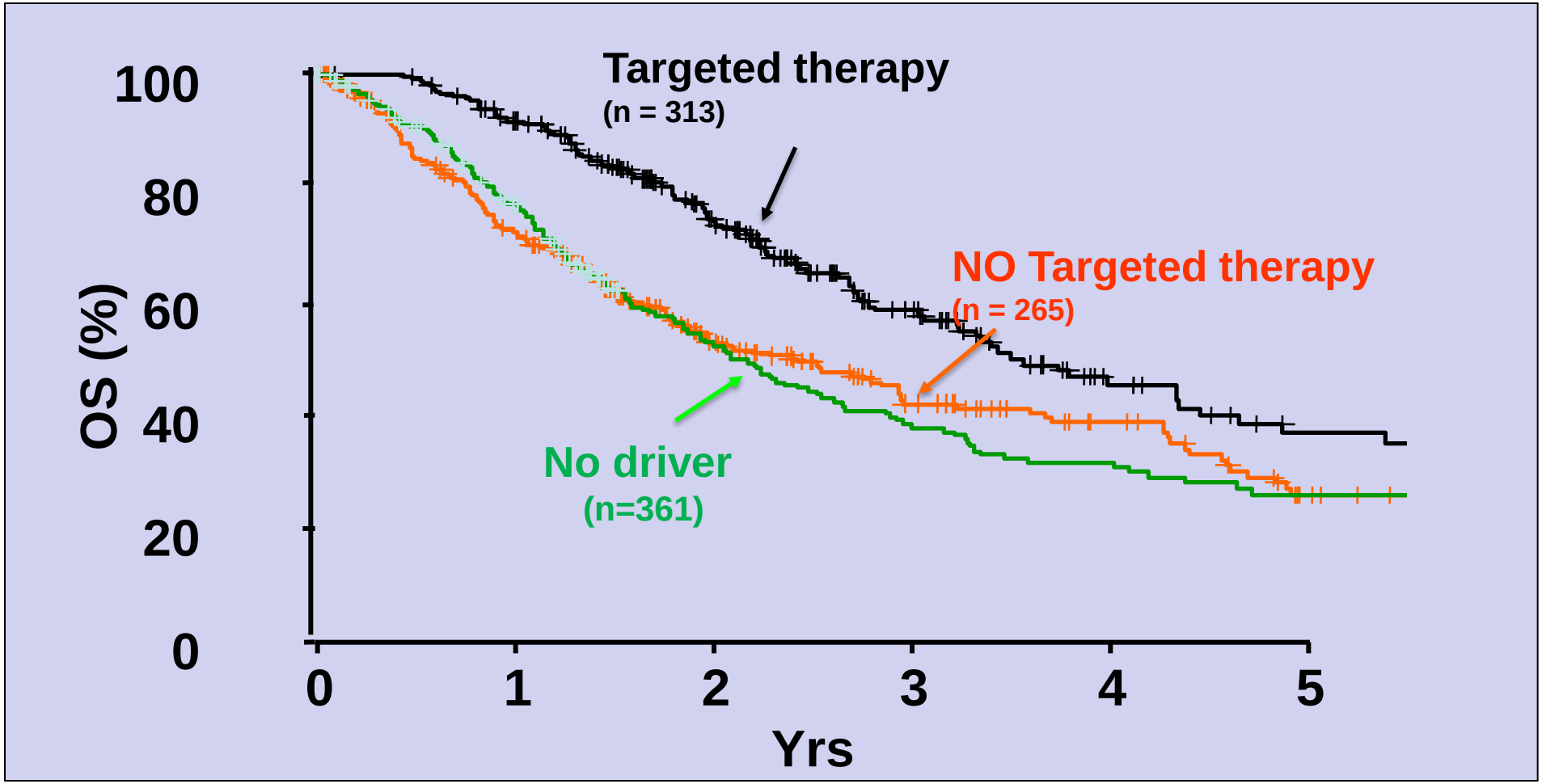
Dalla prima generazione di inibitori di EGFR al superamento delle resistenze

Rita Chiari

Oncologia Medica

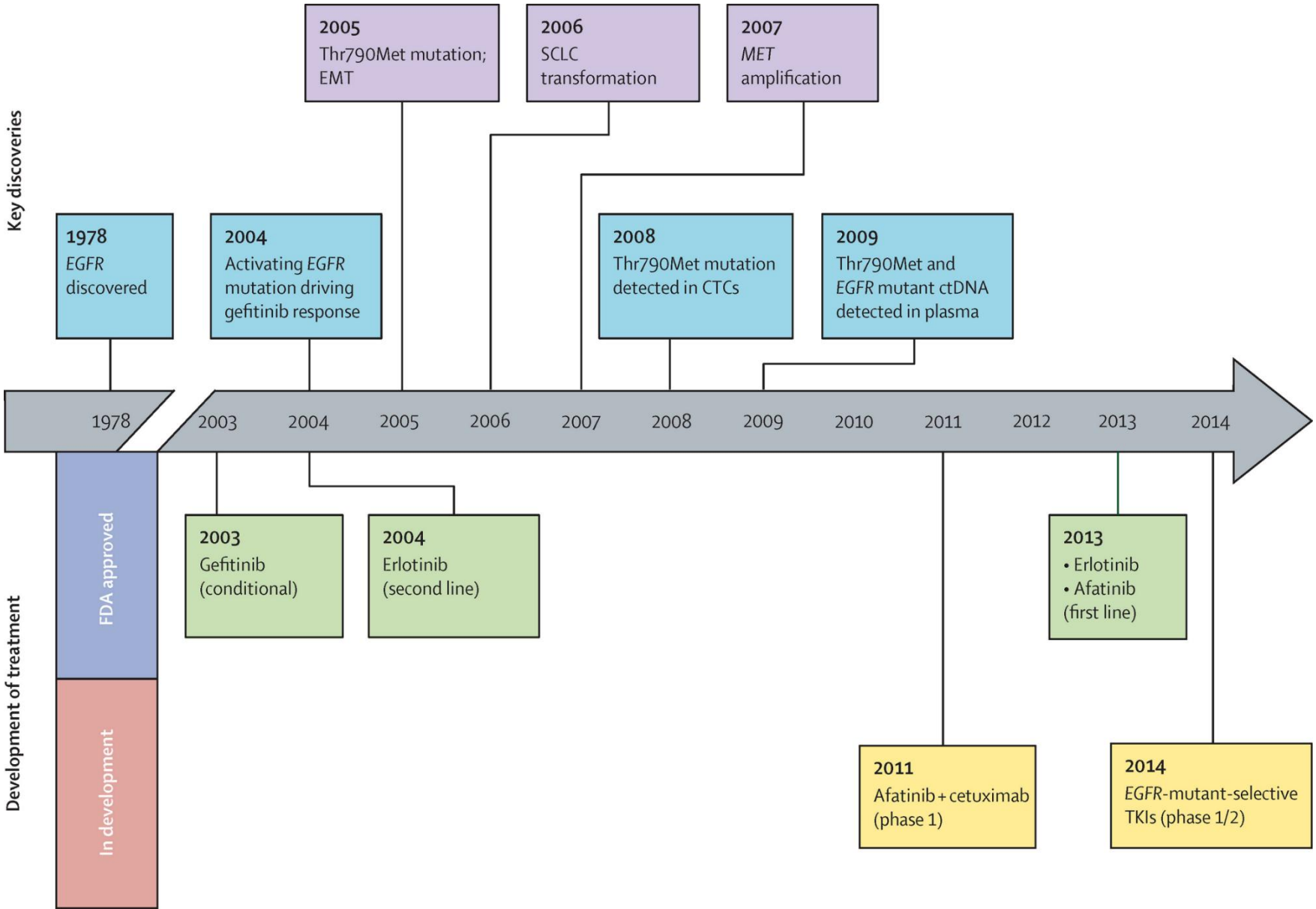
Azienda Ospedaliera di Perugia

Targeted therapy for oncogene-driven lung cancer



Kris MG et al, JAMA May 2014

EGFR timeline:…a quite long lag time from key discoveries to development of treatments!



NSCLC EGFR-mutated

- **First-line**
  - **In first line we have to always use an EGFR-TKI?**
  - **Which EGFR-TKI? First, second or third generation?**
  - **What about uncommon mutations?**
- **Mechanisms of resistance**
  - **Primary Resistance**
  - **Acquired Resistance**
- **PD1-axis and EGFR-TKIs**

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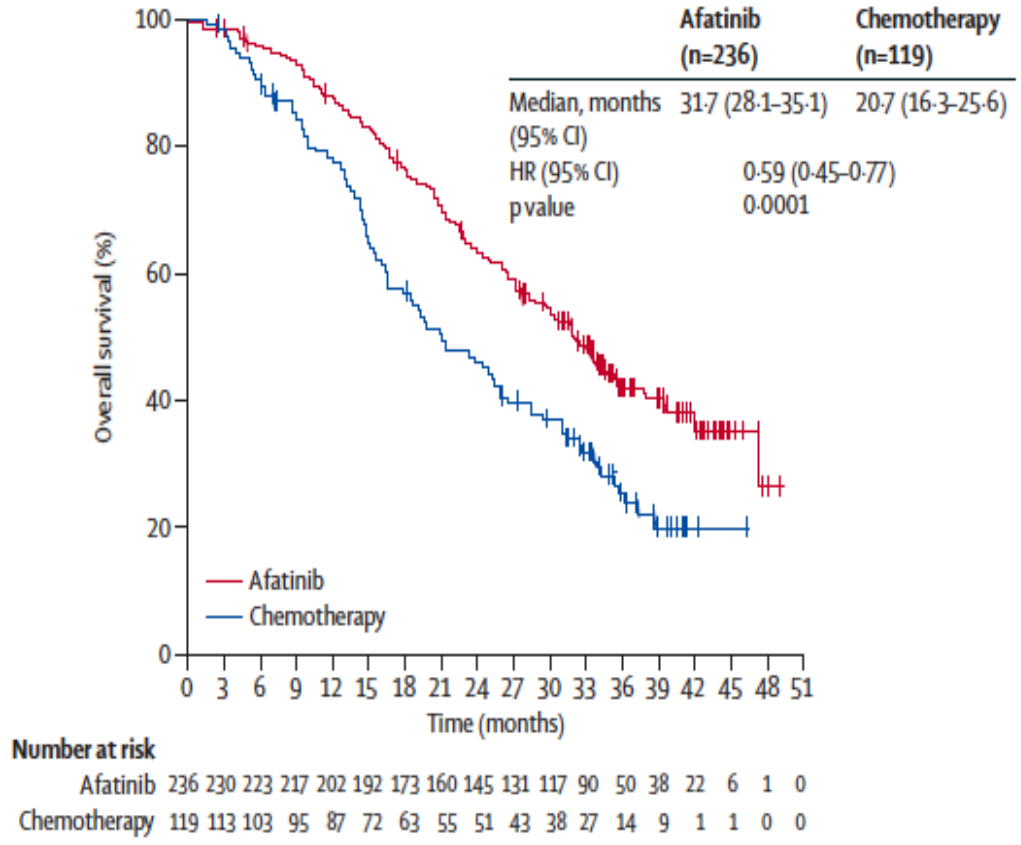
EGFR-TKIs in first-line in EGFR-M+

	Study	N (EGFR mut+)	RR (%)	Median PFS (Months)	Median OS (Months)	
GEFITINIB	IPASS[1,2]	261	71.2 *vs.* 47.3	9.5 *vs.* 6.3	21.6 *vs.* 21.9	
GEFITINIB	First-SIGNAL[3,]	42	84.6 *vs.* 37.5	8.0 *vs.* 6.3	27.2 *vs.* 25.6	
GEFITINIB	WJTOG 3405[4,5]	172	62.1 *vs.* 32.2	9.2 *vs.* 6.3	34.8 *vs.* 37.3	
GEFITINIB	NEJGSG002[6,7]	228	73.7 *vs.* 30.7	10.8 *vs.* 5.4	27.7 *vs.* 26.6	
ERLOTINIB	OPTIMAL[8,9]	154	83 *vs.* 36	13.1 *vs.* 4.6	28.8 *vs.* 22.7	
ERLOTINIB	EURTAC[10,11]	173	58 *vs.* 15	9.7 *vs.* 5.2	28.6 *vs.* 22.1	
AFATINIB	LUX LUNG-3[12,14]	345	56 *vs.* 23	11.1 *vs.* 6.9		Pooled analysis 27.3 *vs.* 24.3
AFATINIB	LUX LUNG-6[13,14]	364	66.9 *vs.* 23.0	11.0 *vs.* 5.6		

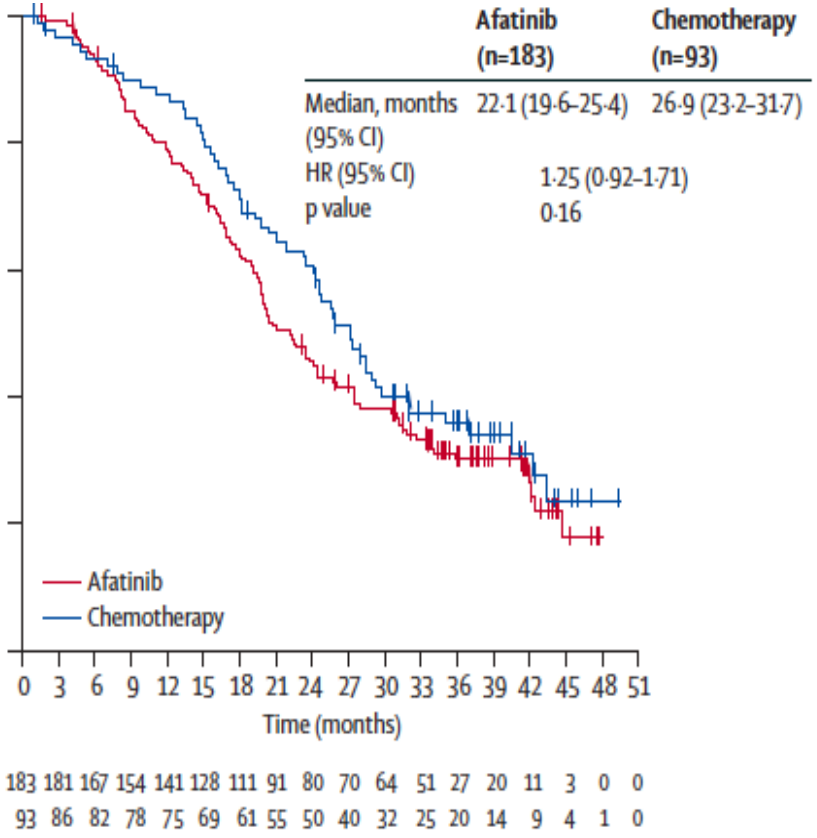
1. Mok TS et al. *N Engl J Med* 2009; 2. Fukuoka M et al. *J Clin Oncol.* 2011; 3. Han JY et al. *J Clin Oncol*. 2012; 4. Mitsudomi T et al. *Lancet Oncol* 2010; 5. Yoshioka H et al. ASCO 2014 Abstract 8117; 6. Maemondo M, et al. *N Engl J Med* 2010; 7. Inoue A et al. *Ann Oncol*. 2013; 8. Zhou C et al. *Lancet Oncol*. 2011; 9. Zhou C et al. ASCO 2012 Abstract 7520; 10. Rosell R et al. *Lancet Oncol*. 2012; 11. Costa C et al. *Clin Cancer Res.* 2014; 12. Sequist LV et al. *J Clin Oncol.* 2013; 13. Yang JC-H, et al , *Lancet Oncol 2014;* Yang JC-H et al, *Lancet Oncol 2015*

Afatinib versus chemotherapy: OS by *EGFR* mutation type

Exon 19

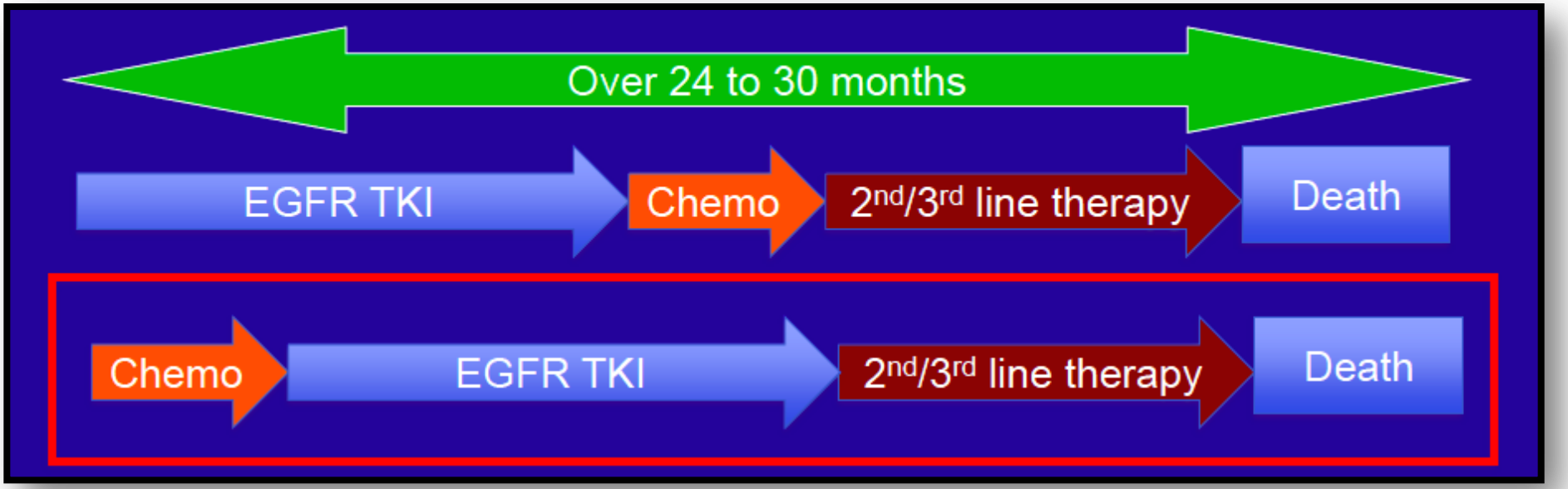


Exon 21



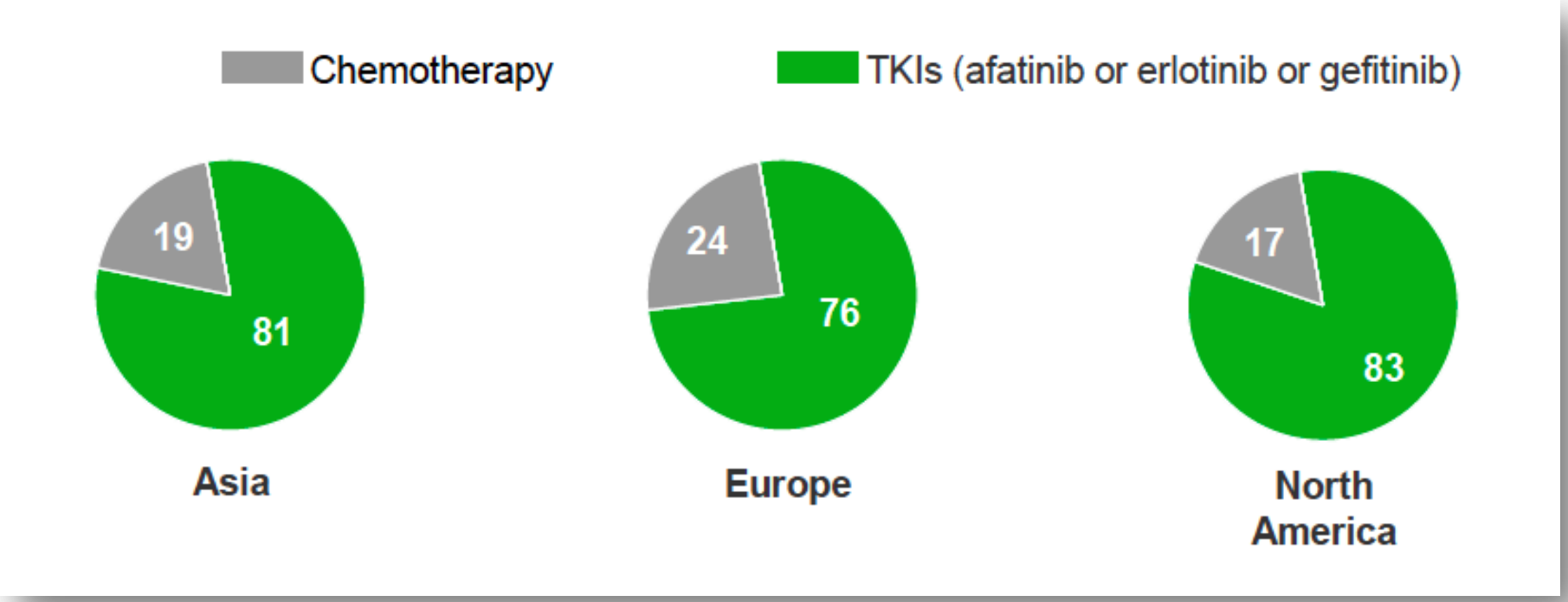
Yang J C-H, et al. Lancet Oncol 2015

First line TKI in EGFRM+ (common)



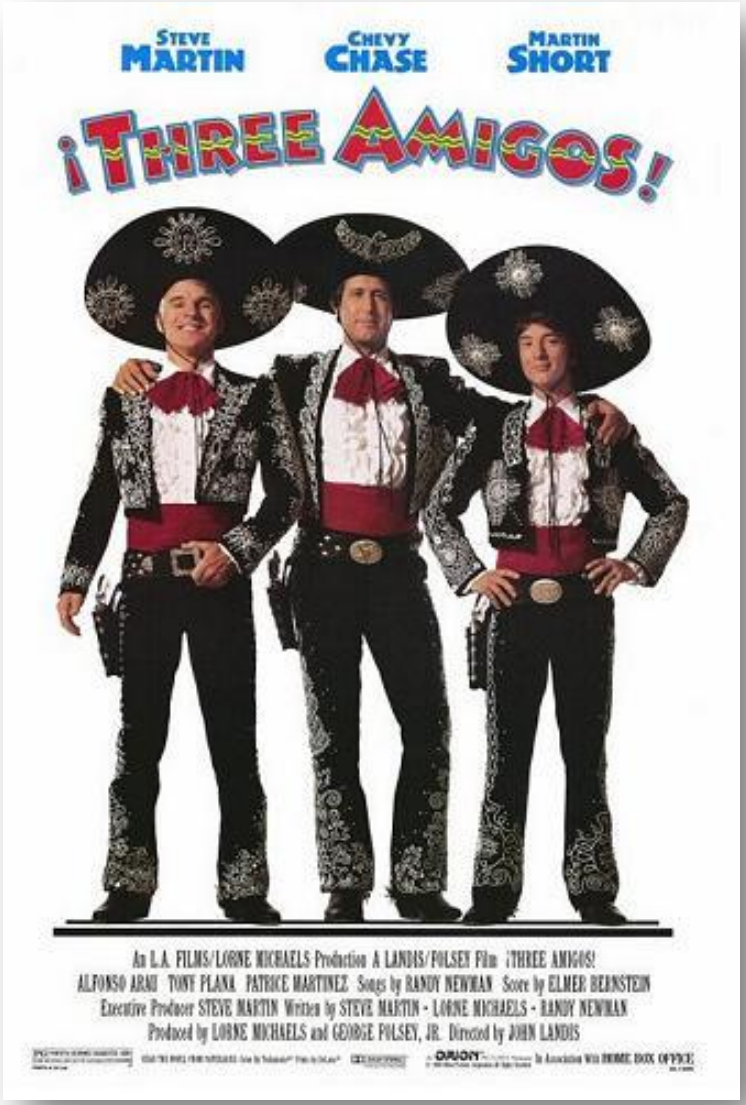
- **The main reason is the risk that some patients will not arrive to second line!!**
- **Chemotherapy in first line in EGFRM+ only if highly symptomatic, no tissue available, plasma EGFR mut neg**
- **Reversible EGFR TKIs are the best option also both in Maintenance (SATURN end INFORM) and in 2nd line (subgroup analysis of INTEREST) if the EGFRM+ pt has not received the drug in first-line**

Survey (n = 562, 10 countries): first-line choice in EGFR mutated



Spicer et al, ELCC 2015

Which EGFR-TKI in first-line in EGFR-M+?

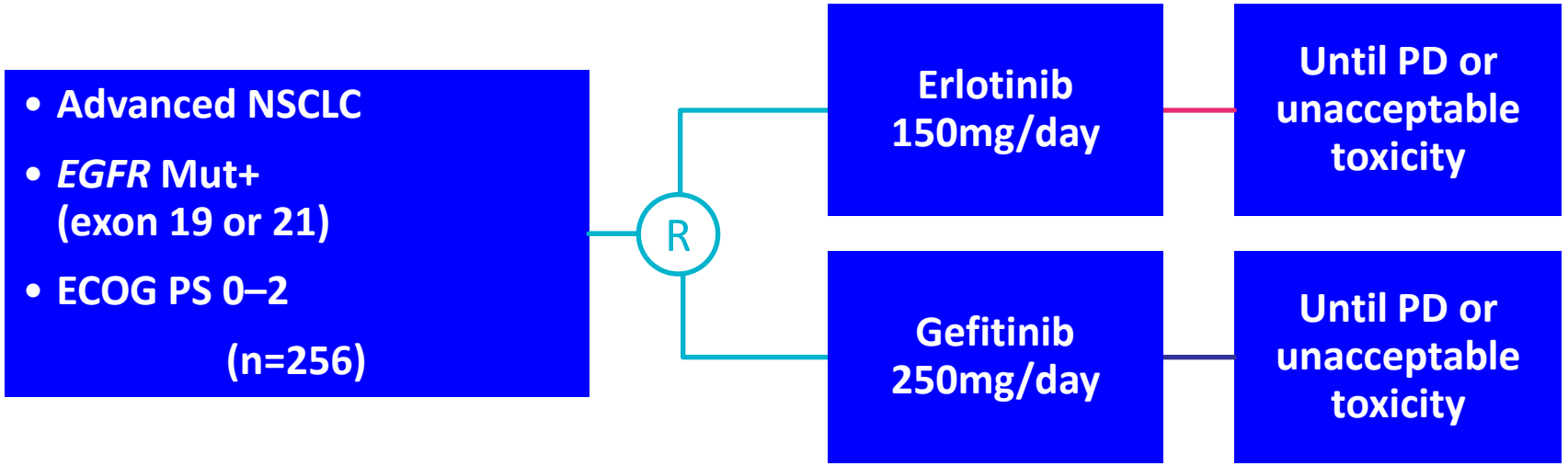


- **Irreversible = Reversible EGFR TKIs in first-line treatment in terms of ORR and PFS**

- **Phase III trials of Irreversible vs Reversible EGFR TKIs in first line are ongoing**

- **This question might be obsolete when we will have the results!**

Erlotinib versus gefitinib in patients with *EGFR*$^{mut+}$: CTONG0901 study

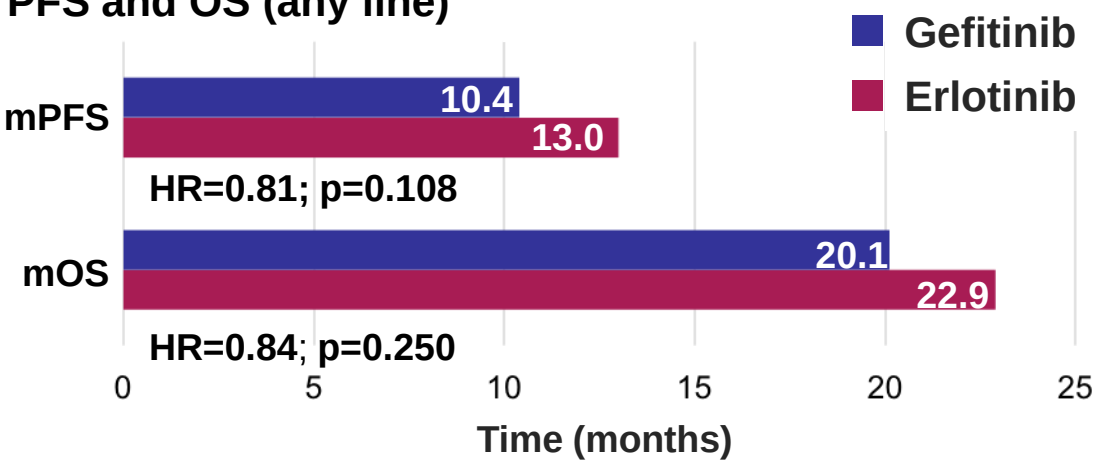


Primary end-point: mPFS

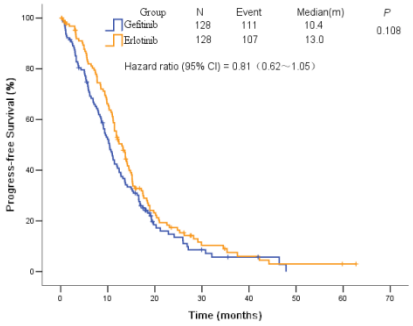
Yang, et al. WCLC 2015

CTONG0901: efficacy and toxicity

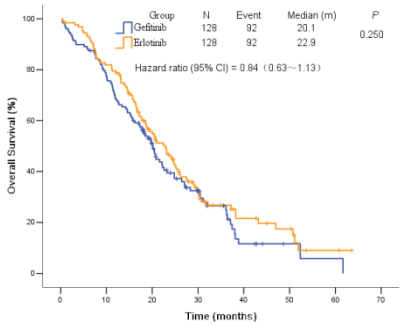
PFS and OS (any line)



PFS



OS



Treatment-emergent AEs >10% in either arm

	Gefitinib n=128		Erlotinib n=128	
AE, %	**All grade**	**Grade ≥3**	**All grade**	**Grade ≥3**
Rash	63	0	70	2
Cough	30	0	23	0
Diarrhoea	19	0	17	0
Hand and foot syndrome	13	0	6	0
Nail changes	13	0	19	0
Anorexia	12	0	5	0

Yang, et al. WCLC 2015

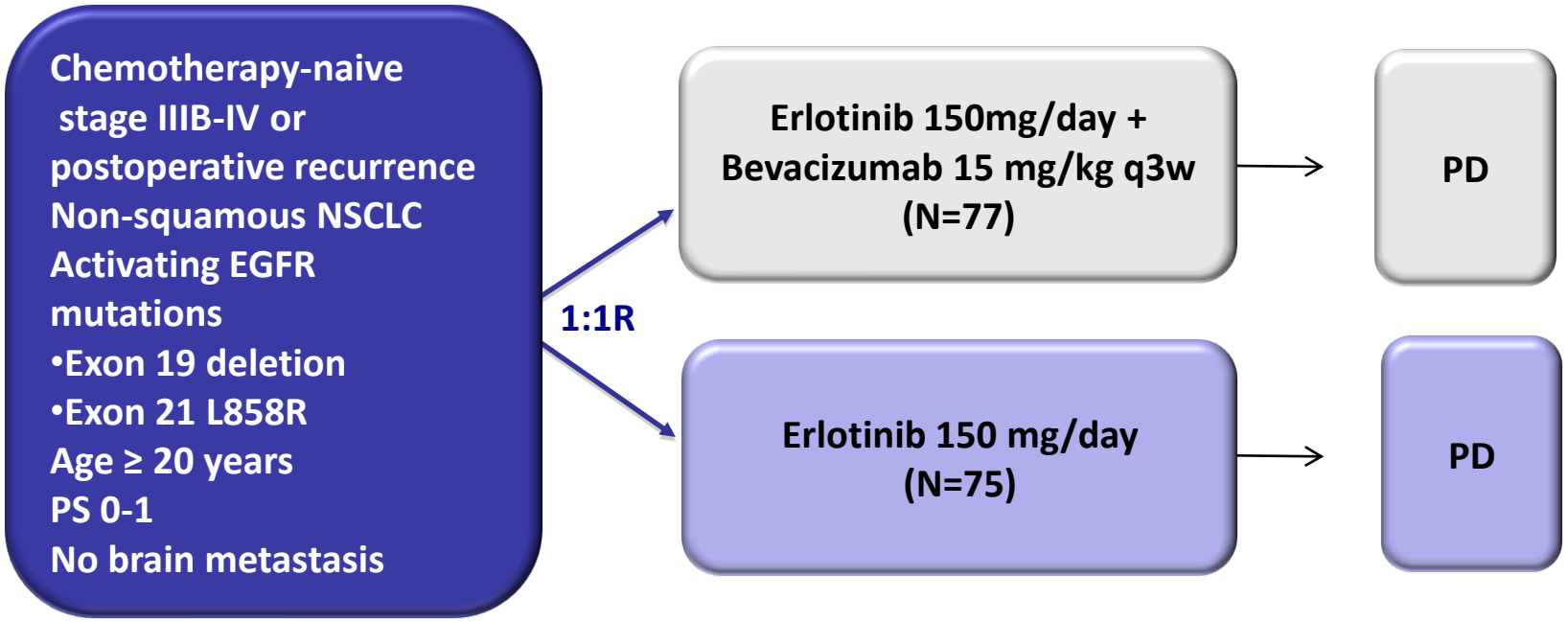
Indirect comparison of toxicities reported with gefitinib or erlotinib or afatinib

	Gefitinib				Erlotinib		Afatinib	
	IPASS* [48] n = 607	First SIGNAL* [49] n = 159	WJTOG 3405 [50] n = 87	NEJ002 [51] n = 114	OPTIMAL [52] n = 83	EURTAC [53] n = 84	LUX-Lung 3 [54] n = 230	LUX-Lung 6 [55] n = 239
Rash	66.2 (3.1)	72.4 (29.3)	85.0 (2.3)	71.0 (5.3)	73.0 (2)	79.7 (13.0)	89.1 (16.2)	80.8 (14.2)
Diarrhoea	46.6 (3.8)	49.7 (2.5)	54.0 (1.1)	34.2 (0.9)	25.0 (1)	57.1 (5)	95.2 (14.4)	88.3 (5.4)
Fatigue	16.8 (0.3)	28.3 (10.0)	39 (2.2)	10.5 (2.6)	5.0 (0)	57.1 (0)	17.5 (1.3)	10 (0.4)
Anorexia	21.9 (1.5)	44.6 (13.8)	NR	14.9 (5.3)	NR	31 (0)	20.5 (3.1)	10 (1.3)
Stomatitis	17.0 (0.2)	40.2 (1.9)	21.8 (0)	NR	13.0 (1)	NR	72.1 (8.7)	51.9 (5.4)
Paronychia	13.5 (0.3)	NR	32.1 (1.1)	NR	4.0 (0)	NR	56.8 (11.4)	32.6 (0)
Vomiting	12.9 (0.2)	18.9 (0)	NR	NR	1.0 (0)	NR	17.0 (3.1)	9.6 (0.8)

***Shown data include all patients treated with gefitinib**
Data are reported as percentage of AEs of any grade and, in parenthesis, of grade 3

Landi L , Expert Opin Pharmacother 2014

Erlotinib versus erlotinib+bevacizumab as first-line therapy in *EGFR*$^{mut+}$ NSCLC: phase IIR study

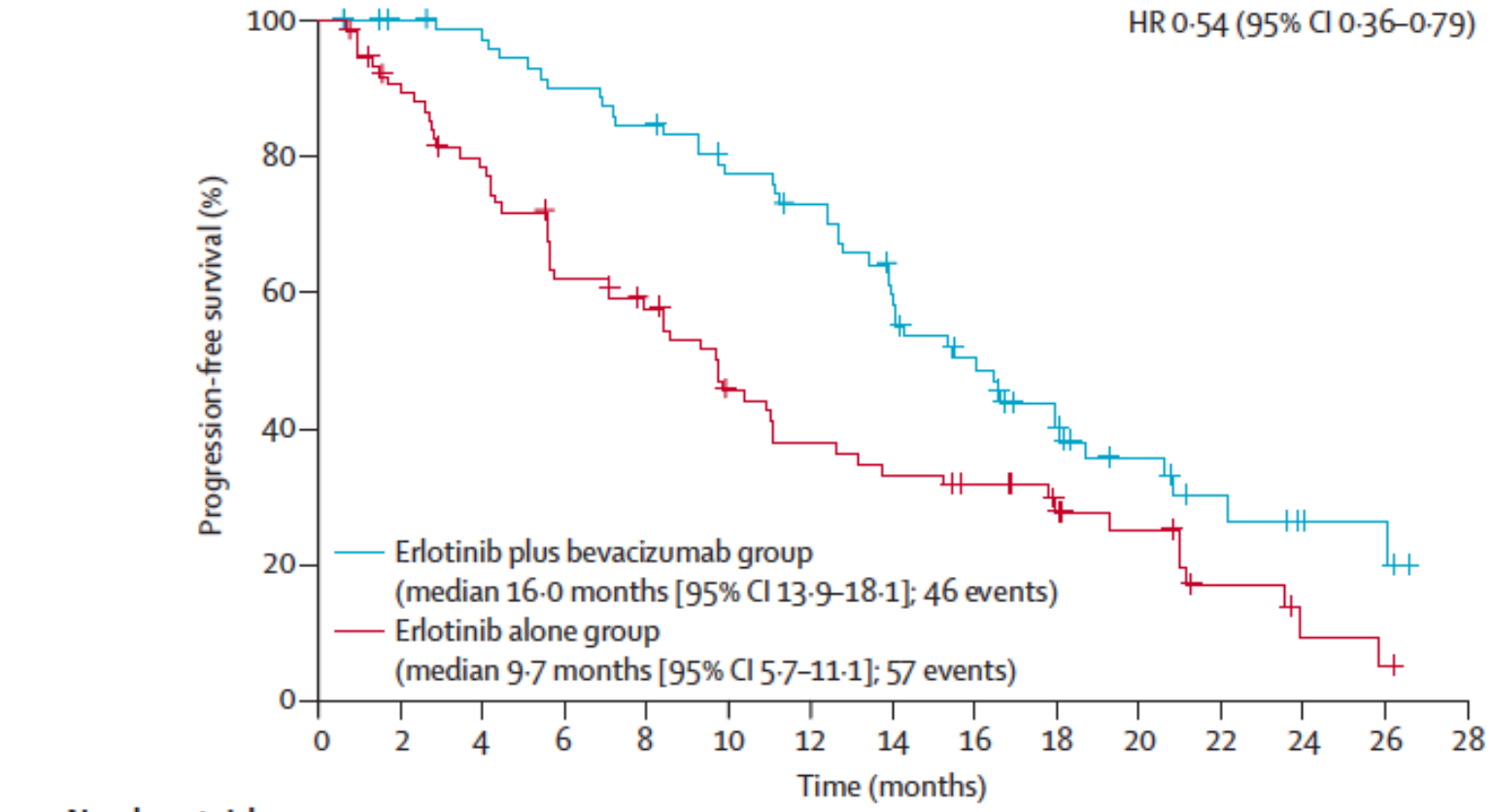


Primary end-point: PFS

Secondary End points: OS, ORR, QoL, symptoms improvement FACT-L scale and safety

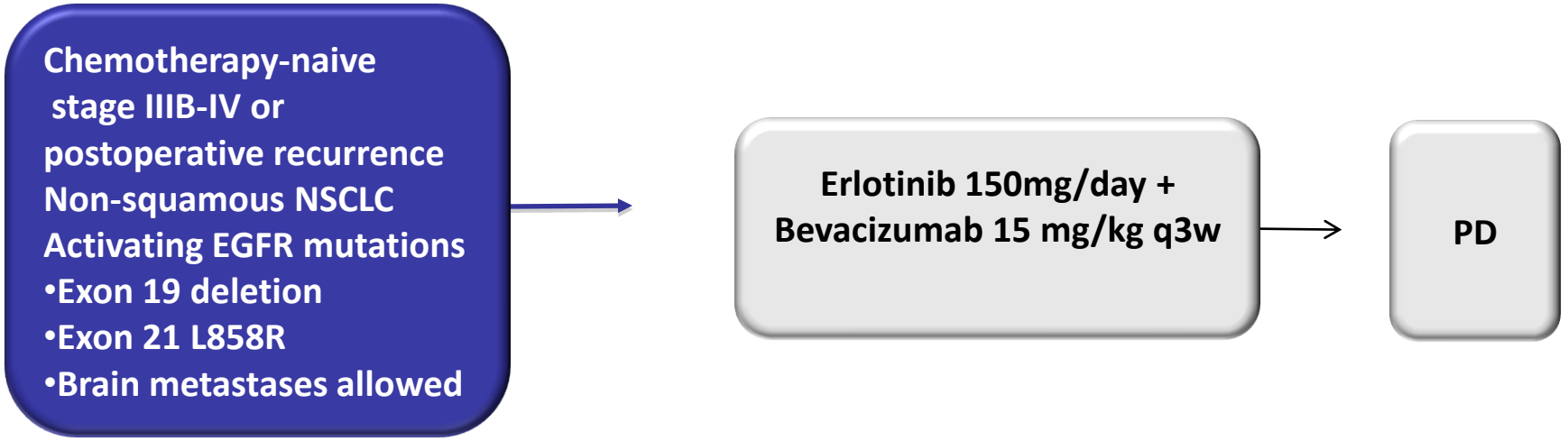
Seto T, et al. Lancet Oncol 2014

Erlotinib versus erlotinib+bevacizumab as first-line therapy in *EGFR*$^{mut+}$ NSCLC: PFS



Seto T, et al. Lancet Oncol 2014

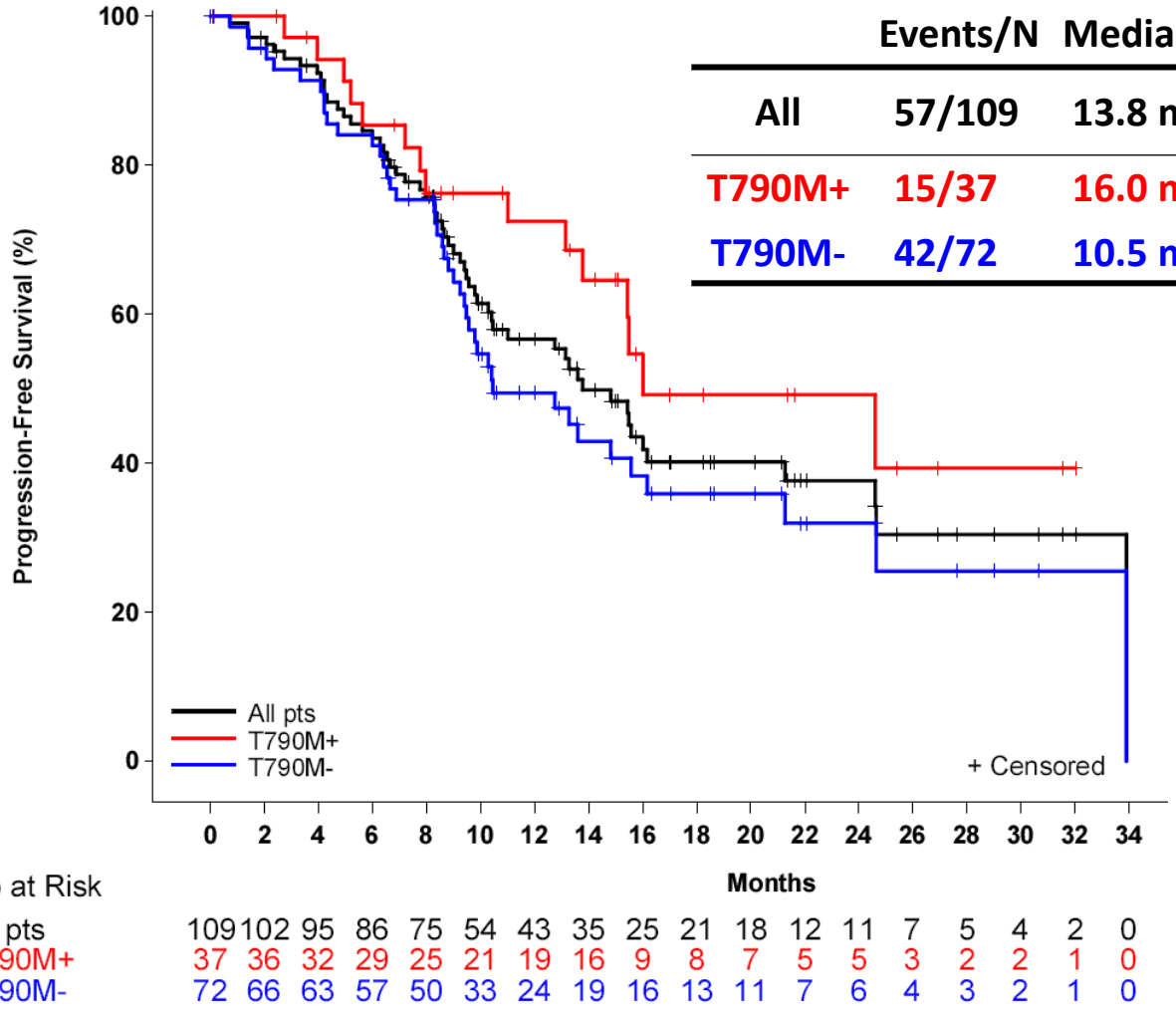
Erlotinib+bevacizumab as first-line therapy in *EGFR*$^{mut+}$ NSCLC: the BELIEF phase II study



Primary end-point: PFS

Stahel, et al. ECC 2015

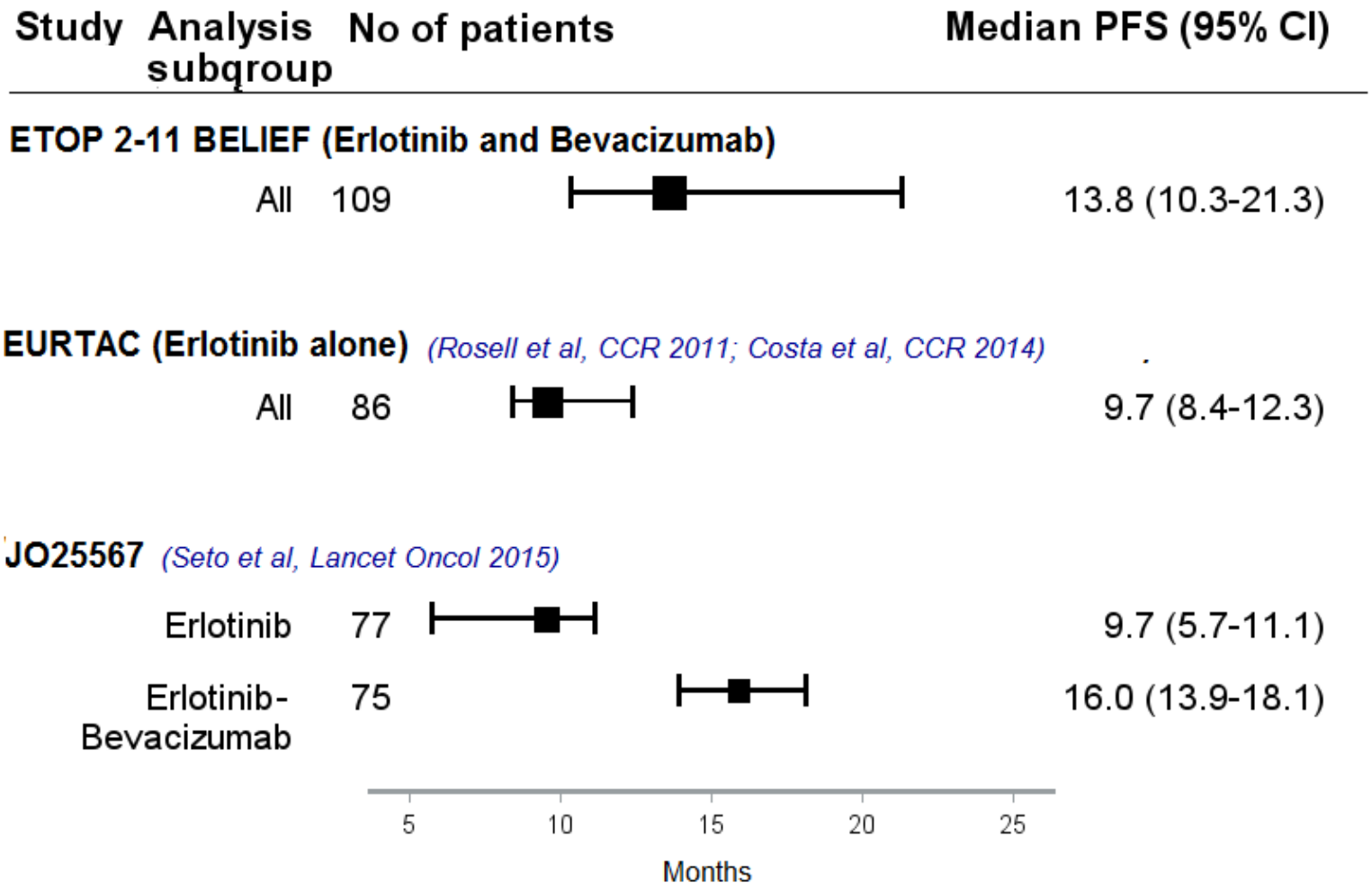
BELIEF: PFS by T790M mutation



	Events/N	Median PFS (95%CI)	12m PFS (95%CI)
All	57/109	13.8 m (10.3-21.3)	56.7% (46.0-66.0)
T790M+	15/37	16.0 m (13.1-NE)	72.4% (53.4-84.7)
T790M-	42/72	10.5 m (9.2-16.2)	49.4% (36.6-61.0)

Stahel, et al. ECC 2015

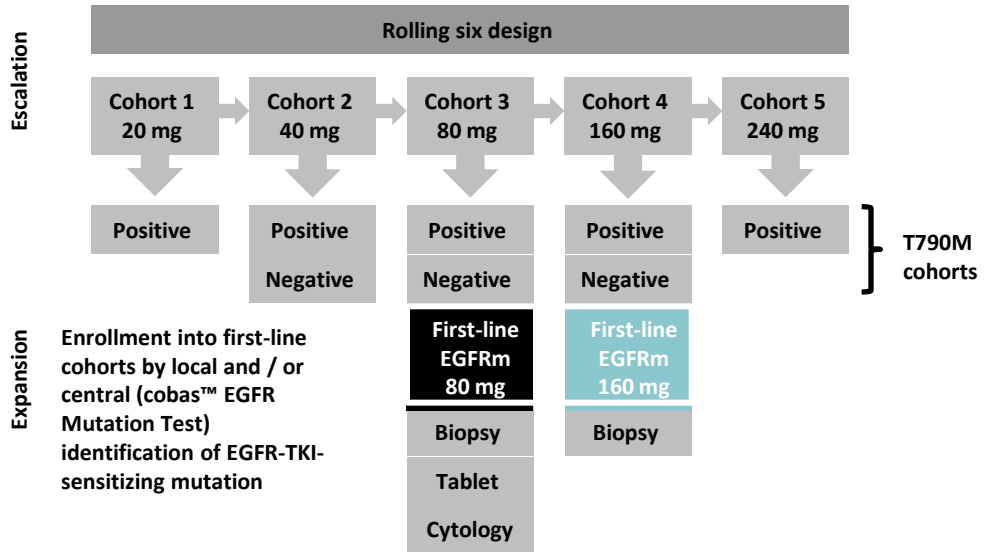
BELIEF: data on context with other studies



Stahel, et al. ECC 2015

AURA Phase I dose escalation / expansion global study design

First-line cohort objective
Safety and tolerability of AZD9291 (80 mg or 160 mg orally) as first-line therapy for patients with EGFRm positive NSCLC



Key inclusion criteria:

- Locally advanced or metastatic NSCLC
- No prior therapy for advanced disease
- Measurable disease
- Patients must have EGFRm positive tumor status from a local test

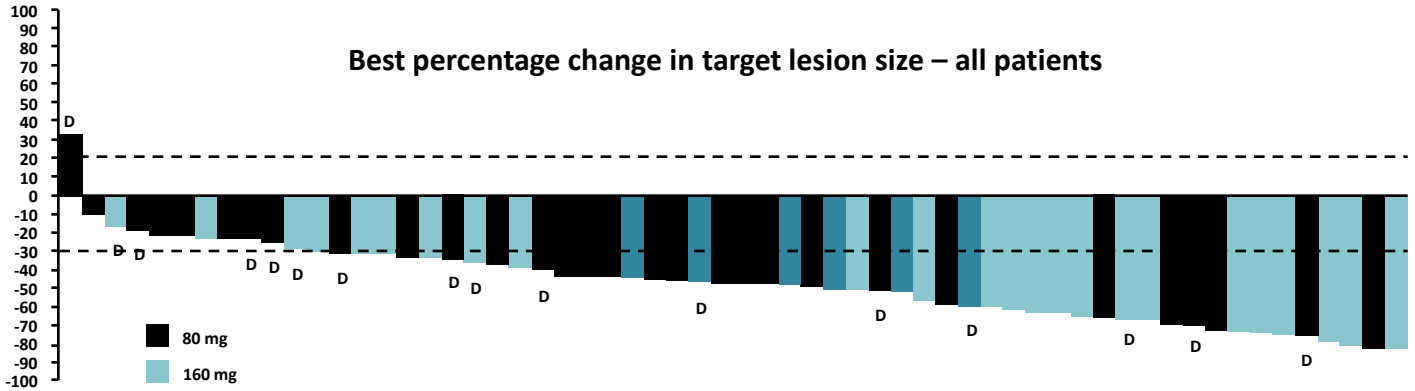
Key exclusion criteria:

- Prior history of ILD
- Symptomatic brain metastases

Data cut-off August 1, 2015
Data from cohorts in grayed out boxes are not included in the analyses reported here
ILD, interstitial lung disease

Ramalingam et al, WCLC 2015

Tumor response in AZD9291 first-line cohorts by dose



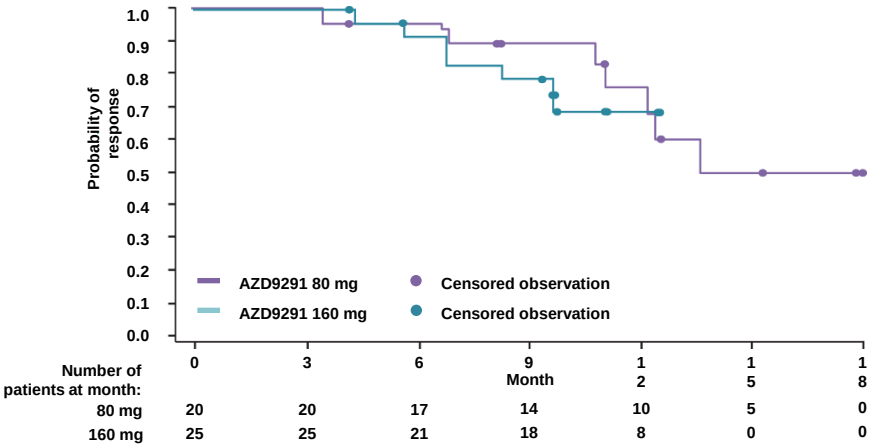
	80 mg N=30	160 mg N=30	Total N=60
Confirmed objective response rate	**67% (95% CI 47, 83)**	**83% (95% CI 65, 94)**	**75% (95% CI 62, 85)**
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Best objective response			
Complete response	0	2*	2*
Partial response	20	23	43
Stable disease	8	5	13
Progressive disease	2	0	2

Population: evaluable for response, data cut-off August 1, 2015; RECIST 1.1, programmatically calculated from investigator-recorded tumor measurement
CI, confidence interval; D, discontinued

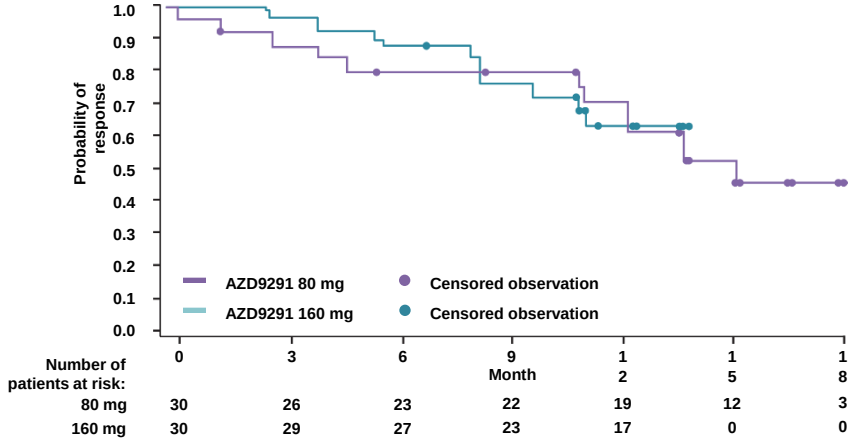
Ramalingam et al, WCLC 2015

DoR and PFS in AZD9291 first-line cohorts
(investigator assessed)

Duration of response



Progression-free survival



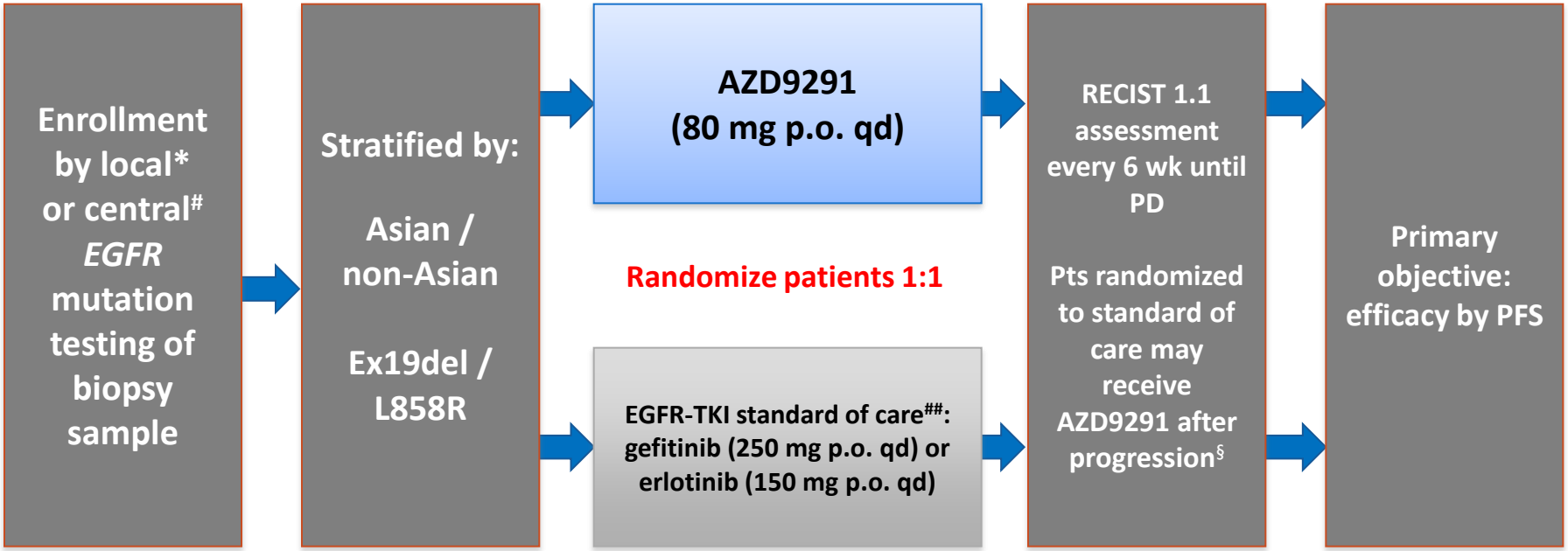
	80 mg N=20	160 mg N=25	Total N=45
Median DoR,* months (95% CI)	13.6 (11.1, NC) Maturity: 35%	NC (9.7, NC) Maturity: 28%	NC (12.3, NC) Maturity: 31%
Maximum DoR, months	18.0+	12.6+	18.0+
Remaining in response,† % (95% CI)			
9 months	89 (64, 97)	78 (56, 90)	83 (68, 92)
12 months	76 (46, 90)	69 (45, 84)	71 (53, 83)

	80 mg N=30	160 mg N=30	Total N=60
Median PFS,‡ months (95% CI)	NC (12.3, NC) Maturity: 40%	NC (11.1, NC) Maturity: 30%	NC (13.7, NC) Maturity: 35%
Maximum PFS, months	19.2+	13.8+	19.2+
Remaining alive and progression-free,† % (95% CI)			
9 months	83 (64, 93)	80 (60, 90)	81 (69, 89)
12 months	75 (55, 87)	69 (48, 82)	72 (58, 82)

Population: all dosed patients, data cut-off August 1, 2015
Progression events that do not occur within 14 weeks of the last evaluable assessment (of first dose) are censored
***Duration of response is the time from first documentation of response until date of progression or death or last evaluable RECIST assessment for patients who do not progress;**
†Calculated using the Kaplan-Meier technique; ‡Progression-free survival is the time from date of first dosing until the date of objective disease progression or death
DoR, duration of response; NC, not calculable; PFS, progression-free survival

Ramalingam et al, WCLC 2015

FLAURA Study Design

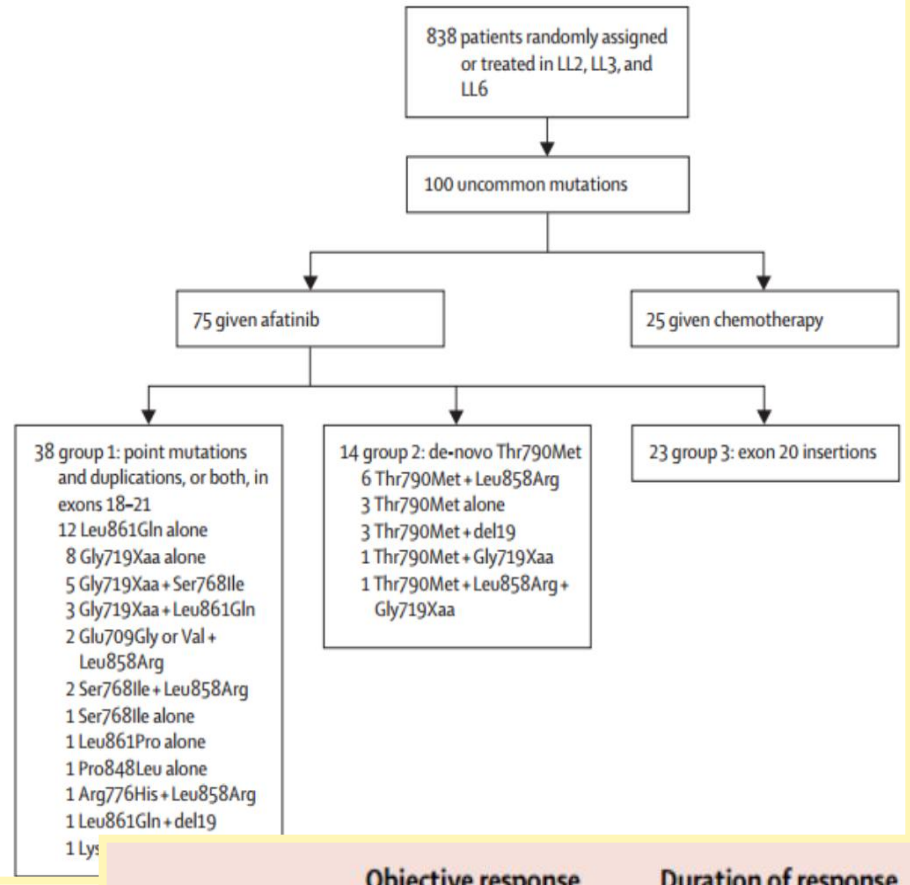


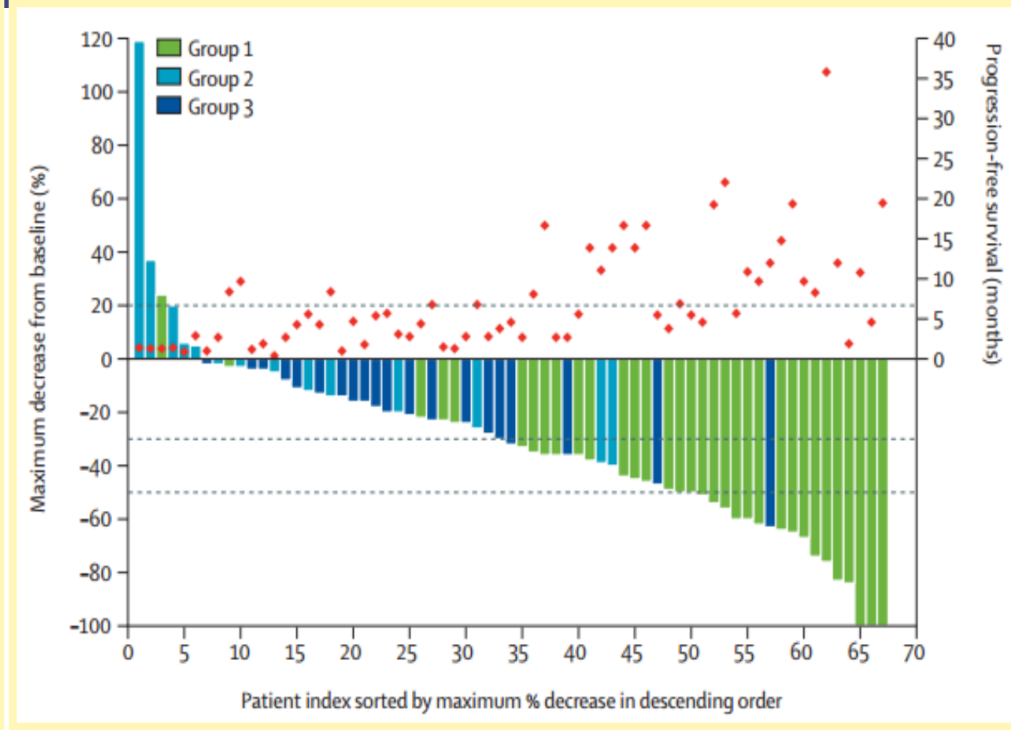
*With central laboratory assessment performed for sensitivity
#cobas™ EGFR Mutation Test (Roche Molecular Systems)
##Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation
§Patients randomized to the standard of care treatment arm may receive open-label treatment with AZD9291 on central confirmation of both objective disease progression and T790M positive tumor
OS, overall survival; PFS2, second progression-free survival (time from randomization to second progression); p.o., orally

Presented by Suresh Ramalingam at the 2015 ASCO Congress. J Clin Oncol 33, 2015 (suppl; abstr 8000).

Rare and Uncommon Mutations…..even an issue to define it properely

- ✓Exon-19 del and L858R are described as classic *EGFR* mutations
- ✓Uncommon mutations with known clinical significance: G719X, S768I, T790M, insertions in exon-20, and L861Q
- ✓Rare *EGFR* mutations are considered all other *EGFR* mutations





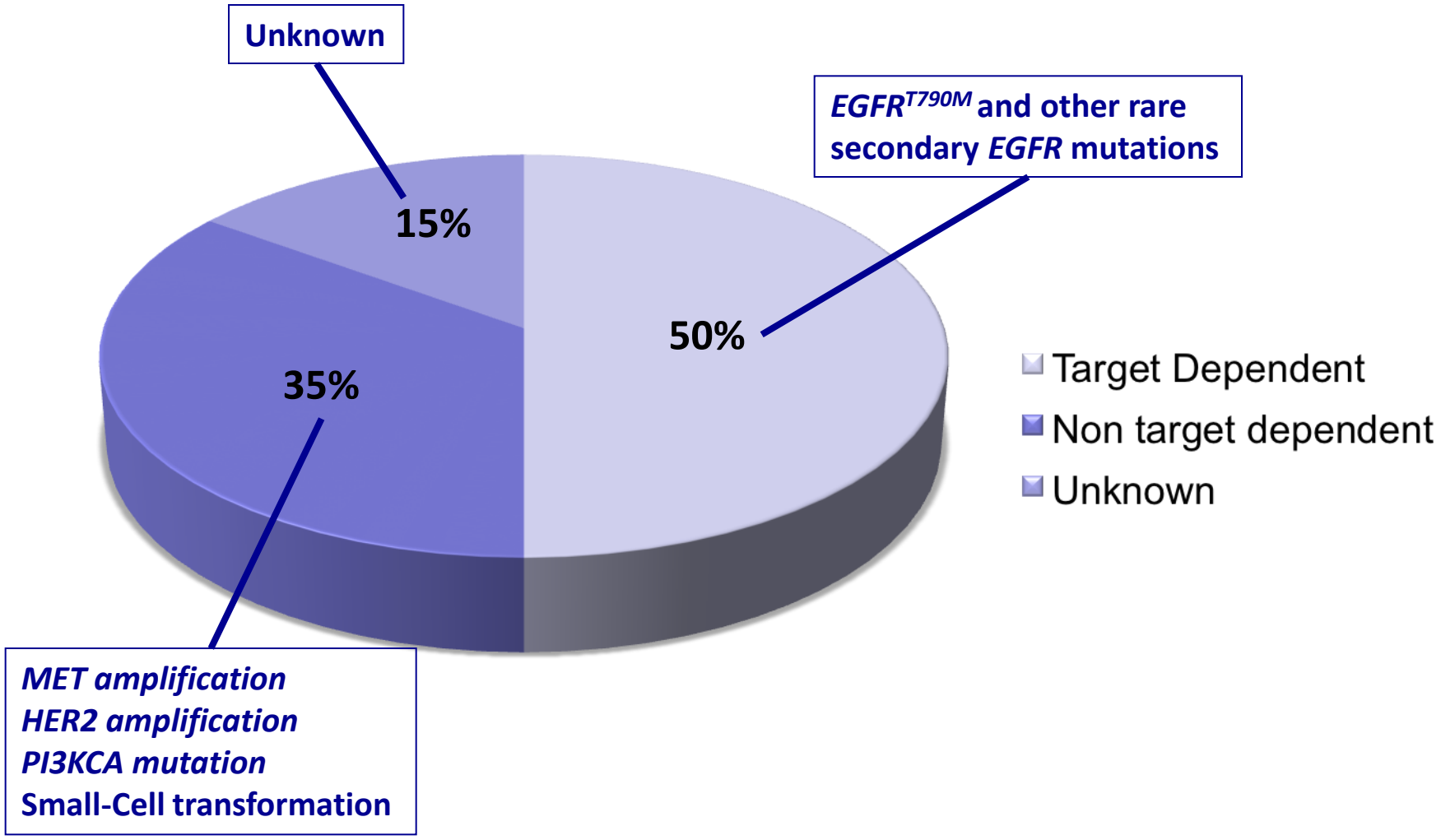
	Objective response	Duration of response (months)	Disease control	Progression-free survival (months)	Overall survival (months)
Group 1 (n=38)*	27 (71·1%, 54·1–84·6)	11·1 (4·1–15·2)	32 (84·2%, 68·7–94·0)	10·7 (5·6–14·7)	19·4 (16·4–26·9)
Group 2 (n=14)†	2 (14·3%, 1·8–42·8)	8·2 (4·1–12·4)	9 (64·3%, 35·1–87·2)	2·9 (1·2–8·3)	14·9 (8·1–24·9)
Group 3 (n=23)‡	2 (8·7%, 1·1–28·0)	7·1 (4·2–10·1)	15 (65·2%, 42·7–83·6)	2·7 (1·8–4·2)	9·2 (4·1–14·2)

J Yang et al Lancet Oncol 2015

NSCLC EGFR-mutated

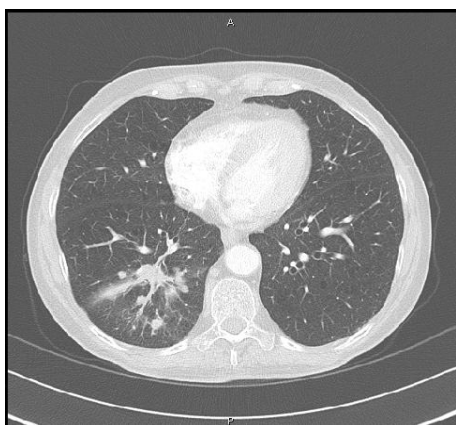
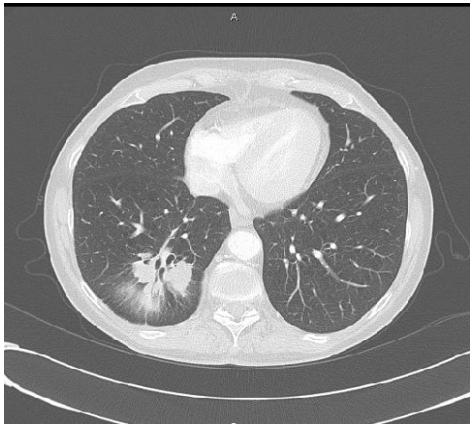
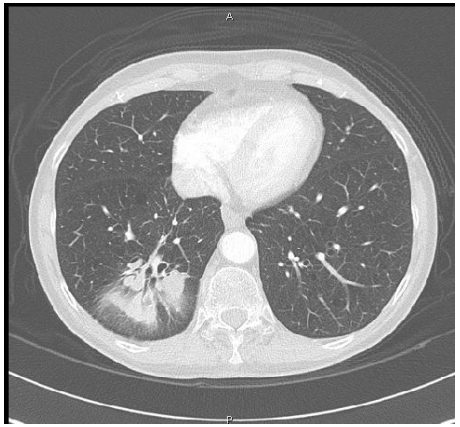
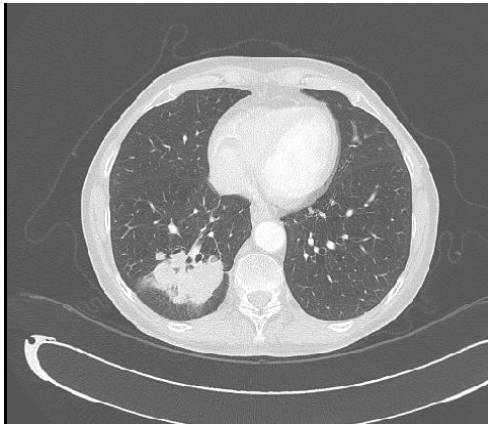
- First-line
  - In first line we have to always use an EGFR-TKI?
  - Which EGFR-TKI? First, second or third generation?
  - What about uncommon mutations?
- **Mechanisms of resistance**
  - **Primary Resistance**
  - **Acquired Resistance**
- PD1-axis and EGFR-TKIs

Mechanisms of acquired resistance to first-generation EGFR-TKIs



No cure with currently available targeted agents

.... in other words the awareness that the result is at term!!!

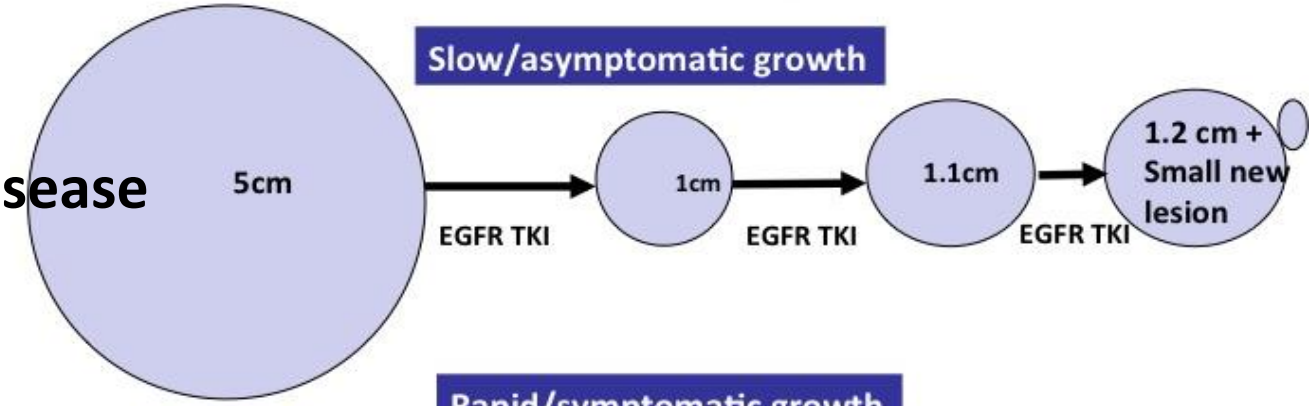
Best response to TT → **Progression**

10 months

Clinical presentations of acquired resistance

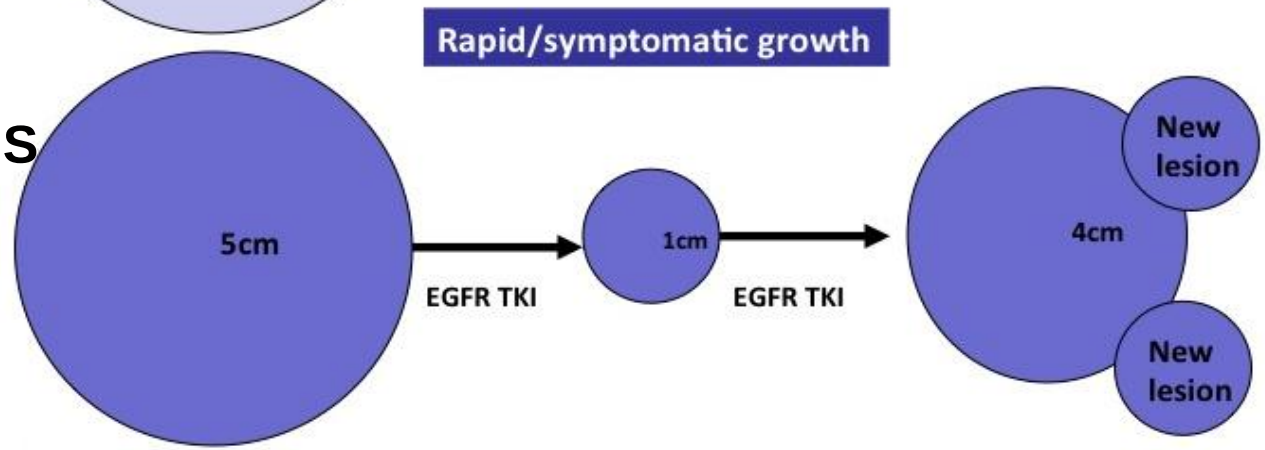
Oligoprogressive disease

Target dependent



Widespread extra CNS disease progression

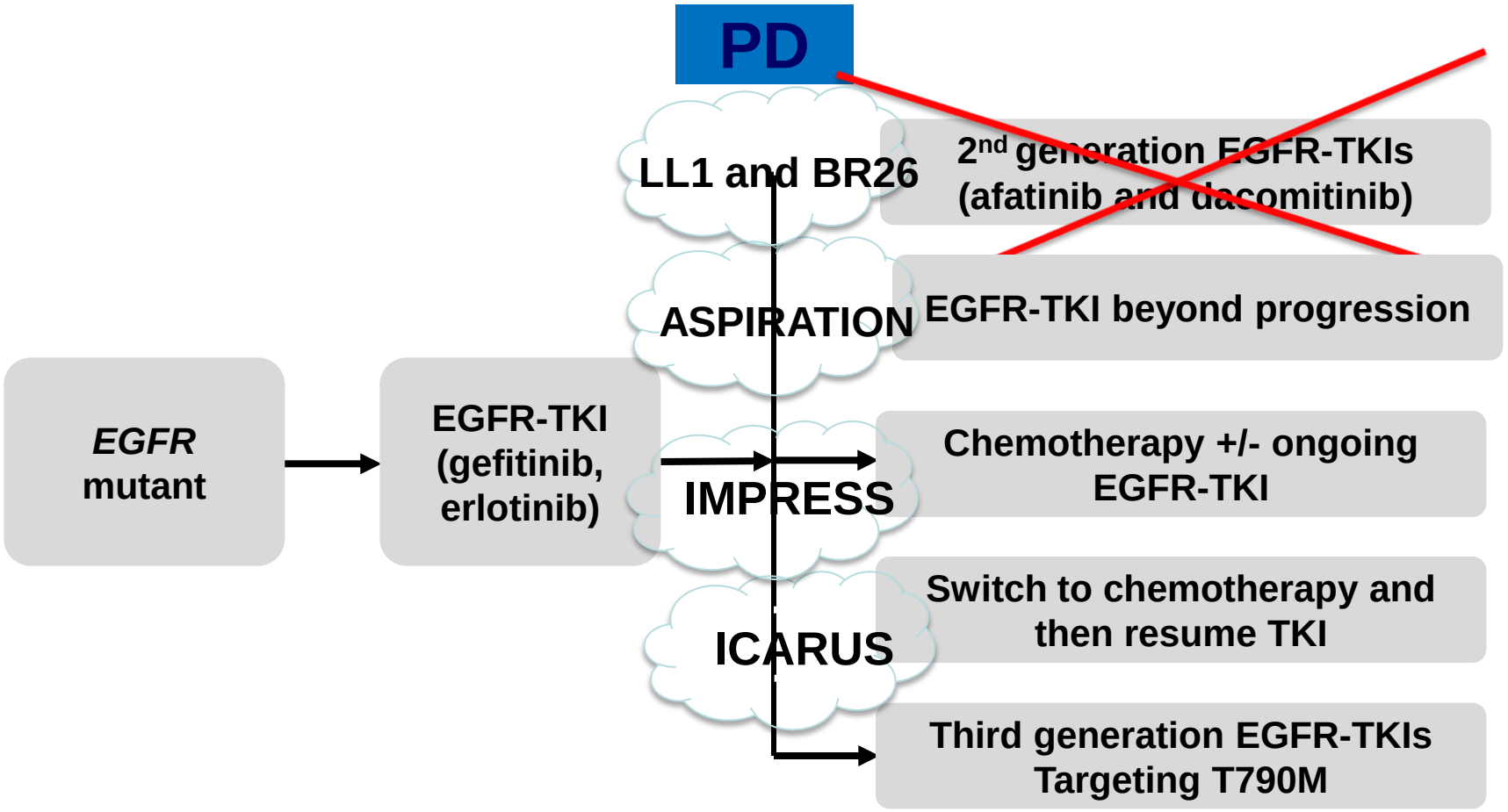
Target independent



CNS progression

Local therapy and continuation of the same TKI vs change in systemic therapy

Options at acquired resistance to an EGFR-TKI



Studies investigating the role of continuing EGFR-TKIs beyond disease progression

	Target Population, Type of trial	N° of pts	RR	PFS	OS
ASPIRATION: Erlotinib	***EGFR* mut+, prospective single arm ph II**	**81**	**NA**	**3.7 mos**	**NA**
IMPRESS: Gefitinib + cis/ Pem *vs* cis/pem	***EGFR* mutant, prospective phIII**	**133 *vs* 132**	**31% *vs* 34%**	**5.4 mos 5.4 mos**	**14.8 mos 17.2 mos (p=0.29)***

PFS=progression-free survival NA=not available. *Immature data.

- Park K, Ahn M, Yu C, et al. 1223O * ASPIRATION: first-line erlotinib (E) until and beyond RECIST progression (PD) in Asian patients with EGFR mutation-positive NSCLC. *Ann Oncol* 2014; **25** (suppl 4)**:** iv426–27.
- Soria J-C, Wu Y-L, Nakagawa K. Gefi tinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on fi rst-line gefi tinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol* 2015;**16:** 990–98.

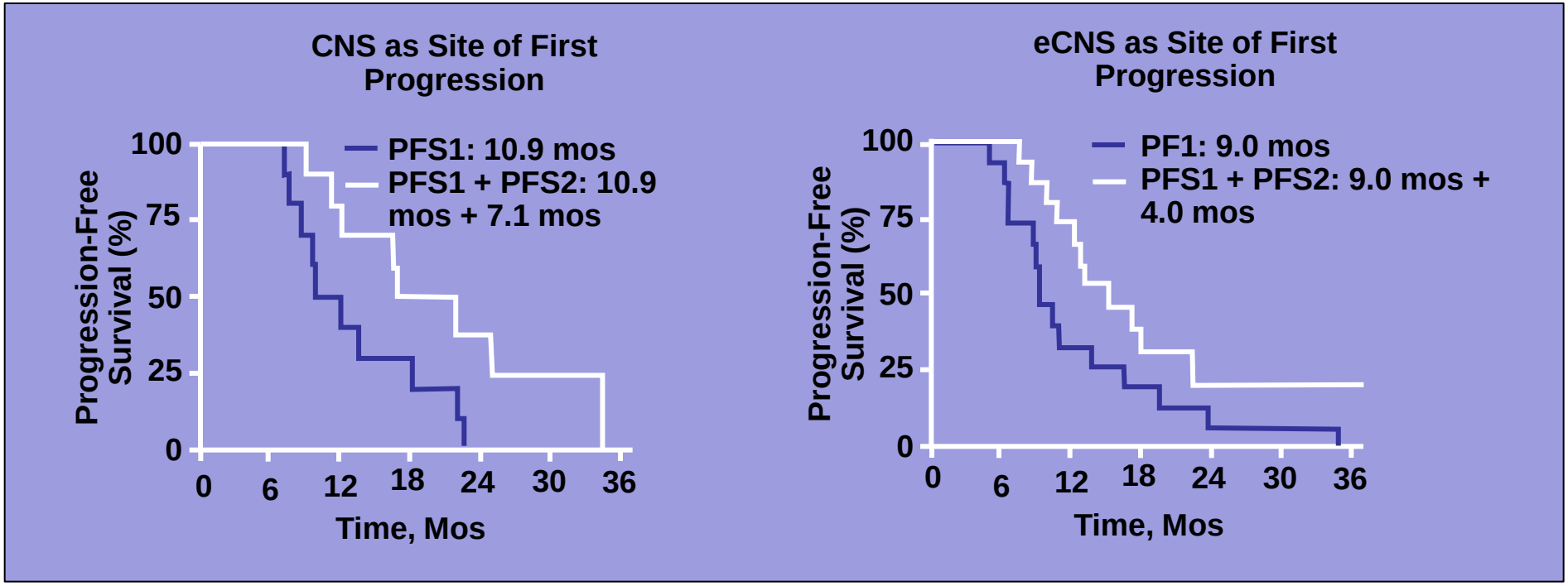
Suggested criteria for considering local Ablative therapy of oligoprogressive disease

1. *EGFR*-mutant metastatic non–small-cell lung cancer
2.EGFR-TKI is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as:
•CNS progression without leptomeningeal disease amenable to WBRT, SRS, or surgical resection.
•Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT, or surgical resection.

Weickhardt et al , JTO 2013

Local Ablative Therapy in Acquired Resistance: University of Colorado Study

- 65 pts (38 ALK+, 27 EGFR mut+) of whom 51 (28 ALK, 23 EGFR) progressed
- 25 (49%) with CNS (no LMC) or ≤ 4 extracranial sites of progression



Weickhardt AJ, et al. J Thorac Oncol. 2012;7:1807-1814.

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii56–vii64, 2012
doi:10.1093/annonc/mds226

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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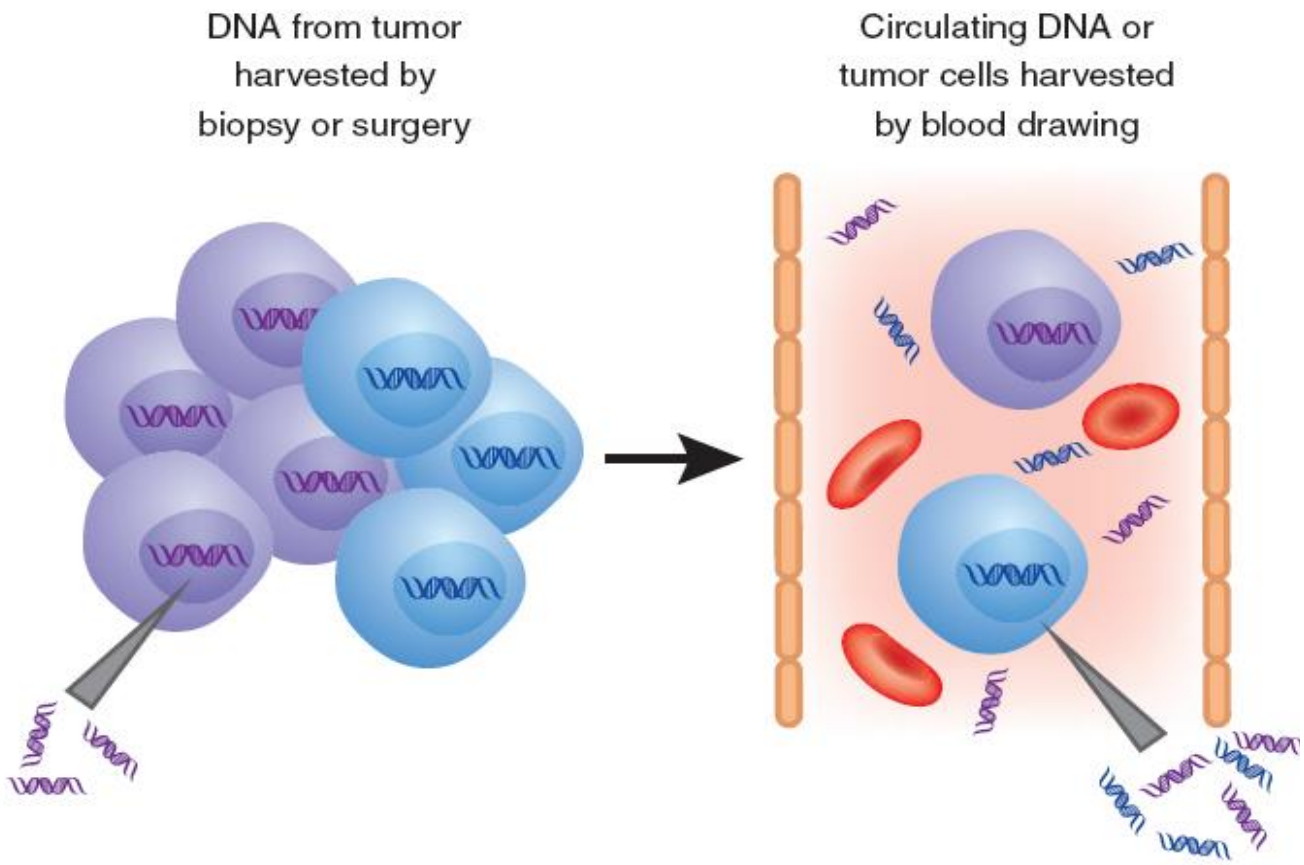
Re-biopsy at disease progression should be considered [7].

Diagnosis (and tests) do not end at the time of diagnosis

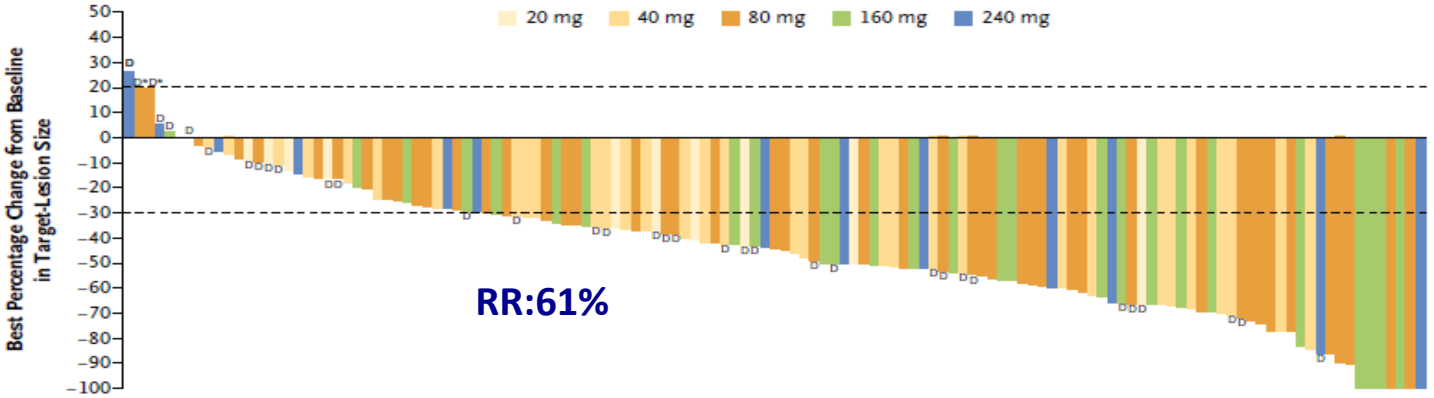
Different sources of tumor DNA



Fleischacker & Schmidt Nat Med 2008

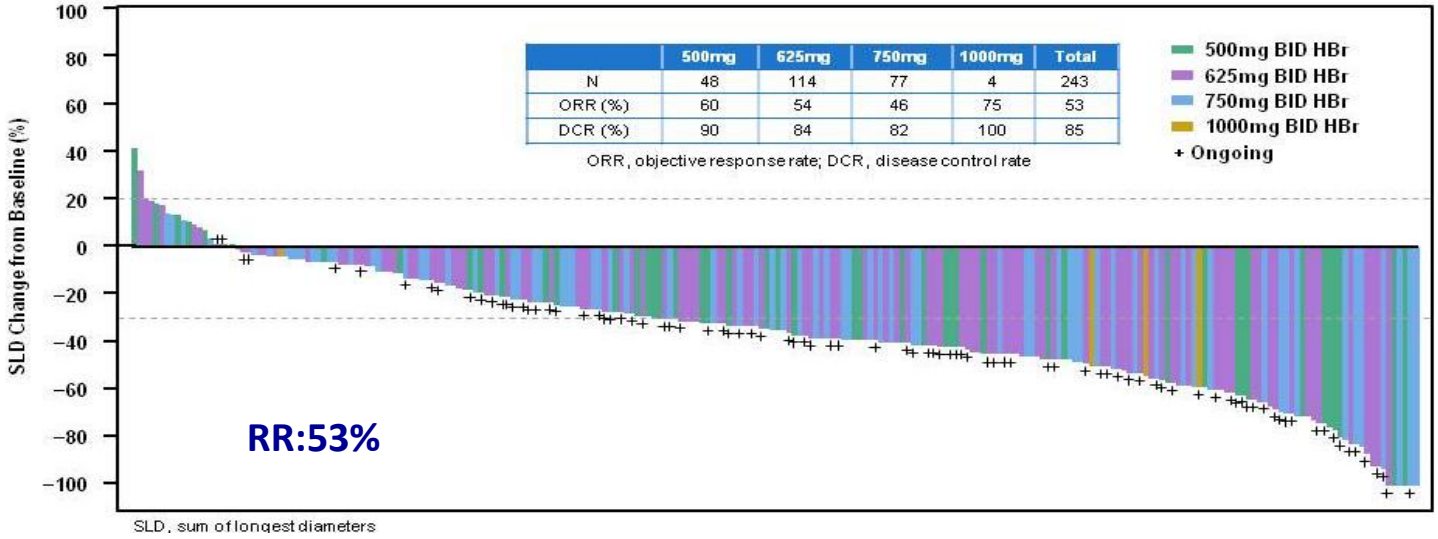
AZD9291 and Rociletinib in patients *EGFR^{T790M+}*

AZD9291



Janne PA, NEJM 2015

Rociletinib



	500mg	625mg	750mg	1000mg	Total
N	48	114	77	4	243
ORR (%)	60	54	46	75	53
DCR (%)	90	84	82	100	85

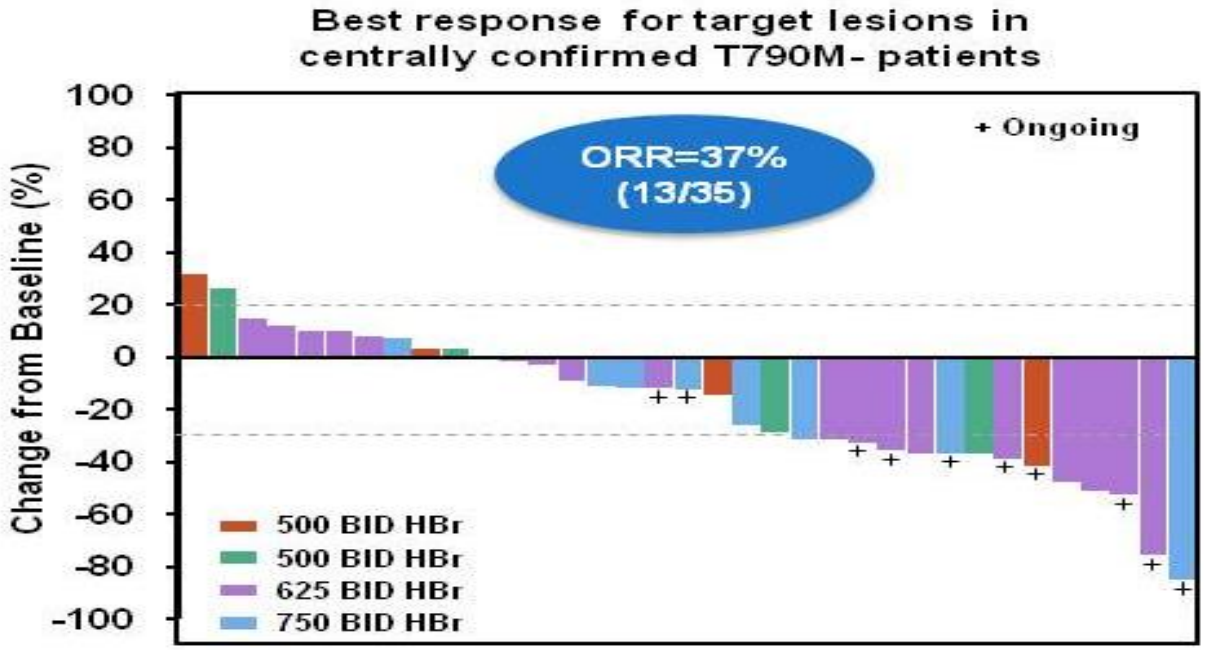
Sequist L, ASCO 2015

Trials with third-generation *EGFR* TKIs

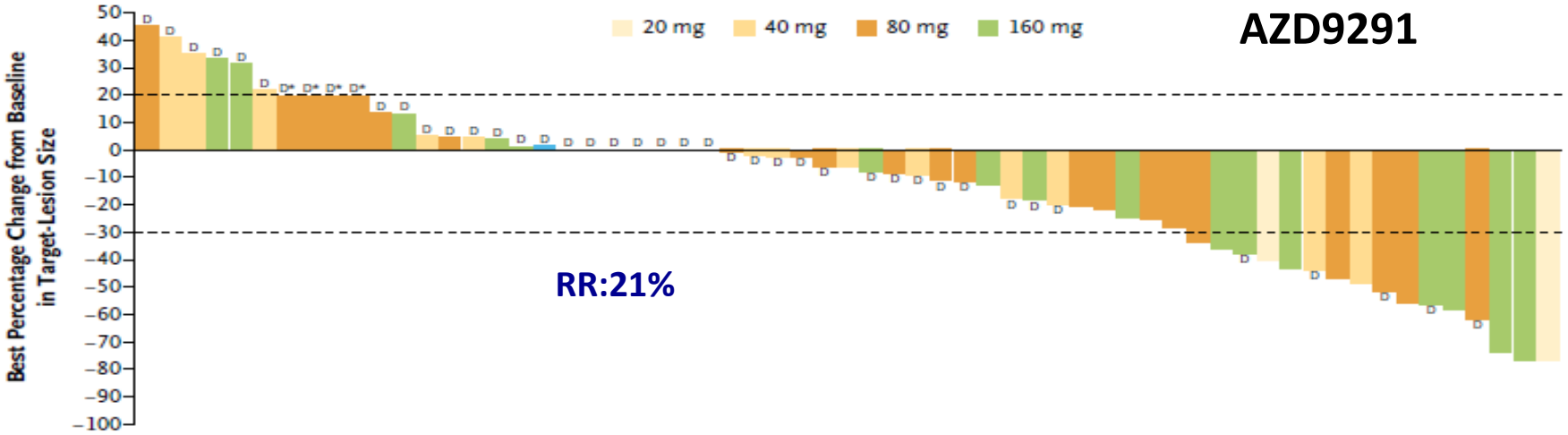
	Phase	Target population	N° of pts	RR %	DCR%	PFS	OS
AZD9291	1/2 (AURA) (NCT01802632)	*EGFR* mutant, progressed on previous EGFR TKI or systemic treatment	253; 138	51 61 T790M+ 21 T790M-	84; 95 61	NA; 9·6 mos; 2·8	NA
Rociletinib[79]	1/2 (TIGER-X) (NCT01526928)	*EGFR* mutant, received previous EGFR TKI	179; 56‡	46 67 T790M+ 36‡ T790M-	84; 89;‡ NA	NA; 10·4 mos;‡ 7·5 mos‡	NA
HM61713	1 (NCT01588145)	*EGFR* mutant, progressed on CHT and EGFR TKI	118; 48	21·7 29.2 11·8	67·5 75‡ 55.9	NA; 4·3 mos;2·3 mos‡	NA
ASP8273[81]	1 (NCT02113813)	*EGFR* mutant, received previous EGFR TKI	31; 13‡	42%; 78%‡	NA	NA	NA

Rociletinib and AZD9291 in patients *EGFR*$^{T790M-}$

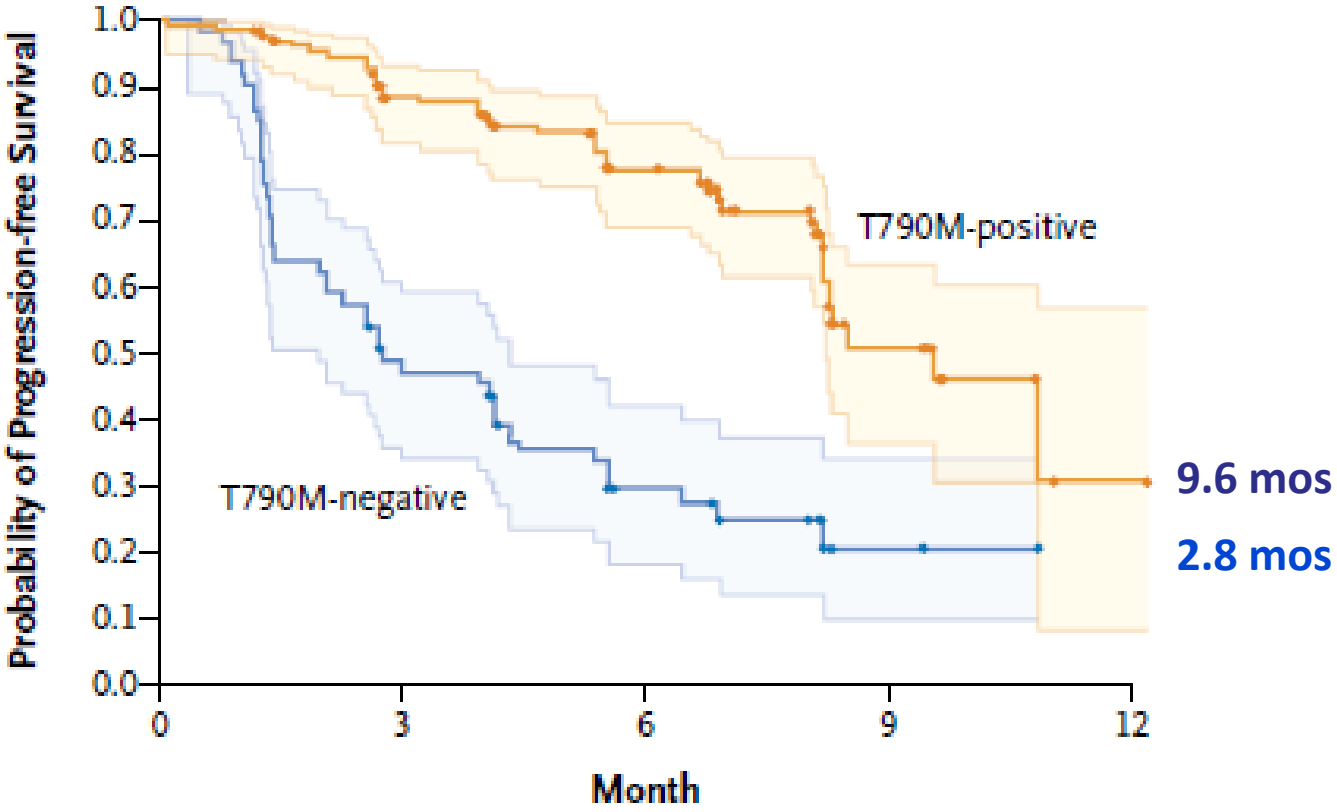
Rociletinib



AZD9291



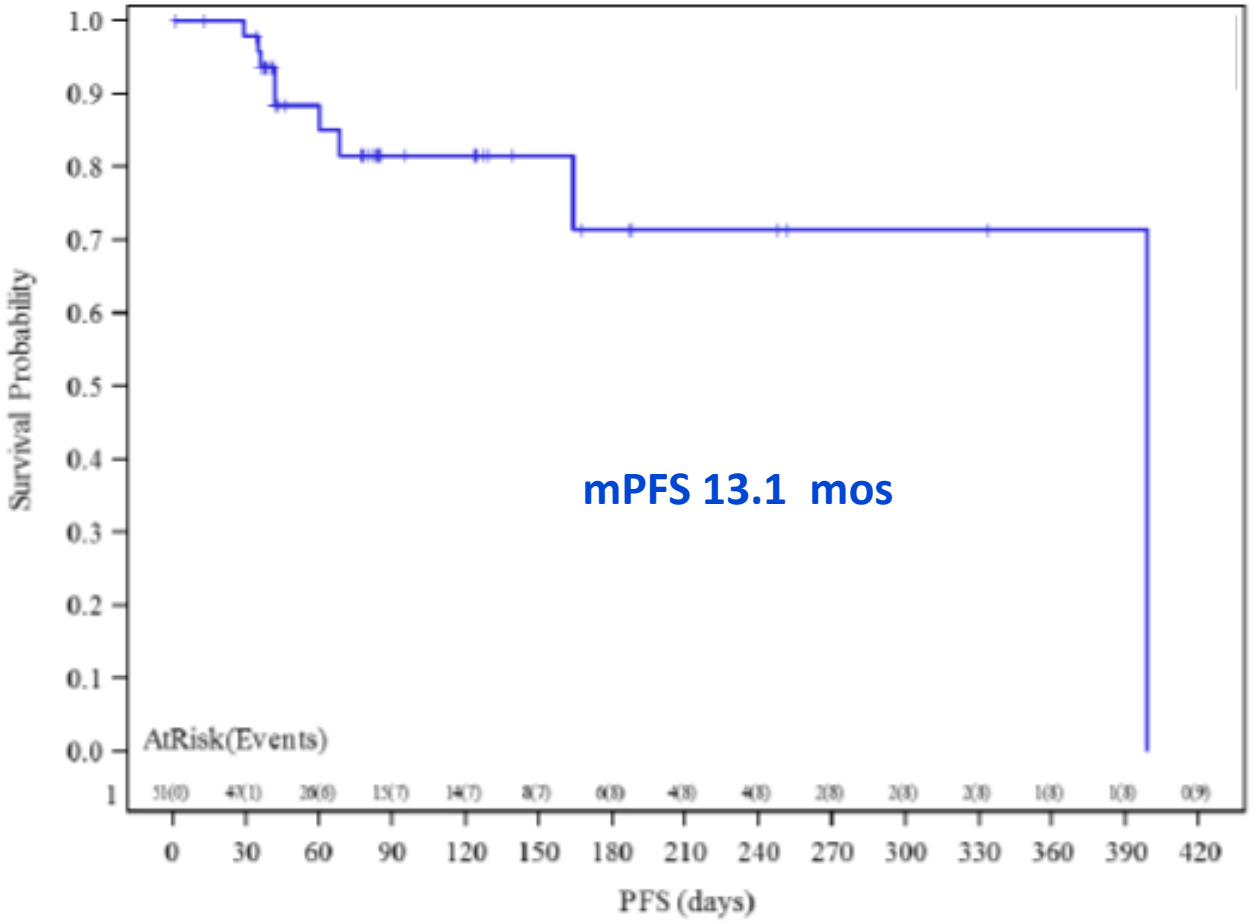
PFS with AZD9291 according to *EGFR* ^{T790M} status



Janne PA, et al. NEJM 2015

Estimated mPFS in patients with confirmed *EGFR* $^{T790M+}$

Rociletanib



Sequist LV, et al. NEJM 2015

	Phase	Primary endpoint	Status	T790M	Key features
AZD9291					
AURA-2 (NCT02094261)	2	ORR	Ongoing but not recruiting	Positive	Failed EGFR TKI; *EGFR* mut+
AURA-3 (NCT02151981)	3	PFS	Recruiting	Positive	Failed first-line EGFR TKI; *EGFR* mut+;vs platinum-based CHT
FLAURA (NCT02296125)	3	PFS	Recruiting	Pos/neg	First-line; *EGFR*mut+;vs gefitinib/erlotinib
NCT02143466	1	Safety and tolerability	Recruiting	Pos/neg	Failed EGFR TKI; *EGFR*mut+; AZD9291 with either MEDI4736 or AZD6094 or selumetinib

Rociletanib

	Phase	Primary endpoint	Status	T790M	Key features
	2	PFS	Recruiting	Pos/neg	First-line, randomised; *EGFR* mut+vs erlotinib
TIGER-2 (NCT02147990)	2	Objective response rate	Recruiting	Positive	Single group; *EGFR* mutant;failed first-line EGFR TKI
TIGER-3 (NCT02322281)	3	PFS	Not yet recruiting	Pos/neg	Failed EGFR TKI and platinum doublet CHT *EGFR* mutant;vs: single-agent CHT

Treatment-related AEs occurring in patients receiving Rociletinib or AZD9291

AZD9291

Event	20 mg (N=21)	40 mg (N=58)	80 mg (N=90)	160 mg (N=63)	240 mg (N=21)	Total (N=253)
	number of patients (percent)					
Diarrhea						
Any grade	5 (24)	24 (41)	30 (33)	43 (68)	16 (76)	118 (47)
Grade 3–5	0	1 (2)	1 (1)	1 (2)	1 (5)	4 (2)
Rashes and acne‡						
Any grade	5 (24)	13 (22)	29 (32)	40 (63)	15 (71)	102 (40)
Grade 3–5	0	0	0	2 (3)	0	2 (1)
Nausea						
Any grade	3 (14)	10 (17)	16 (18)	19 (30)	7 (33)	55 (22)
Grade 3–5	1 (5)	0	0	0	0	1 (<0.5)
Decreased appetite						
Any grade	7 (33)	11 (19)	14 (16)	16 (25)	6 (29)	54 (21)
Grade 3–5	1 (5)	0	1 (1)	0	0	2 (1)
Dry skin						
Any grade	2 (10)	9 (16)	10 (11)	25 (40)	5 (24)	51 (20)
Grade 3–5	0	0	0	0	0	0
Pruritus						
Any grade	2 (10)	11 (19)	15 (17)	12 (19)	7 (33)	47 (19)
Grade 3–5	0	0	0	0	0	0

Rociletinib

Event	Any Grade	Grade 1	Grade 2	Grade 3
	number (percent)			
Hyperglycemia†	43 (47)	14 (15)	9 (10)	20 (22)
Nausea	32 (35)	16 (17)	14 (15)	2 (2)
Fatigue	22 (24)	9 (10)	9 (10)	4 (4)
Diarrhea	20 (22)	16 (17)	4 (4)	0
Decreased appetite	18 (20)	10 (11)	7 (8)	1 (1)
Vomiting	13 (14)	9 (10)	2 (2)	2 (2)
QTc prolongation	11 (12)	3 (3)	3 (3)	5 (5)
Muscle spasms	10 (11)	9 (10)	0	1 (1)

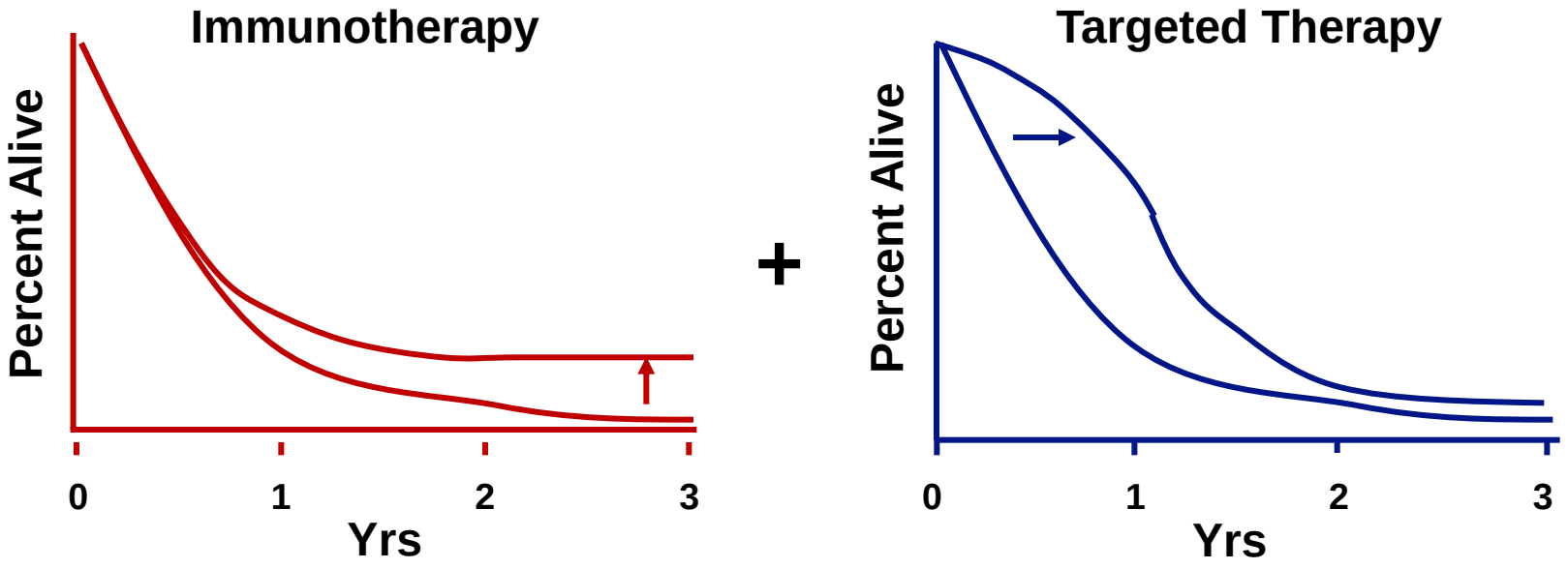
Sequist L, et al. NEJM 2015
Janne PA, et al. NEJM 2015

NSCLC EGFR-mutated

- First-line
  - In first line we have to always use an EGFR-TKI?
  - Which EGFR-TKI? First, second or third generation?
  - What about uncommon mutations?
- Mechanisms of resistance
  - Primary Resistance
  - Acquired Resistance
- **PD1-axis and EGFR-TKIs**

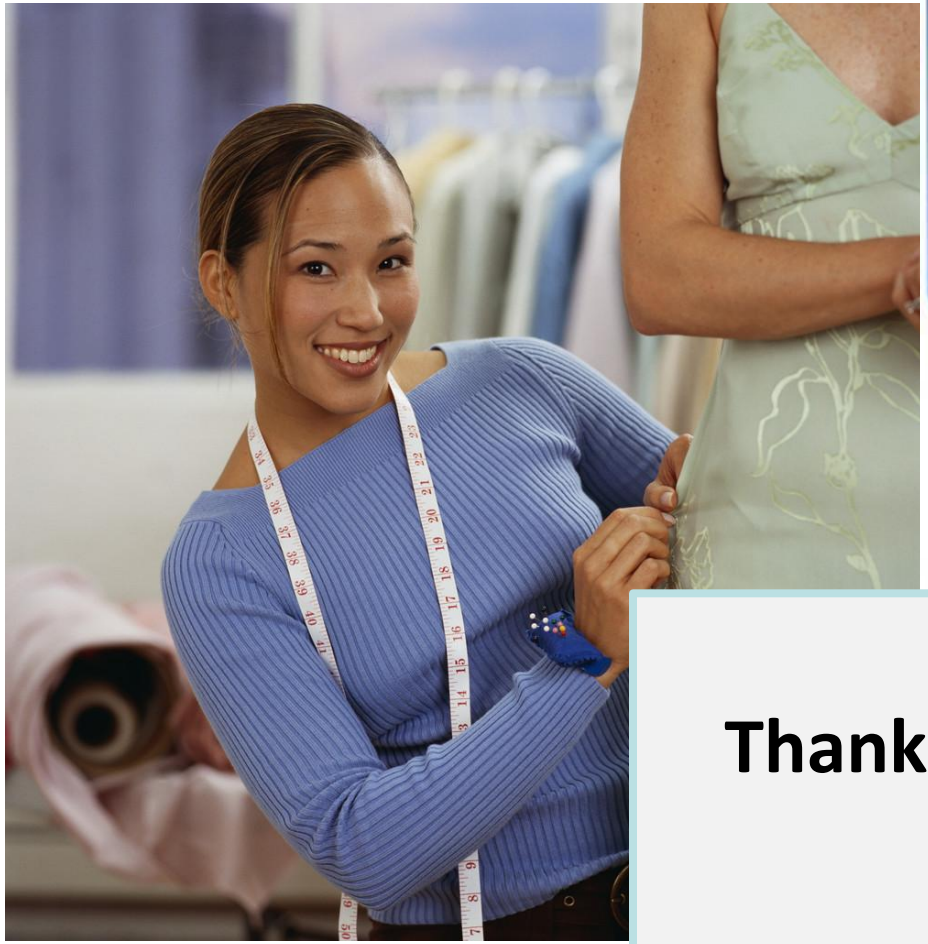
PD1-axis and EGFR-TKIs

- Preclinical data showed that activation of the PD-1 pathway contributed to immune evasion in EGFR-driven lung cancers.
- Phase 1 trials combining EGFR TKIs (1st,2nd and third generation) with immunotherapies are ongoing, including the following:
  - nivolumab (NCT01454102);
  - pembrolizumab (NCT02039674);
  - MPDL3280A (N CT02013219).



Conclusions

- **EGFR mutations are validated biomarkers for NSCLC**
- **An EGFR-TKI is the standard first-line therapy forEGFR mutated patients**
- **Erlotinib, gefitinib and afatinib equally effective, with different toxicity profile**
- **Rociletinib and AZD9291 effective in patients with acquired resistance to first-generation EGFR-TKIs**



Thank you for your attention!

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