New avenues in treatment of EGFR mut NSCLC

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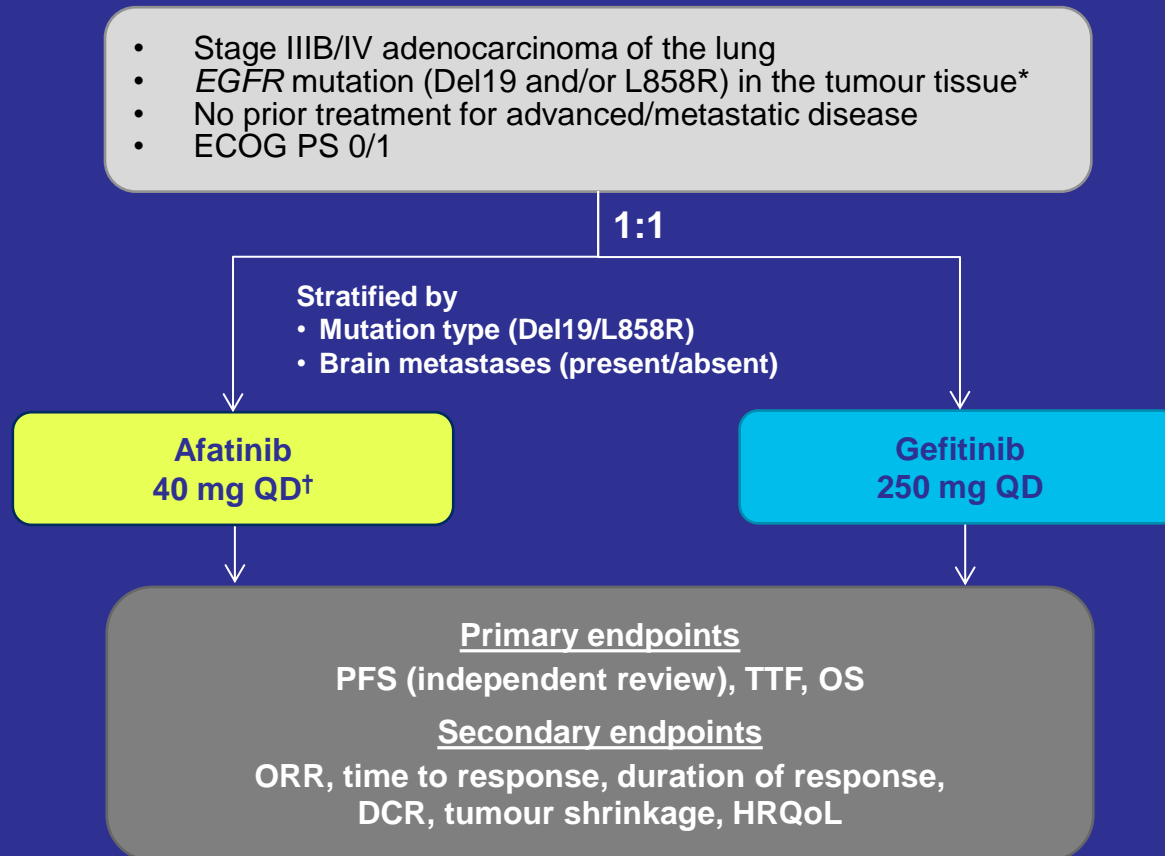
Disclosures

- Consultancy: Eli Lilly
- Advisory Boards: Astra Zeneca, Boehringer Ingelheim, Bayer, Cellgene, Novartis, Clovis, Roche-Genentech, Pfizer, BMS.
- Research Funding: Astra Zeneca, Boehringer Ingelheim, Bayer, Clovis, Roche-Genentech.
- Stock Options: None

- 140PD: LUX-Lung 7 – a phase IIb, global, randomised open-label trial of afatinib vs gefitinib as first line treatment for patients with advanced non-small cell lung cancer harbouring activating EGFR mutations. Park et al.

- 138PD: Impact of dose adjustment on safety and efficacy of afatinib in patients with advanced EGFR mutation positive non-small cell lung cancer: Post- hoc analyses of LUX-Lung 3 and LUX-Lung 6. Schuler et al

- 139PD: Lifetime incidence of brain metastases in EGFR – mutant lung cancer treated with EGFR TKIs. Ng et al.

Background

- Afatinib and other EGFR-targeting agents, erlotinib and gefitinib, are approved first-line treatments for *EGFR*m+ NSCLC

- Afatinib irreversibly inhibits signaling of EGFR, HER2-HER4 *(2nd generation TKI)*, whereas gefitinib and erlotinib reversibly inhibit EGFR *(1st generation TKIs)*

- Q: which is the "better" EGFR TKI?
  - Efficacy vs toxicity

LUX-Lung 7: study design

Stage IIIB/IV adenocarcinoma of the lung
- *EGFR* mutation (Del19 and/or L858R) in the tumour tissue*
- No prior treatment for advanced/metastatic disease
- ECOG PS 0/1

1:1

Stratified by
- **Mutation type (Del19/L858R)**
- **Brain metastases (present/absent)**

Afatinib
40 mg QD[†]

Gefitinib
250 mg QD

Primary endpoints
PFS (independent review), TTF, OS

Secondary endpoints
ORR, time to response, duration of response, DCR, tumour shrinkage, HRQoL

Response Evaluation Criteria In Solid Tumors assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter
*Central or local test; [†]Dose modification to 50, 30, 20 mg permitted in line with prescribing information
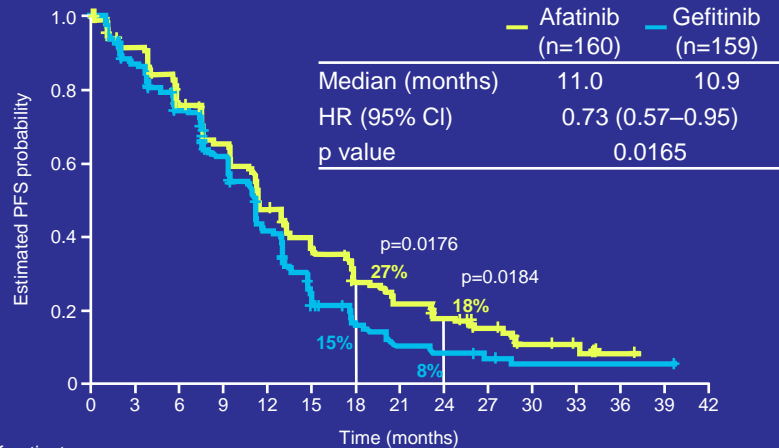DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life;
ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; TTF, time to treatment failure
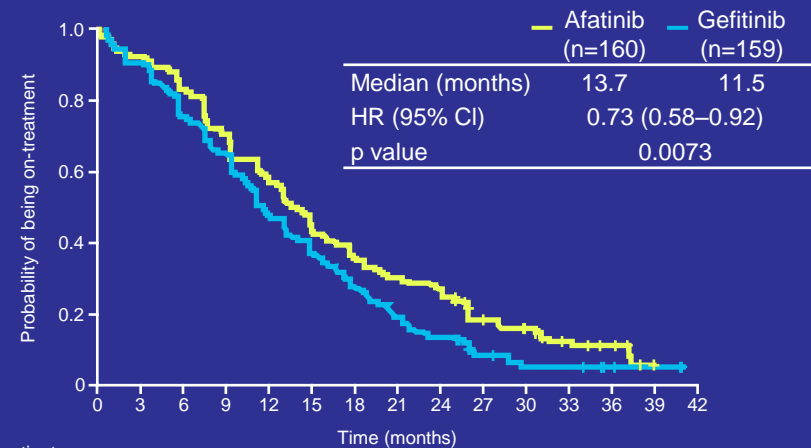
LUX-Lung 7: PFS*, TTF and ORR*
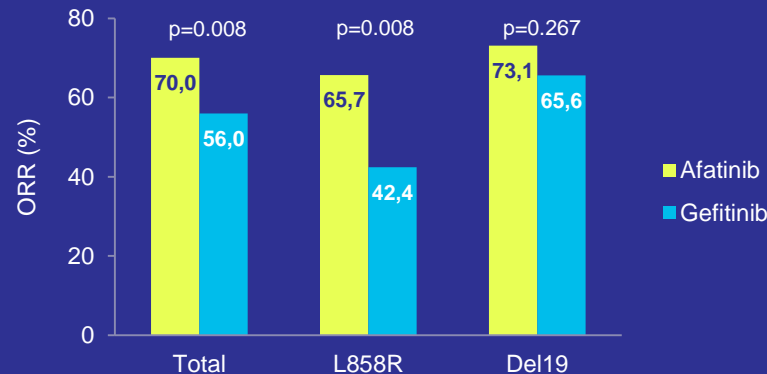## (*independent review)

PFS

	Afatinib (n=160)	Gefitinib (n=159)
Median (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

Estimated PFS probability vs Time (months)

p=0.0176
27%
p=0.0184
18%
15%
8%

No. of patients
Afatinib: 160 142 112 94 67 47 34 27 21 13 6 3 1 0 0
Gefitinib: 159 132 106 83 52 22 14 9 7 5 3 3 1 1 0

TTF

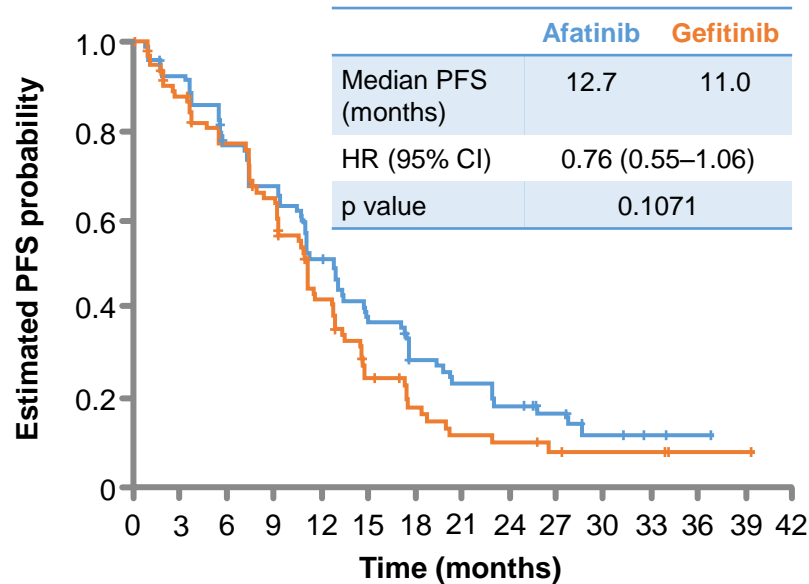|	Afatinib (n=160)	Gefitinib (n=159)
Median (months)	13.7	11.5
HR (95% CI)	0.73 (0.58–0.92)	
p value	0.0073	

Probability of being on-treatment vs Time (months)

No. of patients
Afatinib: 160 148 133 113 91 68 56 48 40 25 18 9 5 0 0
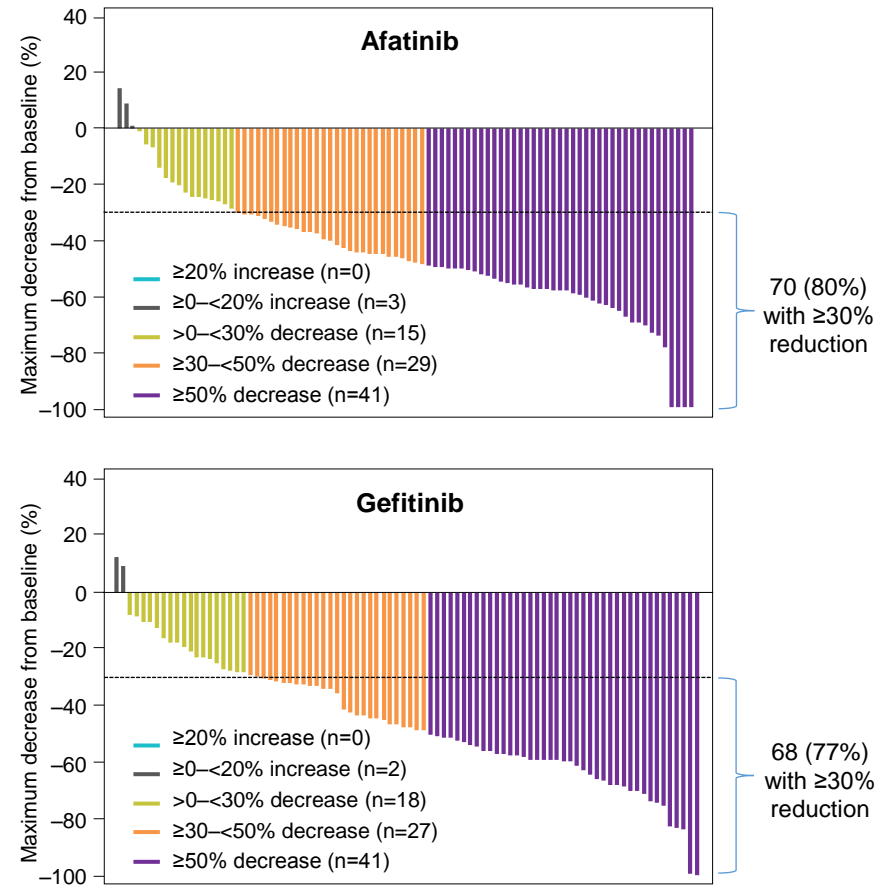Gefitinib: 159 144 120 103 74 59 43 30 21 11 6 6 2 2 0

ORR

ORR (%)

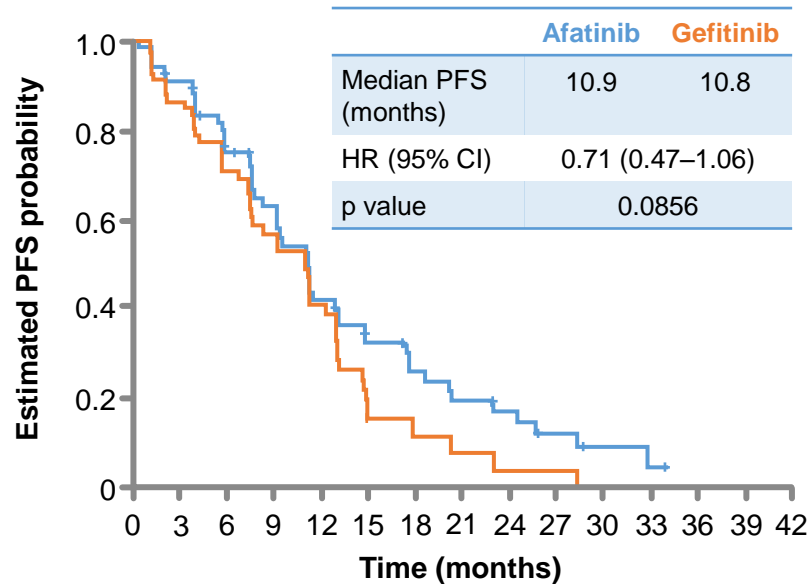|	Total	L858R	Del19
p value	p=0.008	p=0.008	p=0.267
Afatinib	70,0	65,7	73,1
Gefitinib	56,0	42,4	65,6

CI, confidence interval; HR, hazard ratio

Efficacy in patients with Del19

	Afatinib	Gefitinib
Median PFS (months)	12.7	11.0
HR (95% CI)	0.76 (0.55–1.06)	
p value	0.1071	

No. of patients

Afatinib	93	83	67	58	43	31	22	18	14	9	4	2	1	0	0
Gefitinib	93	76	64	53	32	17	11	7	6	4	3	3	1	1	0

	Afatinib (n=93)	Gefitinib (n=93)
ORR	73%	66%

Afatinib

- ≥20% increase (n=0)
- ≥0–<20% increase (n=3)
- >0–<30% decrease (n=15)
- ≥30–<50% decrease (n=29)
- ≥50% decrease (n=41)

70 (80%) with ≥30% reduction

Gefitinib

- ≥20% increase (n=0)
- ≥0–<20% increase (n=2)
- >0–<30% decrease (n=18)
- ≥30–<50% decrease (n=27)
- ≥50% decrease (n=41)

68 (77%) with ≥30% reduction

Efficacy in patients with L858R

	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	

No. of patients
| Afatinib | 67 | 59 | 45 | 36 | 24 | 16 | 12 | 9 | 7 | 4 | 2 | 1 | 0 | 0 | 0 |
| Gefitinib | 66 | 56 | 42 | 30 | 20 | 5 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |

	Afatinib (n=67)	Gefitinib (n=66)
ORR	66%	42%

Afatinib

≥20% increase (n=1)
≥0–<20% increase (n=3)
>0–<30% decrease (n=12)
≥30–<50% decrease (n=21)
≥50% decrease (n=24)

45 (74%) with ≥30% reduction

Gefitinib

≥20% increase (n=4)
≥0–<20% increase (n=4)
>0–<30% decrease (n=23)
≥30–<50% decrease (n=19)
≥50% decrease (n=13)

32 (51%) with ≥30% reduction

LUX-Lung 7: safety

Investigator-reported drug-related AEs (>10%)

AE category, %	Afatinib (n=160)		Gefitinib (n=159)	
	All grades	Grade 3	All grades	Grade 3
Diarrhoea	90.0*	11.9	61.0	1.3
Rash/acne[†]	88.8	9.4	81.1	3.1
Stomatitis[†]	64.4	4.4	23.9	–
Paronychia[†]	55.6	1.9	17.0	0.6
Dry skin	32.5	–	37.1	–
Pruritus	23.1	–	22.6	–
Fatigue[†]	20.6	5.6	14.5	–
Decreased appetite	16.3	0.6	11.9	–
Nausea	16.3	1.3	13.8	–
Alopecia	10.6	–	15.1	–
Vomiting	10.6	–	3.8	0.6
ALT/AST increased	10.0	–	24.5[‡]	8.2

- Afatinib and gefitinib had equally low rates (6%) of treatment discontinuations due to AEs

*Including one (0.6%) patient with grade 4 diarrhoea; [†]Grouped terms of AEs; [‡]Including one (0.6%) patient with grade 4 ALT/AST increased
AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

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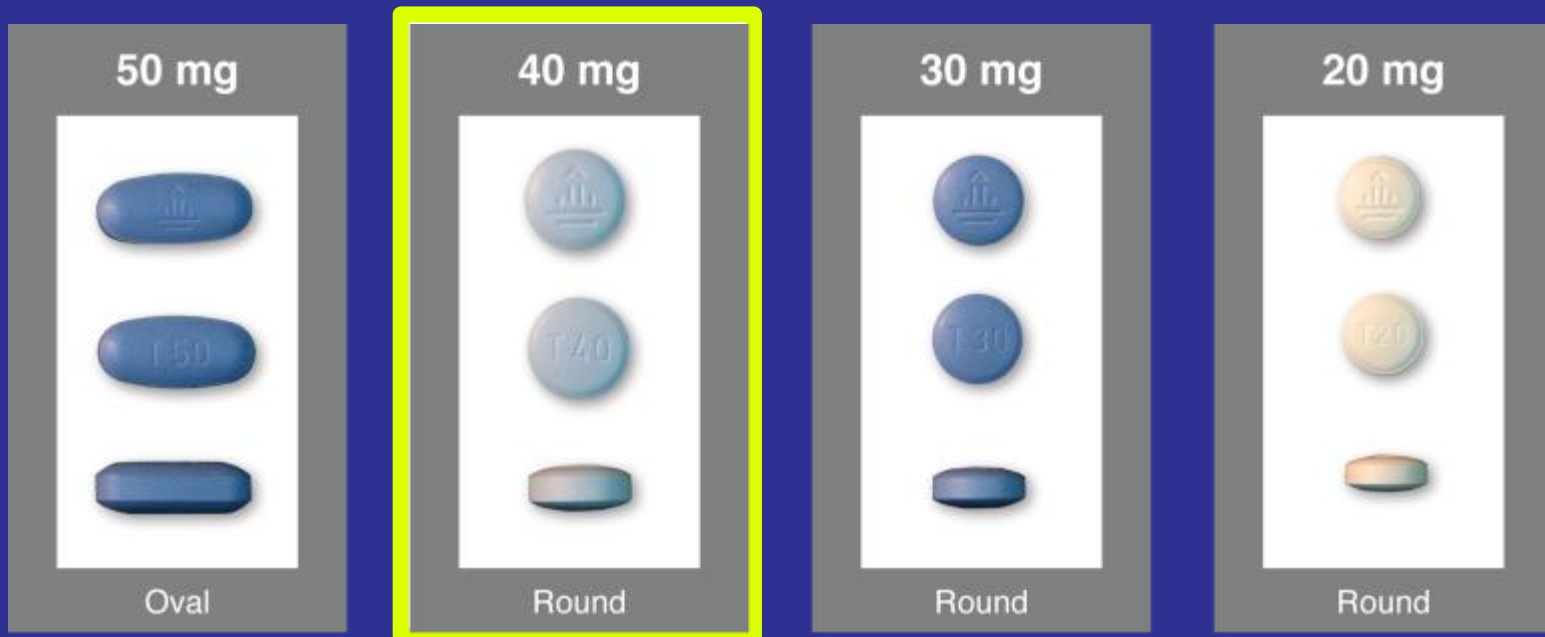
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AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Conclusion

- Afatinib has significantly superior efficacy over gefitinib in EGFR Mut NSCLC
  - L858R
  - Clinical relevance?
  - Toxicity remains issue
    - How about dose reductions?
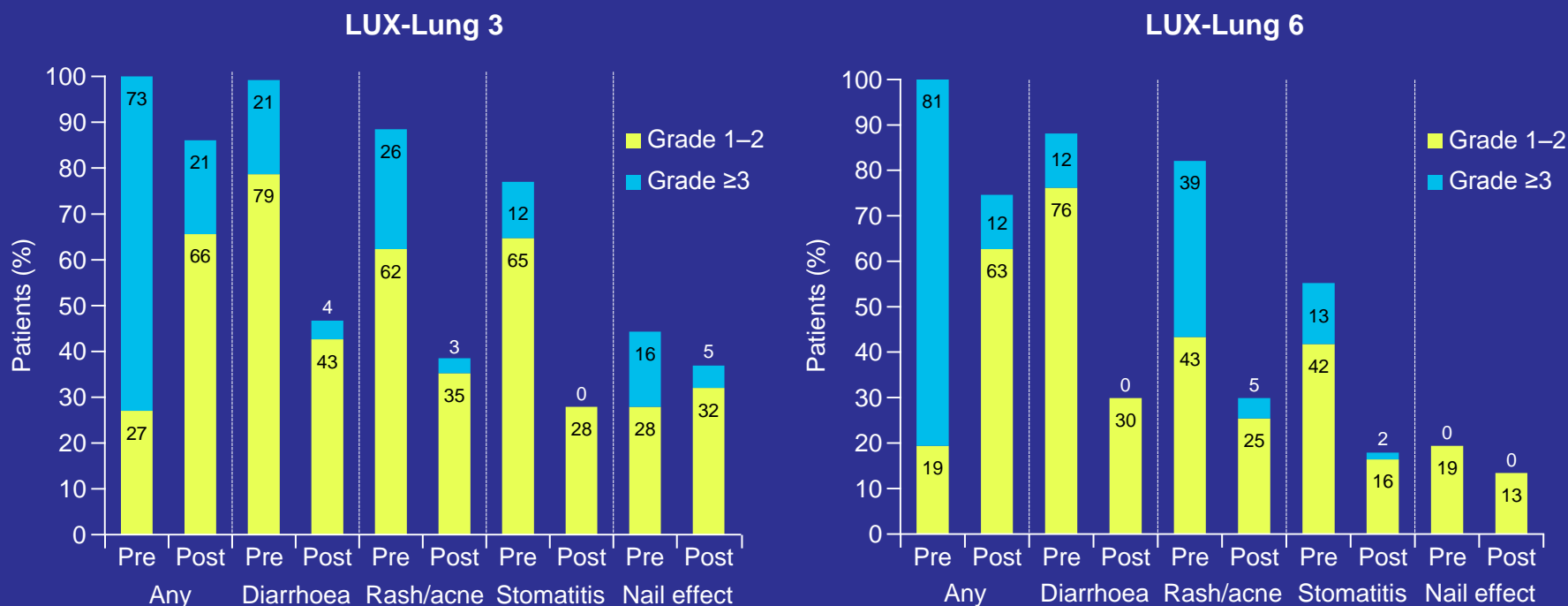
Afatinib Dosing and Administration

- Standard dosing: 40 mg once daily

- Administration: orally (film-coated tablets)

Impact of dose adjustment on the safety and efficacy of afatinib in LUX-Lung 3 and LUX-Lung 6
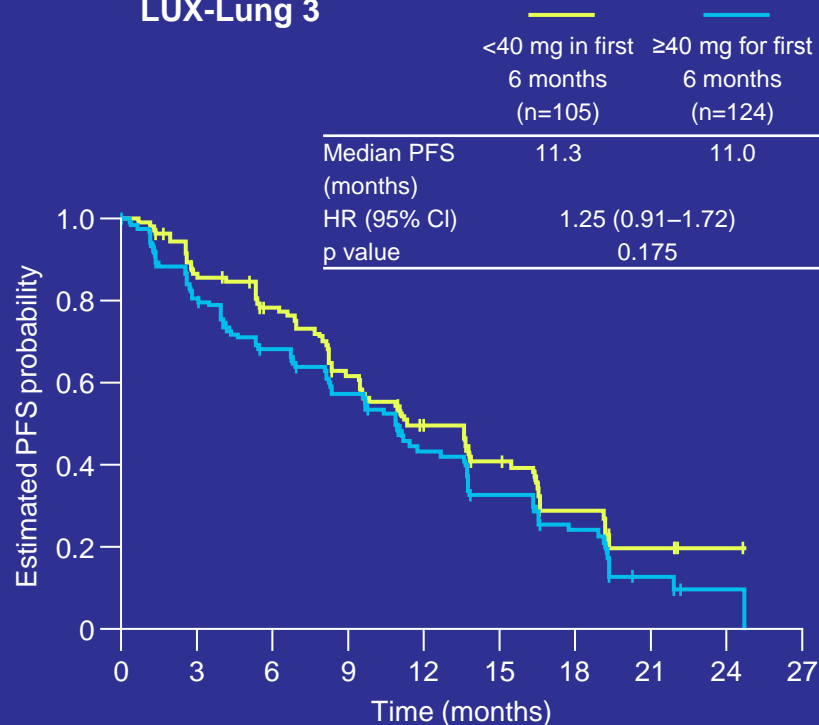
- Post-hoc analyses were performed to assess the influence of afatinib dose reduction on AEs, pharmacokinetics and PFS in the LUX-Lung 3 and LUX-Lung 6 trials
- Dose reductions occurred in 122 of 229 (53%) and 67 of 239 (28%) afatinib-treated patients in LUX-Lung 3 and 6, respectively; most reductions occurred within the first 6 months of treatment

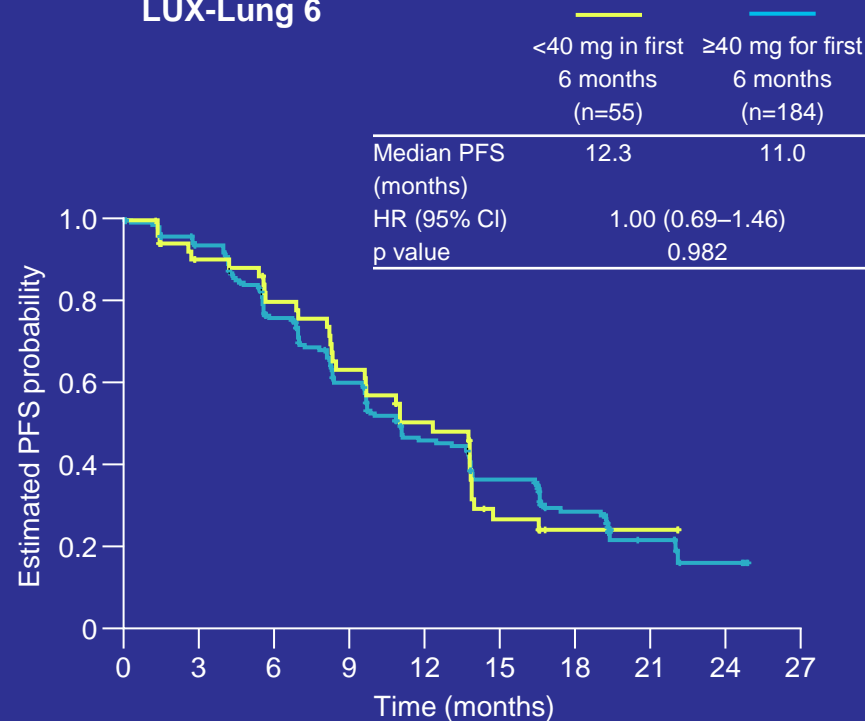## Key treatment-related AEs in patients with dose reductions

LUX-Lung 3

Grade 1–2
Grade ≥3

	Pre	Post
Any	73 / 27	21 / 66
Diarrhoea	21 / 79	4 / 43
Rash/acne	26 / 62	3 / 35
Stomatitis	12 / 65	0 / 28
Nail effect	16 / 28	5 / 32

LUX-Lung 6

Grade 1–2
Grade ≥3

	Pre	Post
Any	81 / 19	12 / 63
Diarrhoea	12 / 76	0 / 30
Rash/acne	39 / 43	5 / 25
Stomatitis	13 / 42	2 / 16
Nail effect	0 / 19	0 / 13

AEs, adverse events; PFS, progression-free survival

PFS in patients with or without dose reduction of afatinib in the first 6 months of treatment

LUX-Lung 3

	<40 mg in first 6 months (n=105)	≥40 mg for first 6 months (n=124)
Median PFS (months)	11.3	11.0
HR (95% CI)	1.25 (0.91–1.72)	
p value	0.175	

LUX-Lung 6

	<40 mg in first 6 months (n=55)	≥40 mg for first 6 months (n=184)
Median PFS (months)	12.3	11.0
HR (95% CI)	1.00 (0.69–1.46)	
p value	0.982	

No. at risk (LUX-Lung 3)

	0	3	6	9	12	15	18	21	24	27
<40 mg in first 6 months	105	87	75	58	41	26	15	6	2	0
≥40 mg for first 6 months	124	93	76	62	36	24	16	4	1	0

No. at risk (LUX-Lung 6)

	0	3	6	9	12	15	18	21	24	27
<40 mg in first 6 months	55	44	38	30	22	10	4	2	0	0
≥40 mg for first 6 months	184	164	128	96	67	50	31	10	4	0

HR, hazard ratio; CI, confidence interval

Afatinib plasma levels in patients who dose reduced to 30 mg or who remained on 40 mg: combined analyses of LUX-Lung 3 and LUX-Lung 6
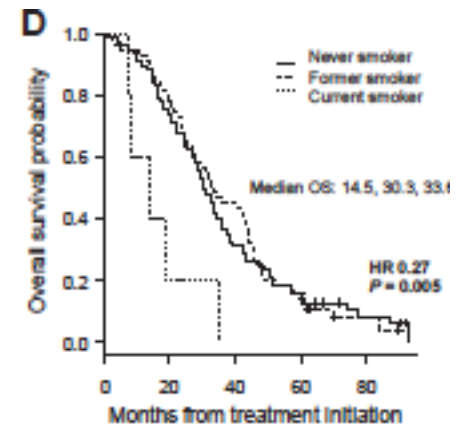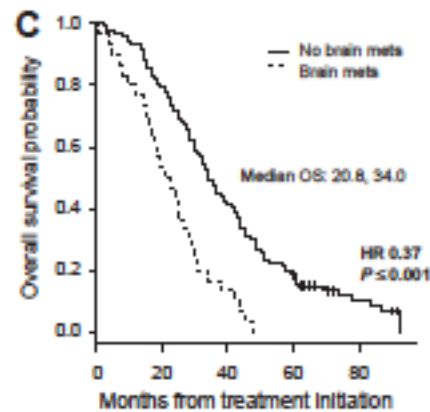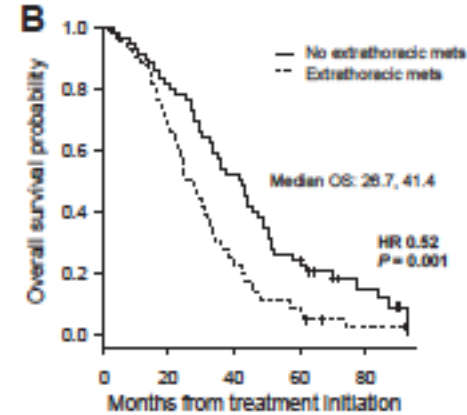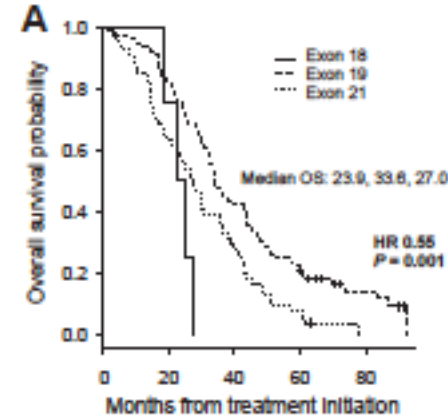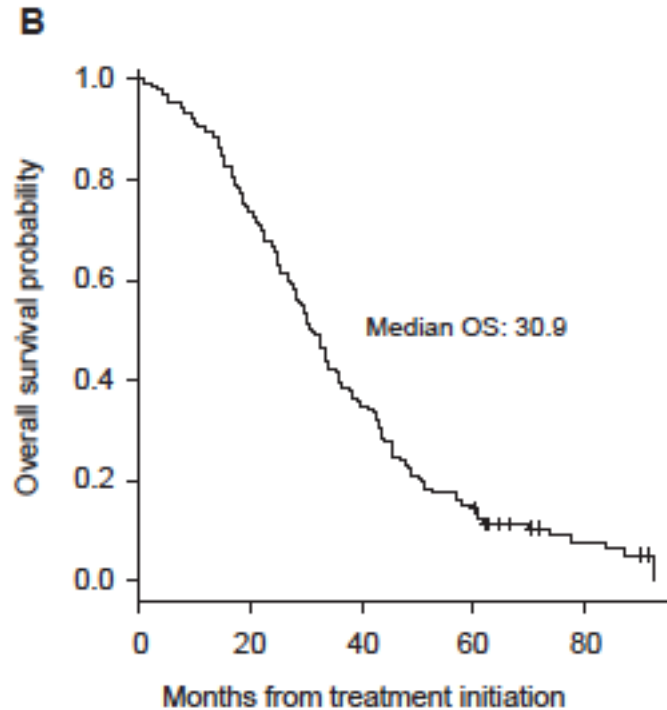

Boxes represent the median and interquartile range; the whiskers represent the 10th and 90th percentiles and the dots show data points outside percentiles. For patients who dose reduced to afatinib 30 mg before day 43 (n = 59), only 22 had valid trough concentrations for afatinib 40 mg at day 22 (the rest had either no pharmacokinetics sampling at this time [n = 15], were already receiving afatinib 30 mg at day 22 [n = 14] or were excluded from the analysis due to invalid sampling [n = 8])
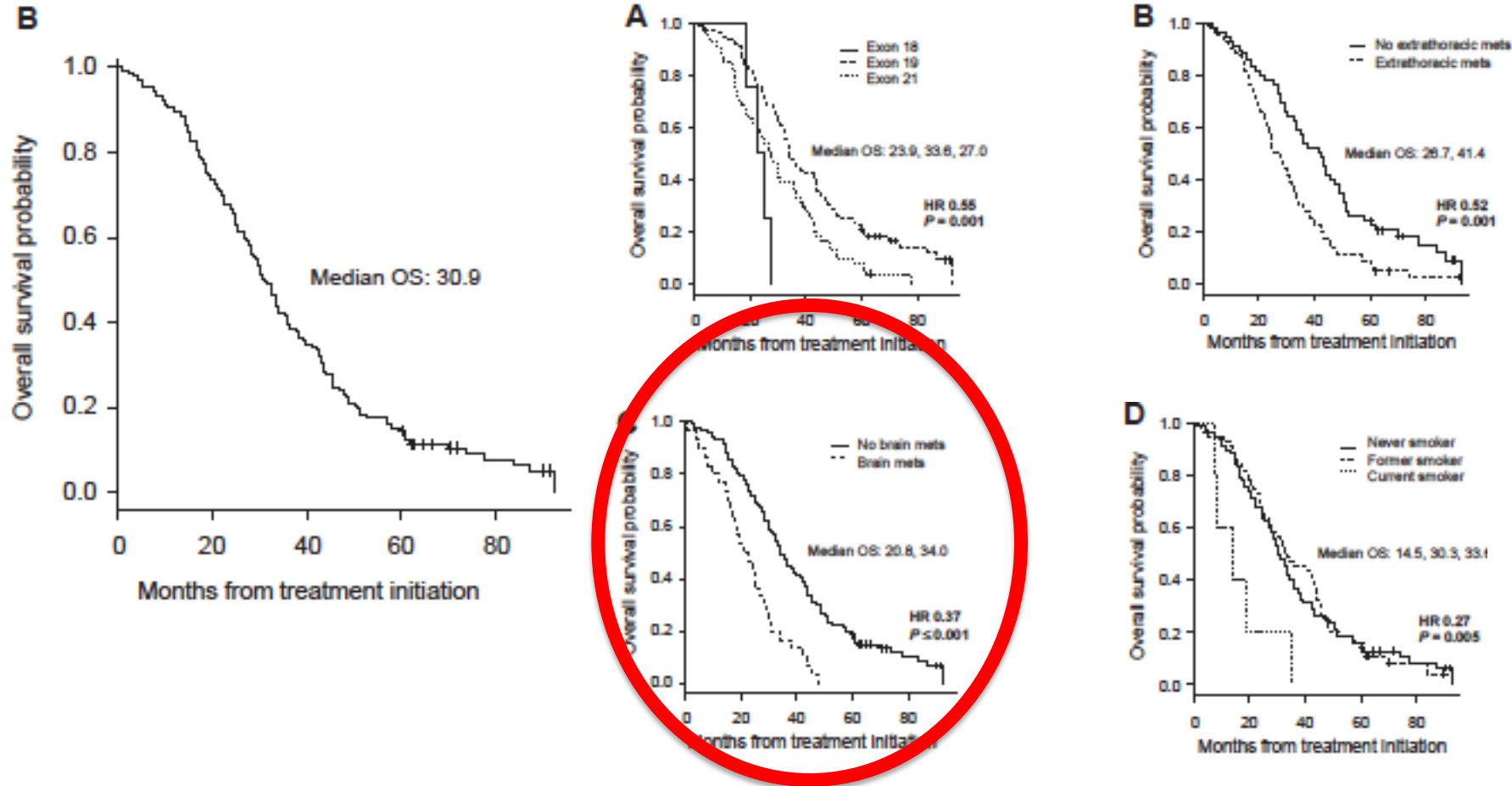
Conclusion

- Afatinib can be dose reduced without loss of efficacy
  - Need larger numbers

- Afatinib plasma levels 40 mg = 30 mg
  - Calls for TDM?

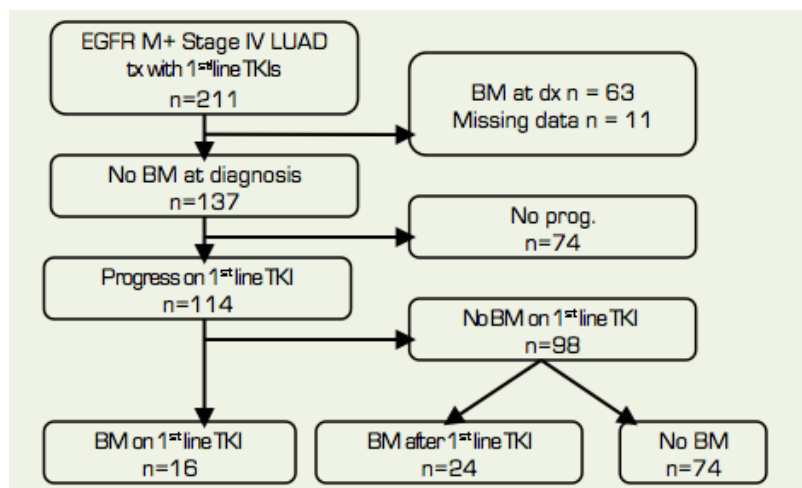- How about further dose reductions?
  - MTD *vs* BOD

Long term survival in EGFR mut NSCLC

Lin et al. 2016

Long term survival in EGFR mut NSCLC Limited by CNS metastases

Lin et al. 2016

```
EGFR M+ Stage IV LUAD
tx with 1ˢᵗ line TKIs
n=211
    │
    ├────────────────→  BM at dx n = 63
    │                    Missing data n = 11
    ↓
No BM at diagnosis
n=137
    │
    ├────────────────→  No prog.
    │                    n=74
    ↓
Progress on 1ˢᵗ line TKI
n=114
    │
    ├────────────────→  No BM on 1ˢᵗ line TKI
    │                    n=98
    ↓                        ↙        ↘
BM on 1ˢᵗ line TKI   BM after 1ˢᵗ line TKI   No BM
n=16                 n=24                    n=74
```

Retrospective Analysis of 211 patients.

Definition of end-points
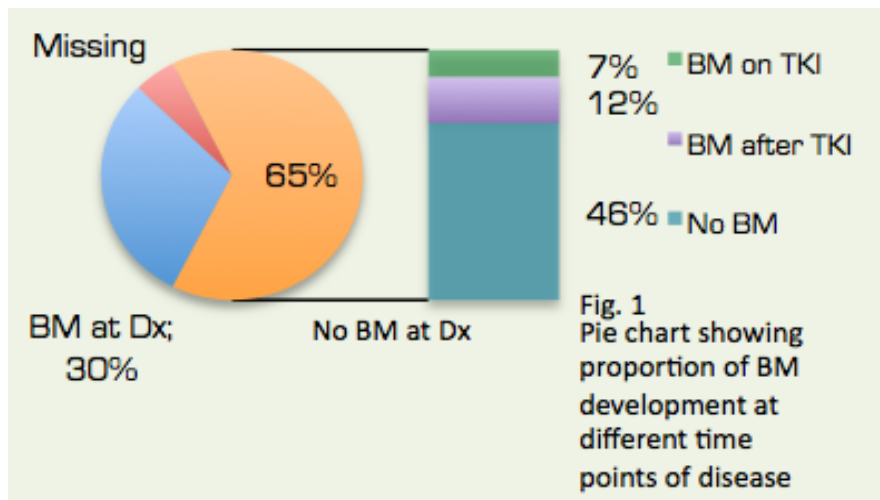Date of BM progression: the date of the first CT/MRI Brain showing progression in the brain

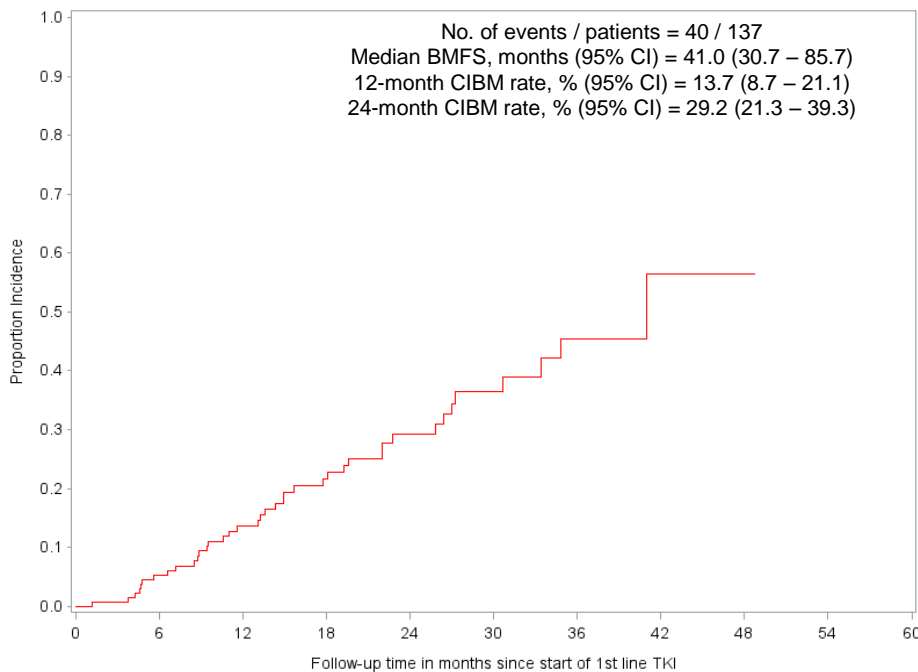Brain Metastases-Free Survival (BMFS) Diagnosis date till date of 1ˢᵗ BM progression, radiologically.

Patient Demographics

	No	%
Total	137	100.0
Age at start of first line TKI, years		
Median (range)	65 (40 – 84)	
Gender		
Female	84	61.3
Male	53	38.7
Ethnicity		
Chinese	116	84.7
Malay	14	10.2
Indian	2	1.5
Others	5	3.6
Smoking status		
Never	108	78.8
Ex	22	16.1
Current	7	5.1
Liver metastases at diagnosis		
No	120	87.6
Yes	17	12.4
First line TKI		
Gefitinib	123	89.8
Erlotinib	6	4.4
Afatinib	8	5.8
Received TKI in subsequent lines of treatment^		
No	97	70.8
Yes	40	29.2
Follow-up duration, months		
Median (range)	31.3 (0.03 – 98.1)	

Fig. 1 Pie chart showing proportion of BM development at different time points of disease

- Missing
- BM at Dx; 30%
- No BM at Dx
- 65%
- 7% BM on TKI
- 12% BM after TKI
- 46% No BM

	No. of events / No. of patients	Hazard ratio (95% CI)	P#
Adrenal metastases at diagnosis			
No	34 / 124	1	**0.033**
Yes	6 / 13	2.54 (1.04 – 6.19)	
Liver metastases at diagnosis			
No	32 / 120	1	**0.027**
Yes	8 / 17	2.37 (1.08 – 5.22)	

•On UVA, presence of liver metastases (HR 2.37, 95% CI 1.08-5.22) and adrenal metastases (HR 2.54, 95% CI 1.04-6.19) were the 2 variables significantly associated with BM development.

No. of events / patients = 40 / 137
Median BMFS, months (95% CI) = 41.0 (30.7 – 85.7)
12-month CIBM rate, % (95% CI) = 13.7 (8.7 – 21.1)
24-month CIBM rate, % (95% CI) = 29.2 (21.3 – 39.3)

	No. of events / No. of patients	Hazard ratio (95% CI)	Wald's P
Overall	40 / 137		<0.001
Liver metastases at diagnosis (Yes vs No)		2.76 (1.25 – 6.10)	

•On MVA, presence of liver metastases at diagnosis (HR 2.76, 95% CI 1.25-6.10) was significantly associated with BM

•Cumulative incidence rate of BM (CIBM) at 12-m was 13.7% (95% CI 8.7-21.1) and was 29.2% (95% CI 21.3- 39.3) at 24-m .
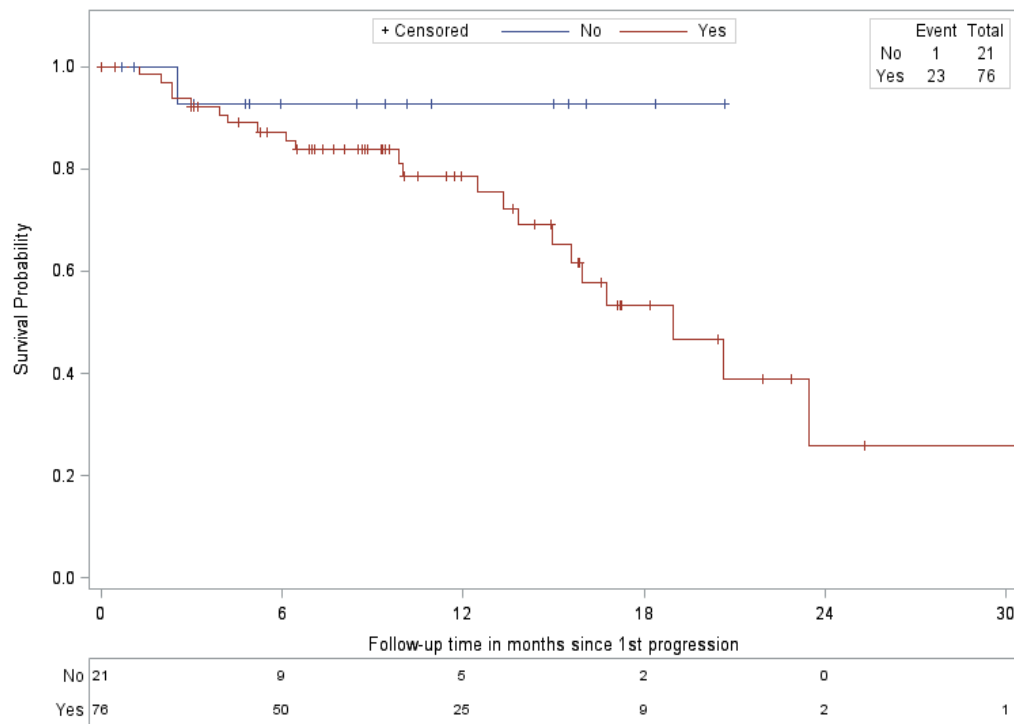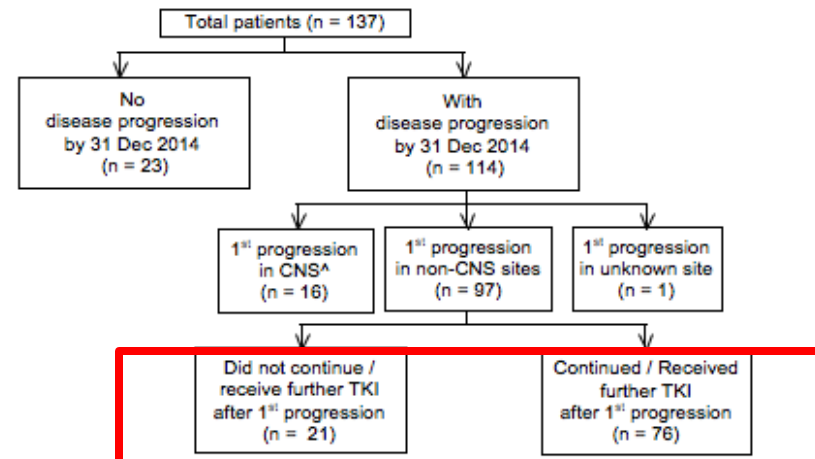
	Event	Total
No	1	21
Yes	23	76

+ Censored — No — Yes

Survival Probability vs Follow-up time in months since 1st progression

	0	6	12	18	24	30
No	21	9	5	2	0	
Yes	76	50	25	9	2	1

Figure 2. Patients for subgroup analysis

Total patients (n = 137)

No disease progression by 31 Dec 2014 (n = 23)

With disease progression by 31 Dec 2014 (n = 114)

1st progression in CNS^ (n = 16)

1st progression in non-CNS sites (n = 97)

1st progression in unknown site (n = 1)

Did not continue / receive further TKI after 1st progression (n = 21)

Continued / Received further TKI after 1st progression (n = 76)

^ Include patients with other sites of progression besides brain metastases

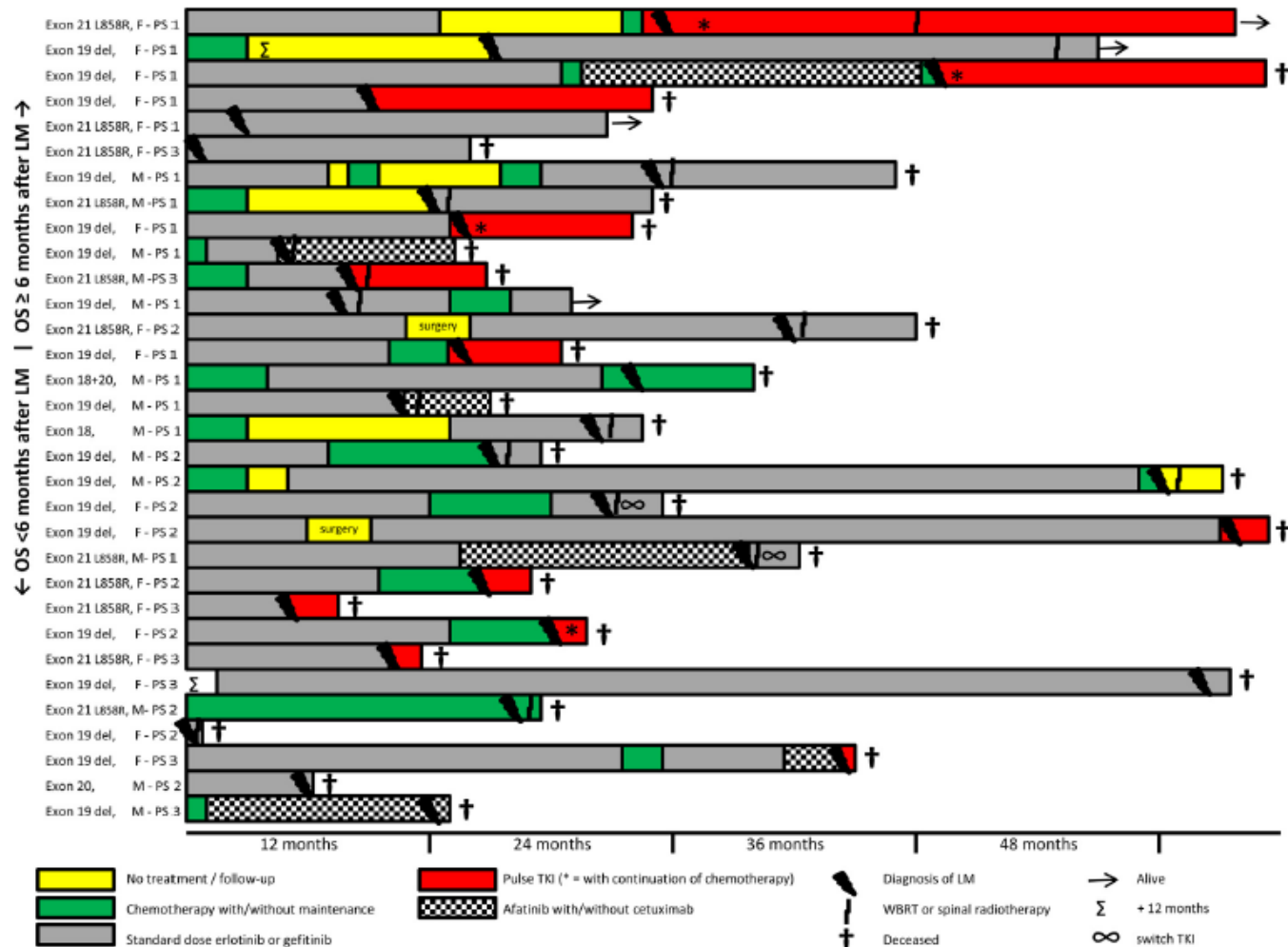|	Whether continued / received further TKI after 1st progression		Log-rank P
	No	Yes	
Median BMFS2, months (95% CI)	NR	19.0 (14.9 – 74.4)	0.123
6-month BMFS2, % (95% CI)	92.9 (59.1 – 99.0)	87.3 (76.2 – 93.5)	
12-month BMFS2, % (95% CI)	92.9 (59.1 – 99.0)	78.6 (64.8 – 87.5)	

•Among the 97 patients who first progressed in non-CNS sites, there was no significant difference in time to BM development after first disease progression between patients who received TKI beyond progression (23/76) and those who did not (1/21) (p = 0.123).

Brain metastasis

	EGFR + N= 42	KRAS + N = 48	WT N = 40	P-value
Brain mets n (%) - at diagnosis mNSCLC - during follow-up - no	 3 (7.1) 8 (19.1) 31 (73.8)	 6 (12.5) 11 (22.9) 31 (64.6)	 6 (15.0) 5 (12.5) 29 (72.5)	 0.395
Time to brain mets months [95% CI]	12.3 [9.8-14.9]	9.1 [2.7-15.6]	11.6 [1.1-22.1]	0.860
1st site PD n (%)	2 (18.2)	2 (11.8)	1 (9.1)	0.422
Only site PD n (%)	3 (27.3)	6 (35.3)	3 (27.3)	0.617
EGFR-TKI before brain mets n (%)	7 (63.6)	0 (0.0)	0 (0.0)	<0.001
> 3 brain mets	9 (81.8)	8 (47.1)	6 (54.5)	0.177
symptomatic n (%)	9 (81.8)	13 (76.5)	11 (100.0)	0.231
WBRT n (%)	6 (54.5)	13 (76.5)	10 (90.9)	0.091
SRS / surgery n (%)	1 (9.1)	8 (47.1)	3 (27.3)	0.261
Post brain mets survival months [95% CI]	5.6 [0-14.5]	8.9 [3.2-14.7]	4.6 [0-11.9]	0.570

WBRT or TKI's for CNS metastases? Retrospective analysis

CNS metastases in EGFR mut NSCLC

- Pharmacological resistance (BBB)
  - High dose ("pulse") treatment

- Novel EGFR inhibitors better penetration in CNS
  - AZD9291
  - AZD3759

Thanks

- Presenters for providing slides ahead of presentation

- You for listening