatinib in patients with BM**



*China, India, Taiwan, Hong Kong, Singapore.
PFS = progression-free survival; TTSP = time to symptomatic progression.
1. Wu et al. WCLC 2018. Abstract 12096.

# Real-World Experience With Afatinib: Case Study #1

May 2018, ADC stage IV (bone, lung mets)
Del 19 positive

↓

MRI: unique brain metastasis with oedema

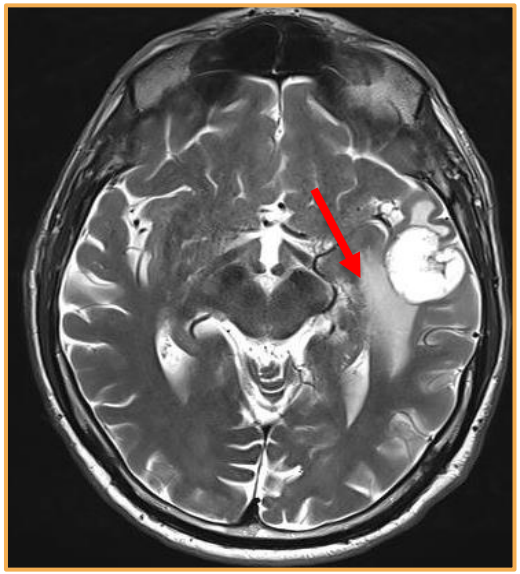
↓

No neurologic symptoms

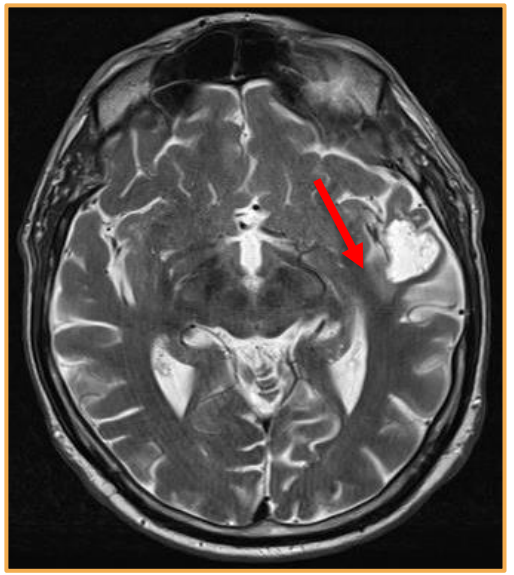
↓

Afatinib 40 mg QD started on May 2018

**MRI May 2018**



**MRI July 2018**

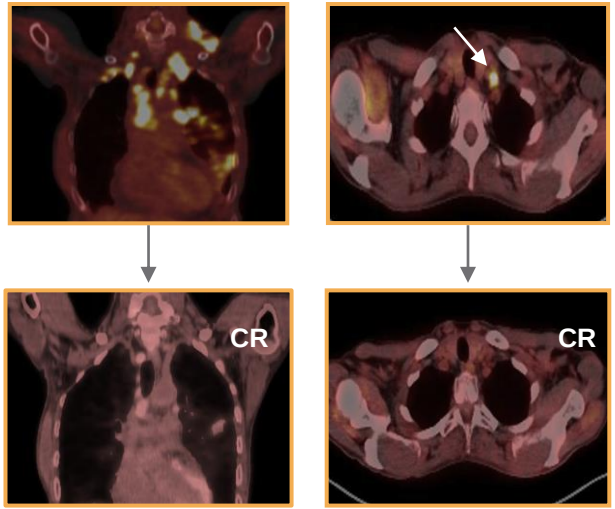


**Systemic & CNS PR after 3 months on afatinib**
**No radiotherapy or corticosteroids applied**



Case report: N. Reguart.
MRI = Magnetic Resonance Imaging.

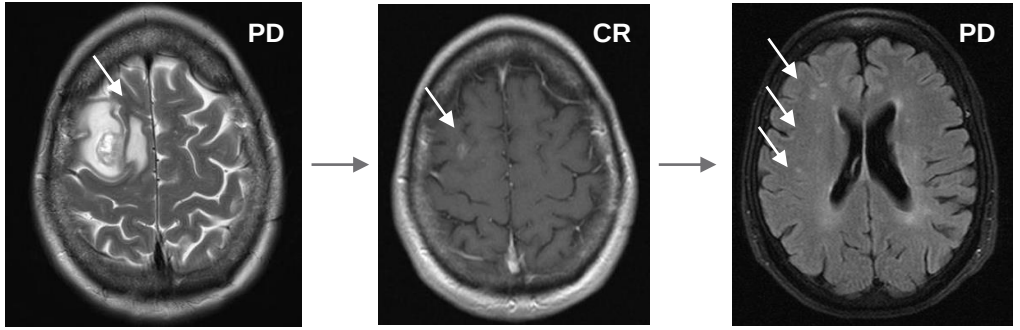
# Real-World Experience With Afatinib: Case Study #2




**Afatinib 40 mg QD**
CR
(Jan 2014)

**1st oligo-PD: node**
SBRT and afatinib continuation
(Sept 2014)

**Stage IV Lung ADC, *EGFR* Ex20 (S768I) and Ex18 (G719X)**




**2nd oligo-PD: CNS**
SBRT and afatinib continuation
(June 2015)

**Multifocal-PD: CNS**
WBRT and 2nd line
(Dec 2015)

Time to first CNS-PD: 18 mo

Time to 2nd CNS-PD: 24 mo

Treatment time on afatinib and local strategies = 24 months



SBRT = stereotactic body radiation therapy.
Case report: N. Reguart.

# Summary

- The first-generation, reversible EGFR TKIs erlotinib and gefitinib have limited intracranial activity in patients with NSCLC[1,2]
- A novel CSF-permeant, reversible EGFR TKI (AZD3759) is in early clinical development[3]
- The third-generation EGFR TKI osimertinib clearly has activity in patients with BM
  - Osimertinib delayed onset and progression of BM independent of treatment line (FLAURA, AURA3)[4-6]
  - Intracranial ORR of 66%[5]
- The second-generation TKI afatinib has a strong body of evidence showing efficacy against and delayed onset of cerebral manifestations
  - First-line afatinib delayed onset and progression of BM (LUX-Lung trials)[7-10]
  - Real-world data showing treatment time of ≈15 months, with an intracranial ORR of 76%, confirm the efficacy of afatinib[11,12]



1. Park et al. *Lung Cancer*. 2012;77:556; 2. Wu et al. *Ann Oncol*. 2013;24:993; 3. Ahn et al. *Lancet Respir Med*. 2017;5:891; 4. Soria et al. *N Engl J Med*. 2018;378:113; 5. Vansteenkiste et al. *J Clin Oncol*. 2018 Aug 28:JCO2018783118. doi: 10.1200/JCO.2018.78.3118. [Epub ahead of print]; 6. Mok et al. *N Engl J Med*. 2017;376:629; 7. Data on file, Boehringer Ingelheim; 8. Girard. Future Oncol. 2018;14:1117; 9. Schuler et al. *J Thorac Oncol.* 2016;11:380; 10. Park et al. *Lancet Oncol*. 2016;17:577; 11. Kim Y, et al. *J Thorac Oncol*. 2017;12:S2209; 12. Wu et al. WCLC 2018. Abstract 12096.