T790M INHIBITOR AS FIRST LINE THERAPY: PROMISES AND PITFALLS

David Planchard (MD, PhD)

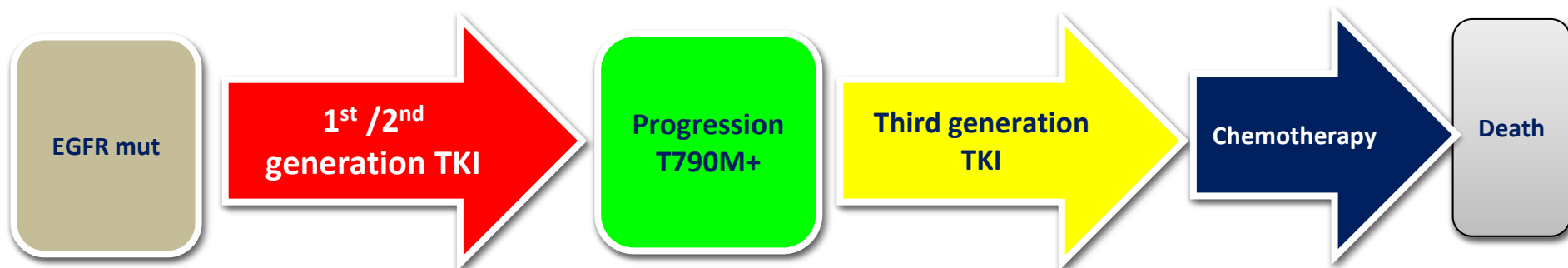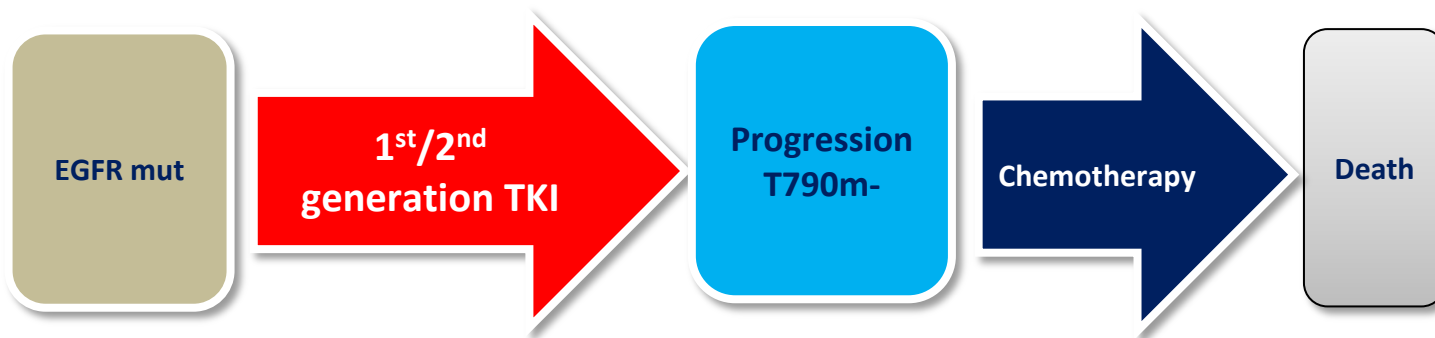Department of Cancer Medicine
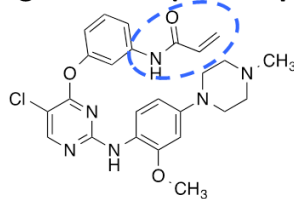
Gustave Roussy – Villejuif (France)

elcc2016.org

DISCLOSURE SLIDE

AstraZeneca, BMS, Clovis, GSK, Lilly, MSD, Pfizer, Roche, Sanofi, Pierre Fabre, Merck, Boehringer Ingelheim,

EGFR mutated lung cancer patient

EGFR mut → **1st/2nd generation TKI** → Progression T790m- → Chemotherapy → Death

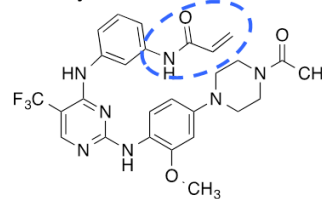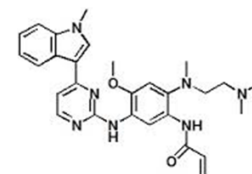EGFR mut → **1st /2nd generation TKI** → Progression T790M+ → **Third generation TKI** → Chemotherapy → Death

Third generation (anilino-pyrimidines)

WZ4002

CO-1686

AZD9291

EGFR-TKI in 1st ligne treatment increase PFS

Trial		N (EGFRmut)	RR	Median PFS(months)
EURTAC[3]	Erlotinib vs cddp/doc	173	58.1% vs 14.9%	9.7 vs 5.2
OPTIMAL[4]	Erlotinib vs carbo/gem	154	83% vs 36%	13.7 vs4.6
IPASS[5]	Gefitinib vs carbo/pacli	261	71.2% vs 47.3%	9.5 vs 6.3
NEJ002[6]	Gefitinib vs carbo/pacli	224	73.7% vs 30.7%	10.8 vs 5.4
WJTOG3405[7]	Gefitinib vs cddp/doc	172	62.1% vs 32.2%	9.2 vs 6.3
LL3[1]	Afatinib vs cddp/pem	345	56% vs 23%	11.1 vs 6.9
LL6[2]	Afatinib vs cddp/gem	364	66.9% vs 23%	11 vs 5.6

9.2-13.7 months

1. Sequist et al. *J Clin Oncol.* 2013;31:3327; 2. Wu et al. *Lancet Oncol.* 2014;15:213; 3. Rosell et al. *Lancet Oncol.* 2012;13:239; 4. Zhou et al. *J Clin Oncol.* 30, 2012 (suppl; ab7520); 5. Fukuoka et al. *J Clin Oncol.* 2011;29:2866; 6. Inoue et al. *Ann Oncol.* 2013;24:54; 7. Mitsudomi et al. *J Clin Oncol.* 30, 2012 (suppl; ab7521).

T790M positive – Progression free survival

Osimertinib 80mg
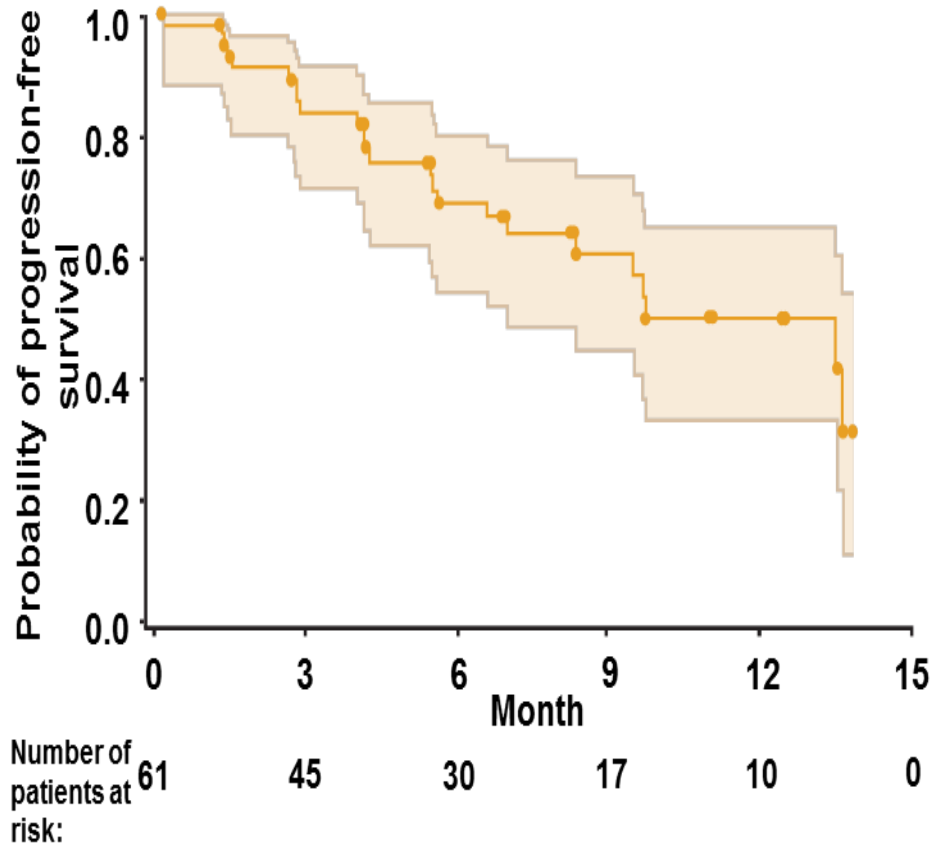
mPFS : 13.5 months

Rocelitinib 500mg or 625mg

mPFS : 8.0 months

Pasi A Janne et al, ELCC 2015 ; LV Sequist et al, ASCO 2015
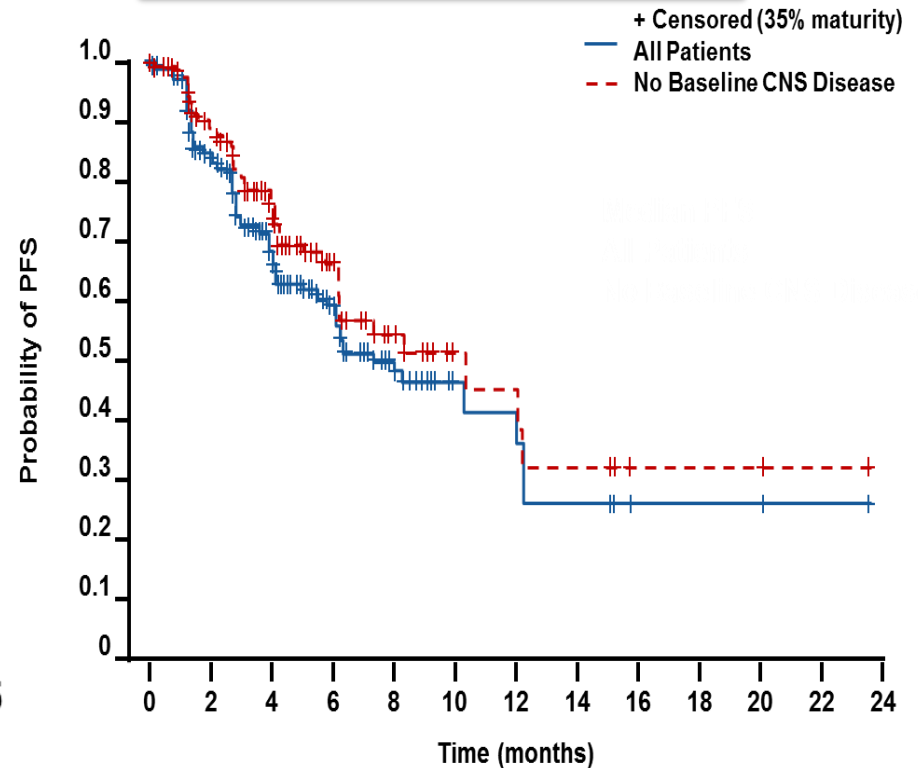
Benefit of T790M inhibitor

| EGFR mut | → 1st/2nd generation TKI → | Progression T790m- | → Chemotherapy → | Death |

| EGFR mut | → 1st /2nd generation TKI → | Progression T790M+ | → Third generation TKI → | Progression | → Chemotherapy → | Death |

PFS1: 9.2-13.7 months

PFS2 Osimertinib: 13.5 months
PFS2 Rocelitinib: 8.0 months

PFS1 + PFS2 : 17.2 to 27.5 months

OS
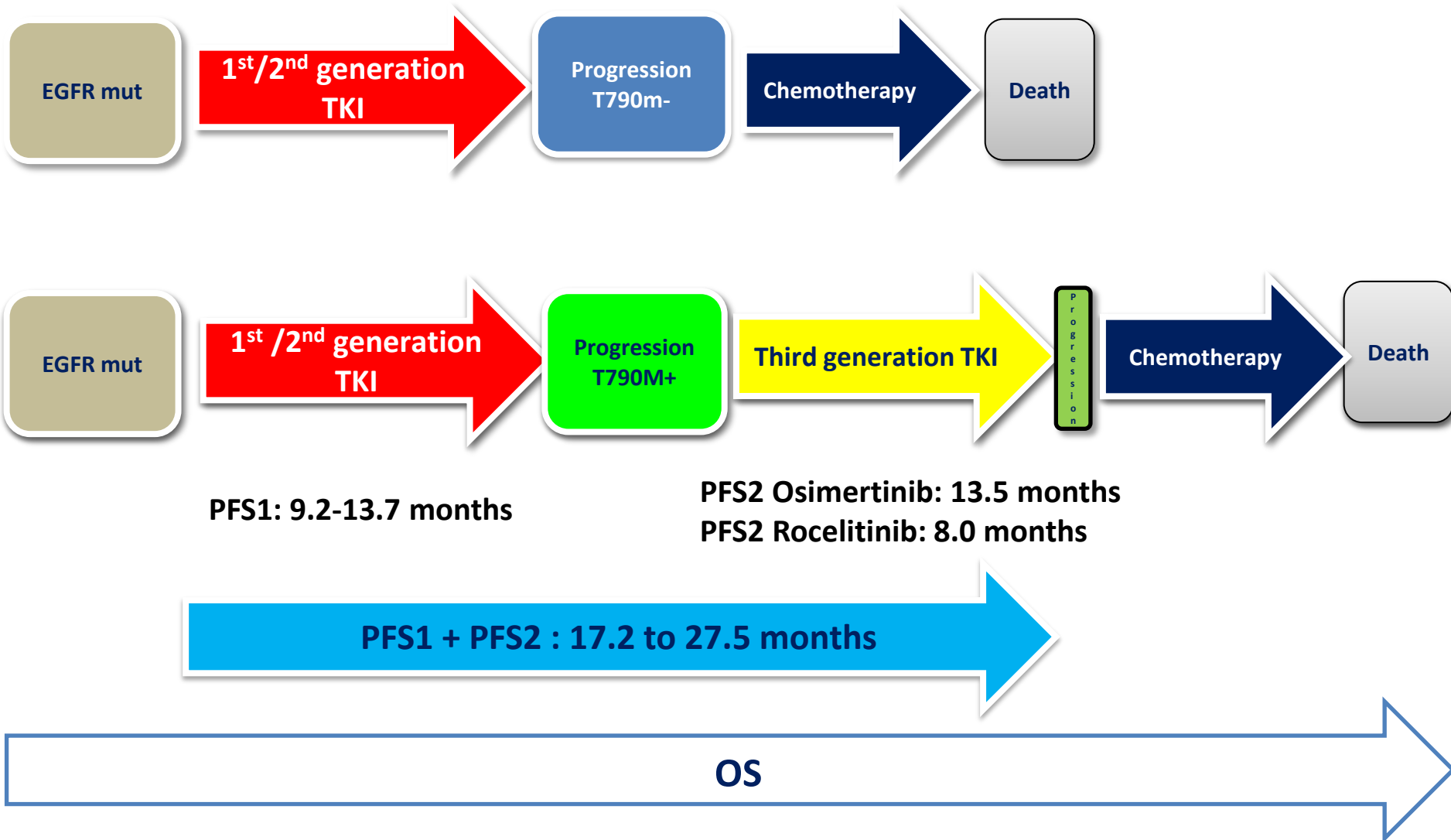
What is the Best Sequence?

Today

EGFR mut → 1st generation TKI → Progression T790m- → Chemotherapy → Death

EGFR mut → 1st generation TKI → Progression T790M+ → Third generation TKI → Progression → Chemotherapy → Death

PFS1

PFS2

PFS1 + PFS2 : 17.2 to 27.5 months

Tomorrow

?

EGFR mut → Third generation TKI → Progression → Chemotherapy

PFS=PFS1+PFS2

OS

T790M inhibitor as first line

- **'Hitting harder' the EGFRm target**
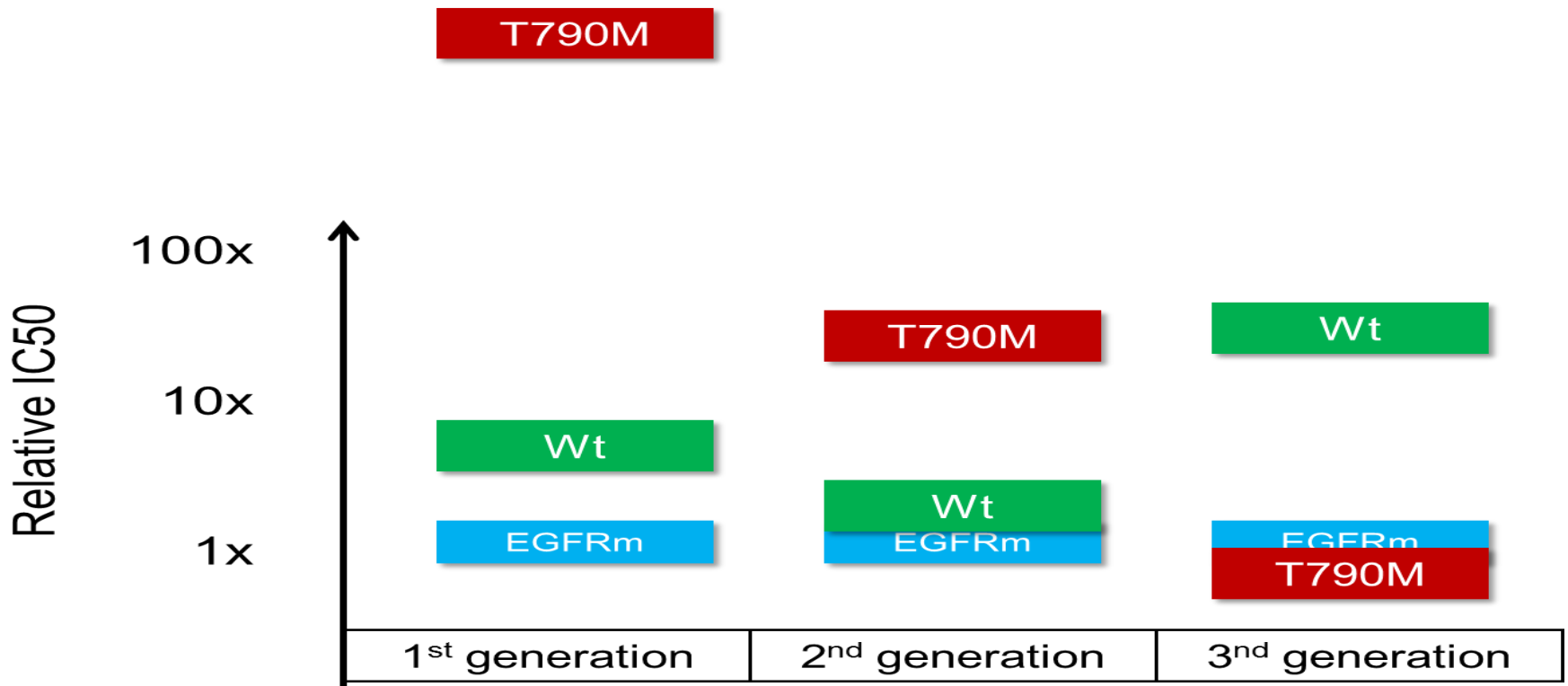 - Inhibits mutant EGFR with sensitising mutation (ex19 or L858R) and dual mutant EGFR with de novo/secondary T790M resistance mutation

Tumour shrinkage in EGFRm+ NSCLC tumour xenografts (Osimertinib)

- AZD9291 induces sustained tumour shrinkage in PC9 and H3255 tumour xenografts

PC9 (EGFR exon 19 deletion)
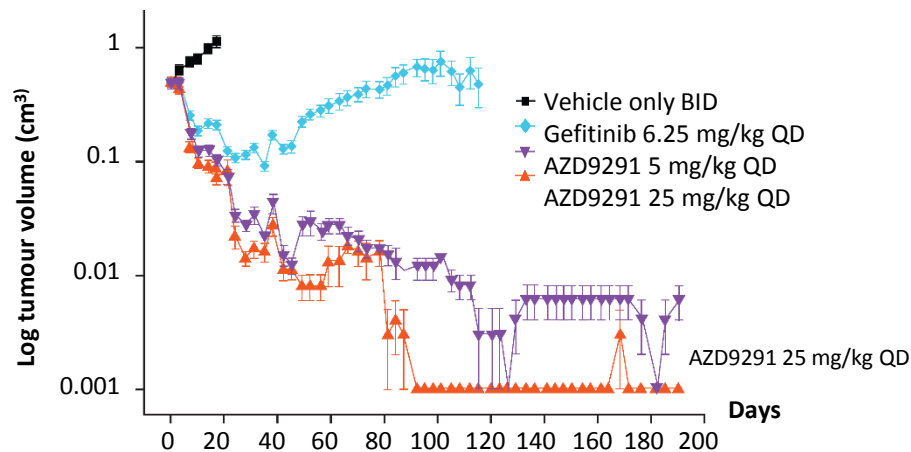
H3255 (EGFR L858R)
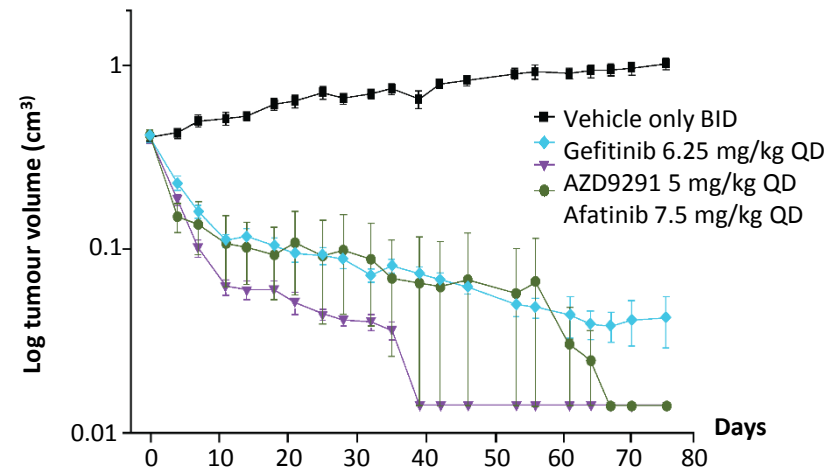
AZD9291 at 25 mg/kg in mouse approximates to clinical exposure of 80 mg once daily, gefitinib at 6.25 mg/kg in mouse approximates to clinical exposure of 250 mg once daily; afatinib at 7.5 mg/kg in mouse approximates to clinical exposure of 40 mg once daily

QD, once daily

Suresh Ramalingam et al, ESMO 2014

Expect a prolonged control of the disease compared to currently available TKis

- *In vitro* in EGFRm+ (exon 19 deletion) PC9 cells, resistance to AZD9291 took significantly longer to emerge compared with other TKIs[1]
  - Resistance to 10 nM AZD9291 took on average 43 days longer to develop than with 0.8 nM afatinib, 30 nM WZ4002, or 20 nM gefitinib
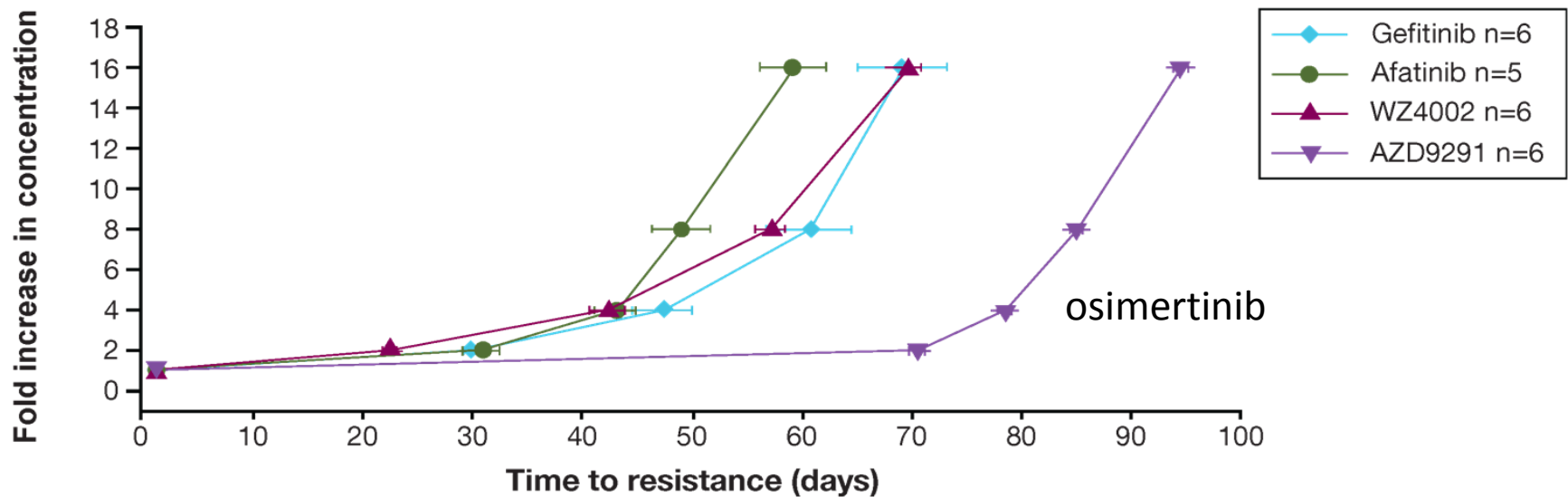
Initial concentration was equal to the proliferative IC50 previously determined for each inhibitor:
gefitinib 20 nM, afatinib 0.8 nM, WZ4002 30 nM, AZD9291 10 nM
n = number of separate resistant populations; error bars are standard error of the mean

Detection of T790M resistance in EGFR-TKI-treated PC9 cell lines

- In contrast to gefitinib and afatinib, AZD9291 acquired resistance *in vitro* in PC9 cell lines was not dependent on T790M[1]
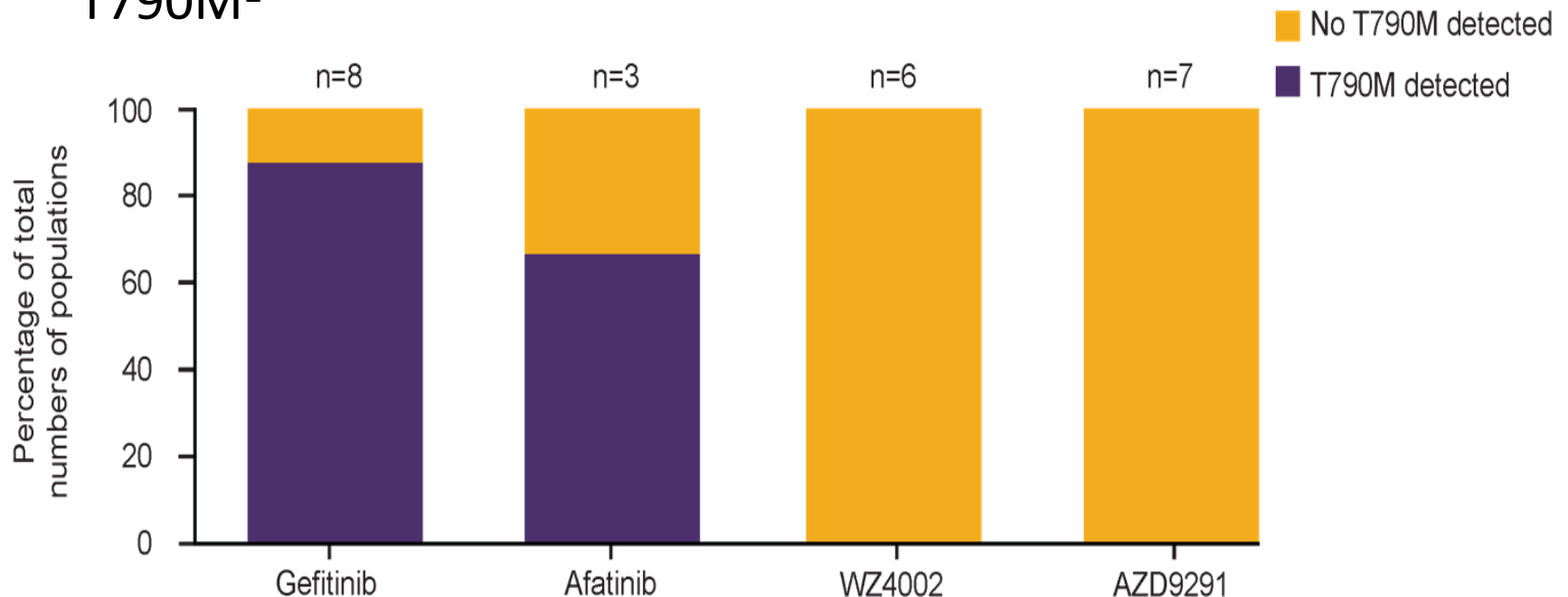
1. Eberlein et al. Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 5–9 April 2014; San Diego, CA, abstract 1722.

Tumors resistant to EGFR inhibitors can arise via different mechanisms

- Acquired resistance caused by
  - pre-existing EGFR T790M positive clones
  - or via genetic evolution of initially EGFR T790M negative drug-tolerant cells
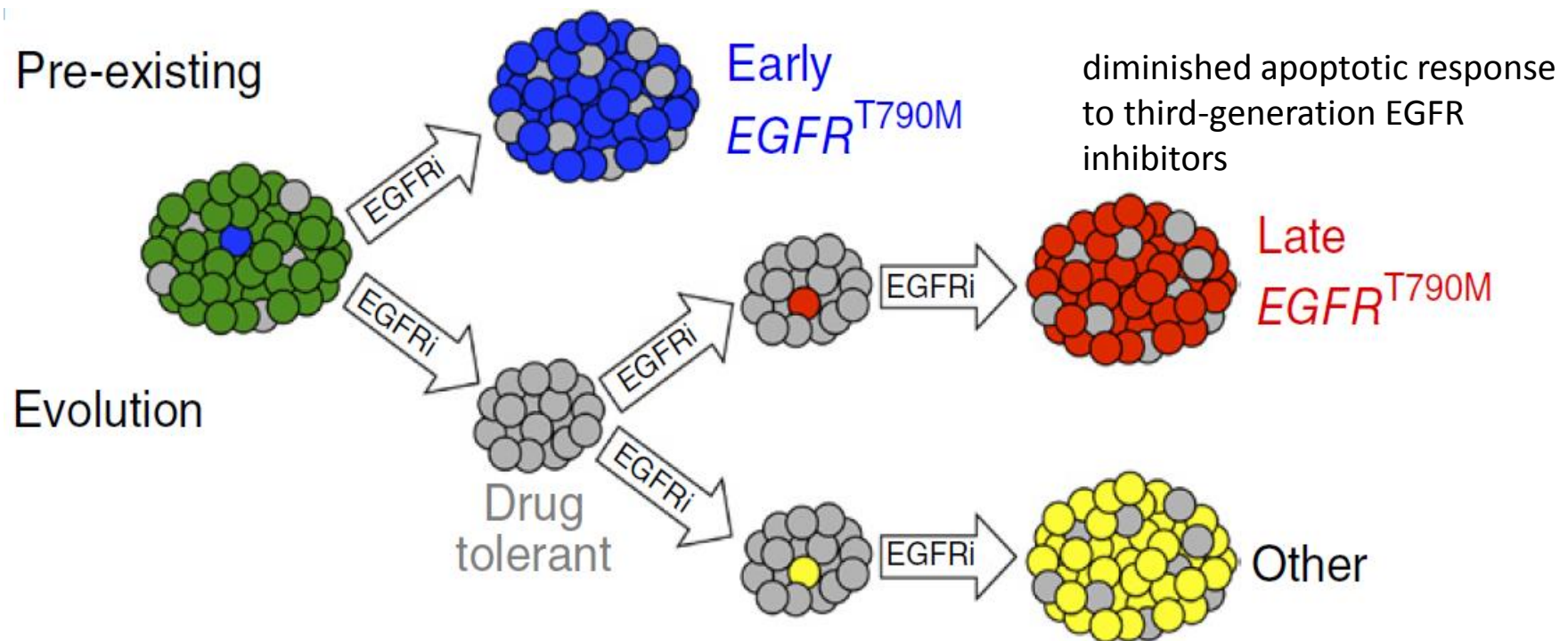
diminished apoptotic response to third-generation EGFR inhibitors

genetic evolution of initially EGFRT790M-negative drug-tolerant cells

Aaron N Hata et al, nature 2016

Wide variation in frequency of de novo EGFR T790M mutations

Ref	Method	Baseline T790M mutation
Maheswaran et al	Scorpion ARMS	38%
Sequist *et al*	Direct seq	5,9%
Nakamura *et al*	MBQ-PQ	9,4%
Rosell et al	TaqMan assay + PNA	34,9%
Wu et al	Direct sequencing	1%
Fujita *et al*	Colony hydridization	78,9%
Su *et al*	MALDI-TOF	25%
Sakai *et al*	SABER	7%
Costa *et al*	Taqman probe+PNA	65,3%
Yu *et al*	MALDI-TOF MS	2%

ARMS, amplification refractorymutation system; MBQ-QP, mutation-biased polymerase chain reaction — quenching probe; PNA, peptide-nucleic acid; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight mass spectrometry; SABER, single allele base extension reaction

Denis MG, Vallée A, Théoleyre S. EGFR T790M resistance mutation in non small-cell lung carcinoma. *Clin Chim Acta.* 2015;444C:81-85.

Erlotinib and bevacizumab in pts with advanced NSCLC with activating EGFR mutations with and without T790M mutation.
BELIEF trial

T790M at diagnosis was documented in 34% of patients

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

No at risk

Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
All pts	109	102	95	86	75	54	43	35	25	21	18	12	11	7	5	4	2	0
T790M+	37	36	32	29	25	21	19	16	9	8	7	5	5	3	2	2	1	0
T790M-	72	66	63	57	50	33	24	19	16	13	11	7	6	4	3	2	1	0

Legend: + Censored; All patients; T790M+; T790M-

Progression-free survival (%)

Stahel et al. Ann Oncol 2015; 26 (suppl 6): abstr 3BA

Pretreatment EGFR T790M Mutation Predicts Shorter EGFR Tyrosine Kinase Inhibitor Response Duration

25.2% EGFR- T790M+

matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) and next-generation sequencing (NGS)

Kang-Yi Su et al, JCO 2012
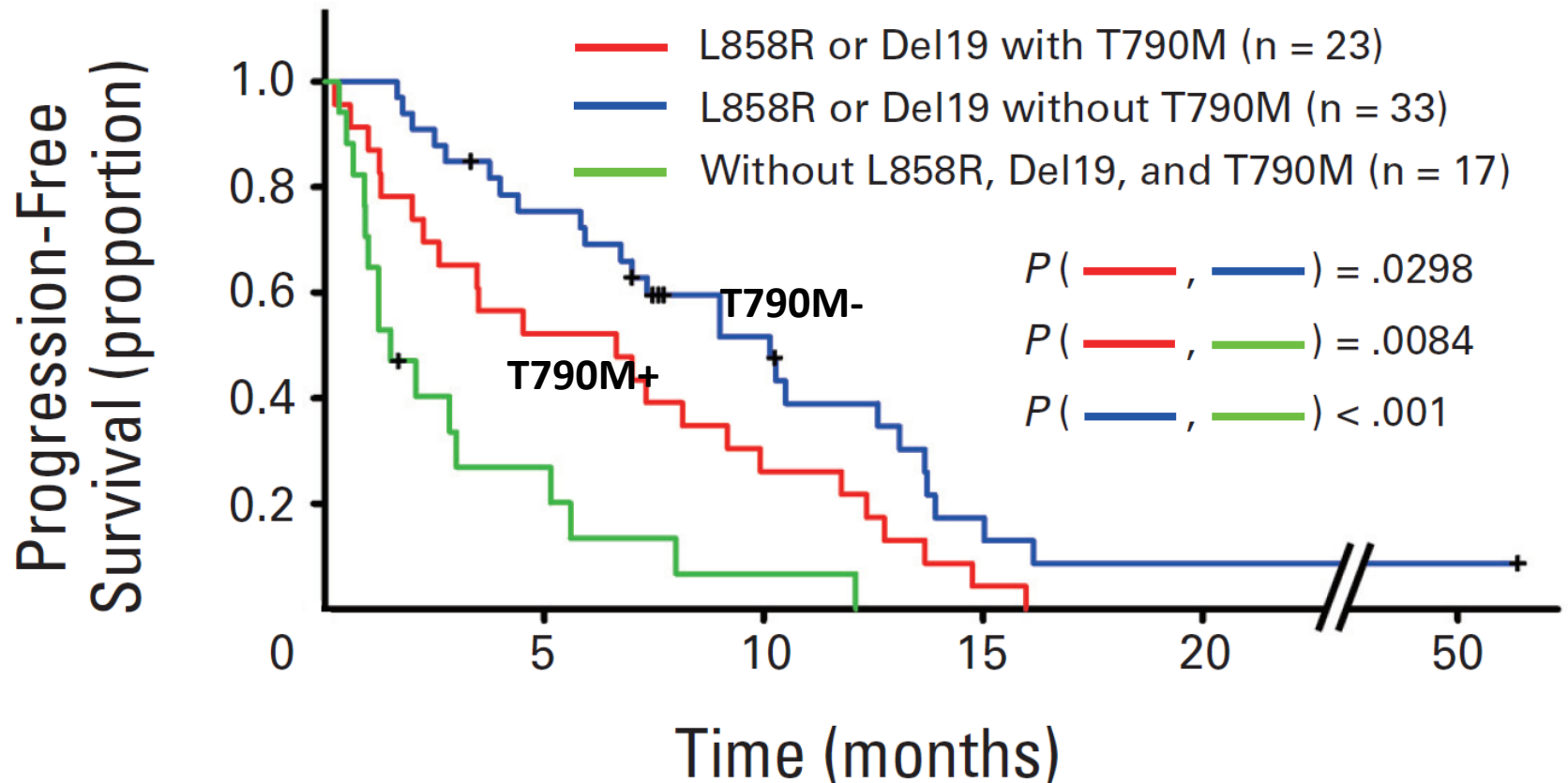
LUX-Lung 7 PFS by independent review

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

p=0.0176

27%

p=0.0184

18%

15%

8%

Time (months)

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

Effect of Afatinib on T790M… ??

Keunchil Park et al, ESMO Asia 2015

SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE
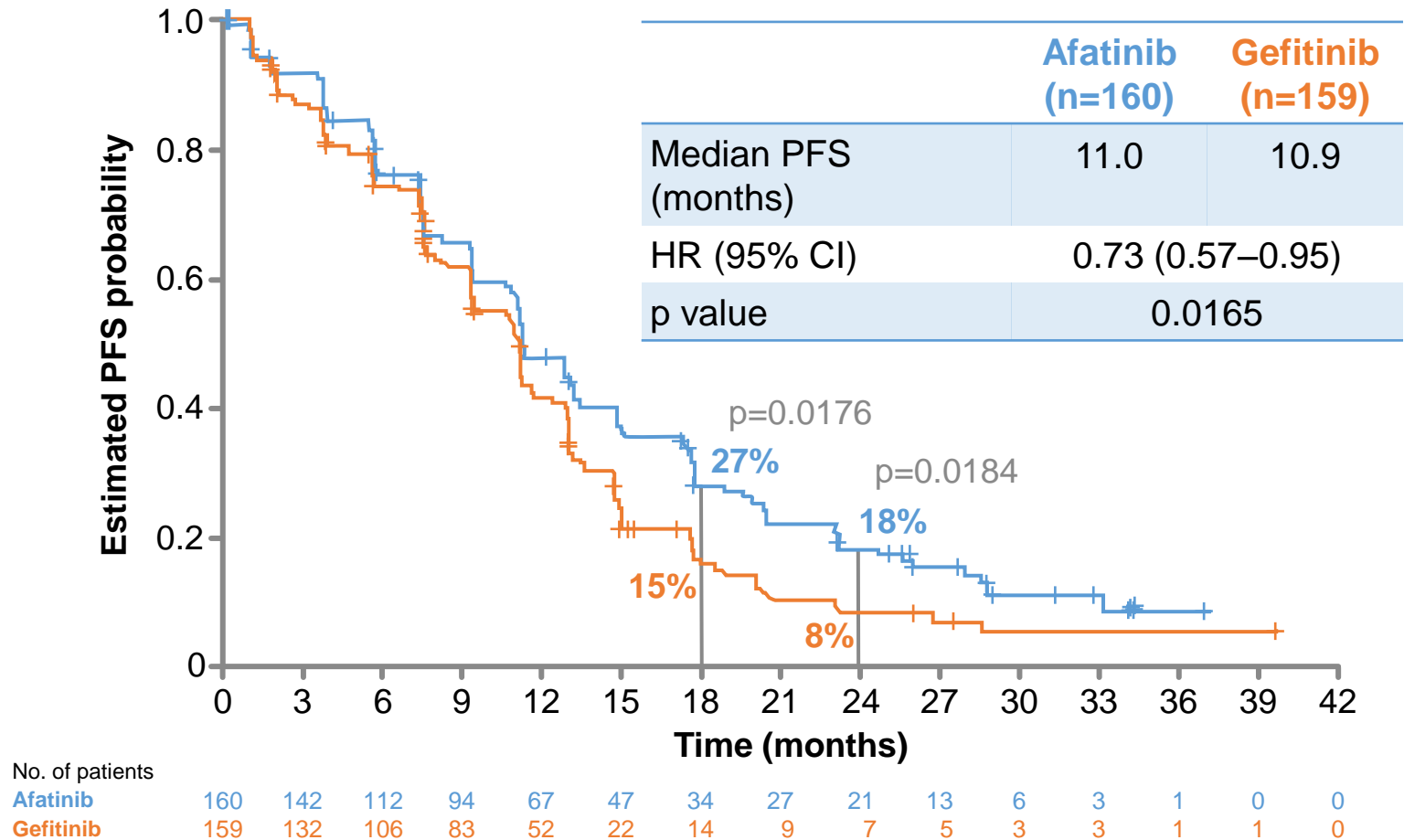
Efficacy in patients with Del19 or L858R mutation

Del 19

	Afatinib	Gefitinib
Median PFS (months)	12.7	11.0
HR (95% CI)	0.76 (0.55–1.06)	
p value	0.1071	
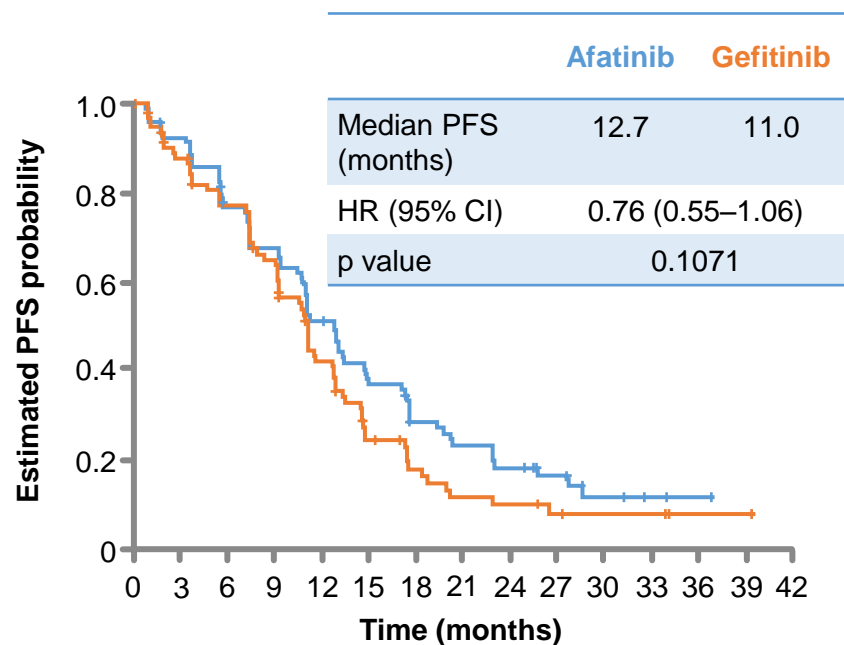
No. of patients
Afatinib 93 83 67 58 43 31 22 18 14 9 4 2 1 0 0
Gefitinib 93 76 64 53 32 17 11 7 6 4 3 3 1 1 0

L858R

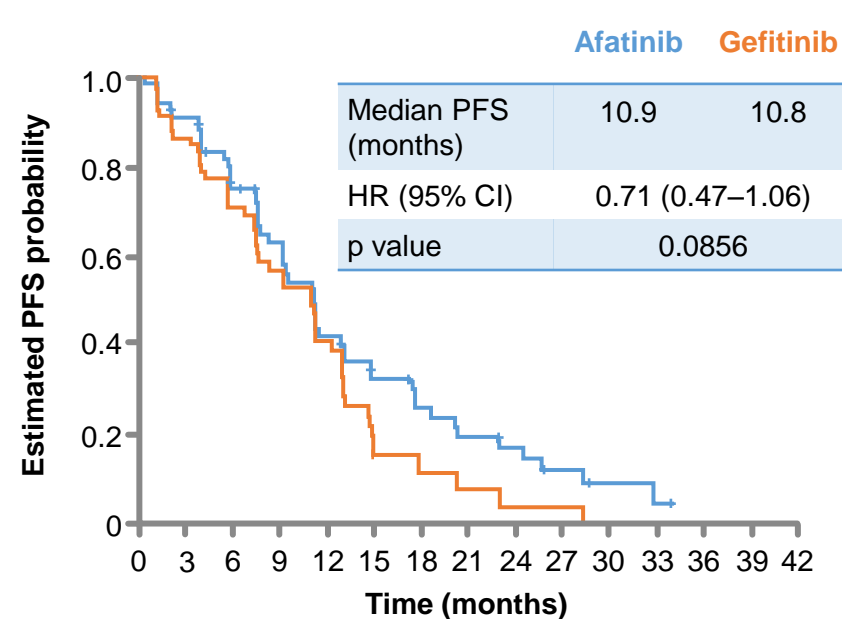|	Afatinib	Gefitinib
Median PFS (months)	10.9	10.8
HR (95% CI)	0.71 (0.47–1.06)	
p value	0.0856	

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

Drug-related AEs (>10%)

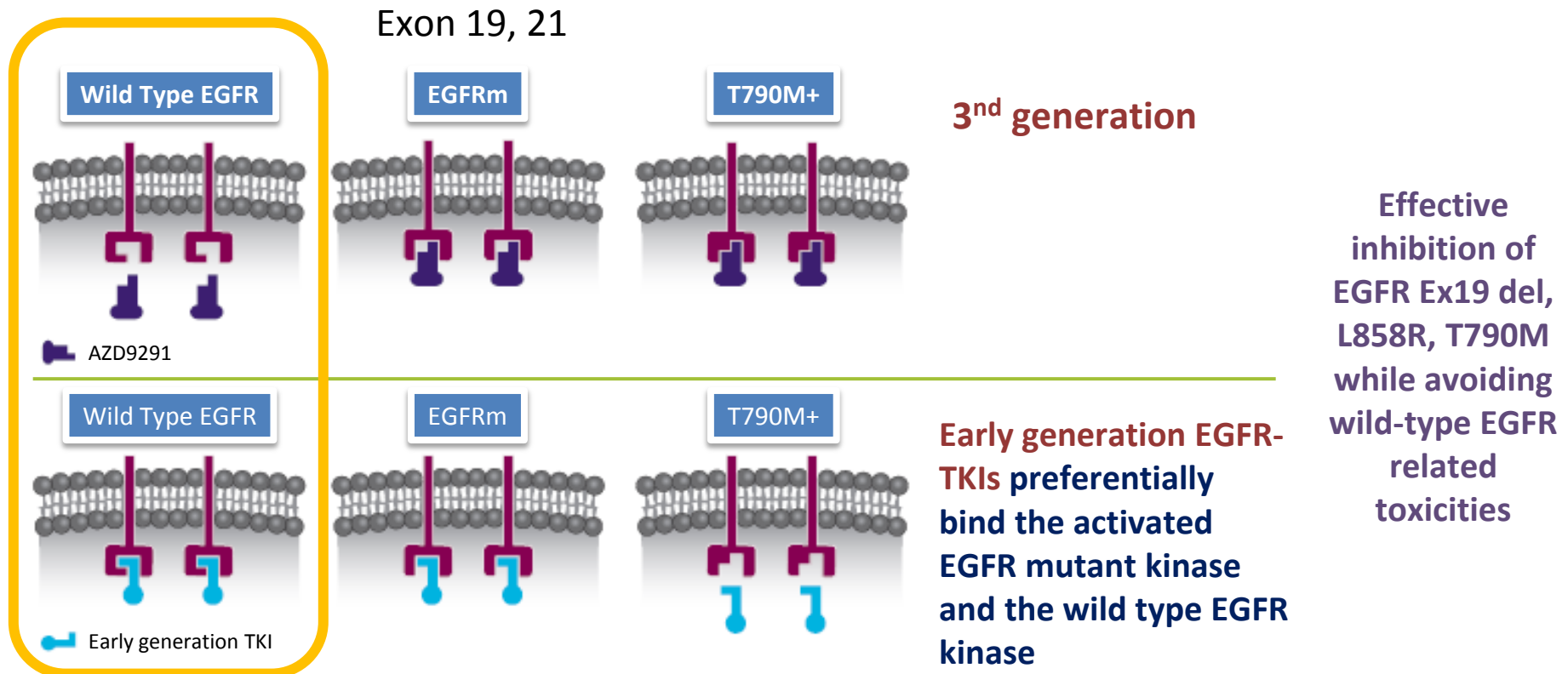| AE category, %	Afatinib (n=160)		Gefitinib (n=159)	
	All	Grade 3	All	Grade 3
Diarrhea	90.0	11.9†	61.0	1.3
Rash/acne*	88.8	9.4	81.1	3.1
Stomatitis*	64.4	4.4	23.9	-
Paronychia*	55.6	1.9	17.0	0.6
Dry skin	32.5	-	37.1	-
Pruritus	23.1	-	22.6	-
Fatigue*	20.6	5.6	14.5	-
Decreased appetite	16.3	0.6	11.9	-
Nausea	16.3	1.3	13.8	-
Alopecia	10.6	-	15.1	-
Vomiting	10.6	-	3.8	0.6
ALT increased	9.4	-	23.9	7.5‡
AST increased	6.3	-	20.8	2.5

*Grouped terms of AEs

T790M inhibitor as first line

- 'Hitting harder' the EGFRm target

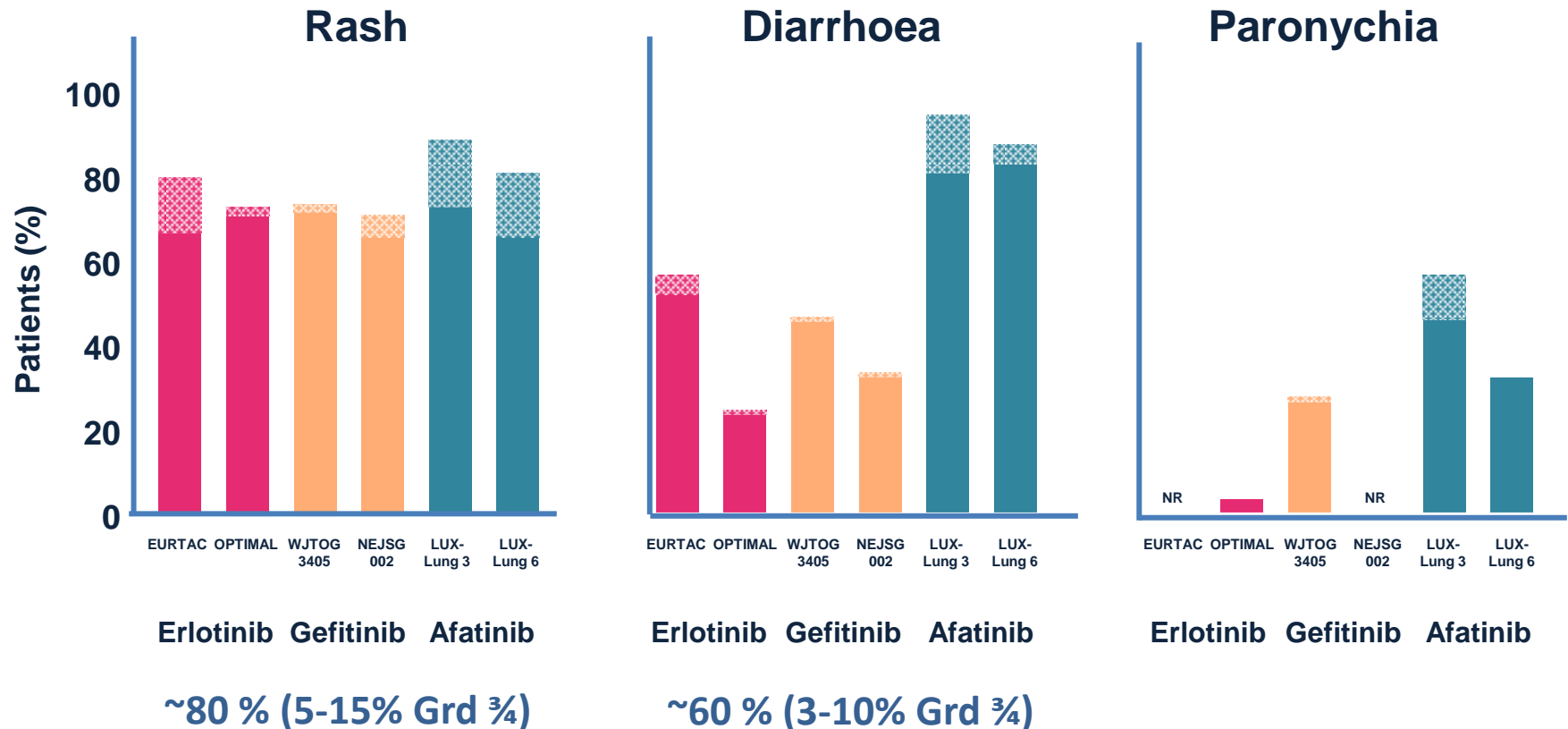- Better tolerability profile versus available EGFR TKIs

higher level of selectivity towards mutant EGFR vs. wild type

- allowing a wider therapeutic margin

- and also a better tolerability profile versus available EGFR TKIs

Exon 19, 21

Wild Type EGFR

EGFRm

T790M+

3rd generation

AZD9291

Wild Type EGFR

EGFRm

T790M+

Early generation TKI

Early generation EGFR-TKIs preferentially bind the activated EGFR mutant kinase and the wild type EGFR kinase

Effective inhibition of EGFR Ex19 del, L858R, T790M while avoiding wild-type EGFR related toxicities

1. Cross et al. Cancer Discov 2014;4:1046–1061;

1ˢᵗ and 2ⁿᵈ generation EGFR -TKI

Grade 1–2   Grade 3–4

Rash

Diarrhoea

Paronychia

Patients (%)

EURTAC OPTIMAL WJTOG 3405 NEJSG 002 LUX-Lung 3 LUX-Lung 6

Erlotinib   Gefitinib   Afatinib

~80 % (5-15% Grd ¾)

~60 % (3-10% Grd ¾)

Rosell, et al. Lancet Oncol 2012; Zhou, et al. Lancet Oncol 2011; Mitsudomi, et al. Lancet Oncol 2010
Maemondo, et al. N Engl J Med 2010; Sequist, et al. J Clin Oncol 2013; Wu, et al. Lancet Oncol 2014

Osimertinib Phase I/II: All-causality adverse events

Patients with an AE, %	20 mg (N=21)		40 mg (N=58)		80 mg (N=103)		160 mg (N=80)		240 mg (N=21)		Total (N=283)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AE by preferred term, occurring in >15% of patients overall												
Diarrhoea	29	0	47	2	36	1	68	3	76	5	50	2
Rash, grouped terms	24	0	33	0	38	0	63	3	76	5	46	1
Decreased appetite	38	10	19	0	26	3	24	0	33	0	25	2
Nausea	14	5	17	0	18	1	34	1	43	0	24	1
Dry skin	14	0	16	0	15	0	36	0	24	0	22	0
Paronychia	14	0	9	0	21	2	29	4	38	5	22	2
Pruritus	14	0	21	0	19	0	20	0	38	0	21	0
Fatigue	24	5	26	0	16	0	19	0	19	5	19	1
Constipation	5	0	26	0	21	0	18	0	14	0	19	0
Cough	19	0	17	0	13	0	21	0	0	0	16	0
Select AEs of interest												
Hyperglycaemia (n=8)	0	0	3	0	4				0	0	3	0
QT pro...												4
ILD-lik...												

LBA2_PR - Osimertinib (AZD9291) in pre-treated pts with T790M-positive advanced NSCLC: updated Phase 1 (P1) and pooled Phase 2 (P2) results

J. Yang[1], S. Ramalingam[2], P. Jänne[3], M. Cantarini[4], T. Mitsudomi[5]; [1]TW, [2]GA/US, [3]MA/US, [4]GB, [5]JP

Popul...
*All IL...

Rocelitinib
Common Treatment-related Adverse Events

Treatment-related adverse events (<u>all grades</u>) seen in >10% of patients, N (%)

AE	Rociletinib dose			
	500mg BID (N=119)	625mg BID (N=236)	750mg BID (N=95)	1000mg BID (N=6)
Hyperglycemia	42 (35)	107 (45)	56 (59)	4 (67)
Diarrhea	39 (33)	94 (40)	28 (30)	4 (67)
Nausea	23 (19)	79 (34)	35 (37)	3 (50)
Fatigue	15 (29)	37 (30)	21 (27)	1 (25)
QTc prolongation	16 (13)	53 (23)	25 (26)	3 (50)
Decreased appetite	18 (15)	38 (16)	24 (25)	2 (33)
Muscle spasms	17 (14)	30 (13)	20 (21)	1 (17)
Vomiting	10 (8)	38 (16)	13 (14)	0 (0)
Weight loss	12 (10)	21 (9)	16 (17)	1 (17)

<u>Grade 3/4</u> treatment-related adverse events seen in >10% of patients, N (%)

AE	Rociletinib dose			
	500mg BID (N=119)	625mg BID (N=236)	750mg BID (N=95)	1000mg BID (N=6)
Hyperglycemia	20 (17)	56 (24)	34 (36)	2 (33)

- No ILD observed in 500mg BID dose group
  - 7/456 cases overall (1.5%)
  - Rociletinib continuation possible with steroid cover
  - No fatal ILD in program
- No paronychia or stomatitis observed; trivial rash
- Grade 3 QTc prolongation at 500mg BID = 2.5%
- Treatment-related AEs leading to drug discontinuation seen in 2.5% of cases at 500mg BID (4% overall)
- Hyperglycemia readily managed with oral agents
  - No contraindication for pre-existing diabetic patients

ILD=interstitial lung disease.

Lecia V. Sequist et al, ASCO2015

PRESENTED AT: ASCO Annual '15 Meeting
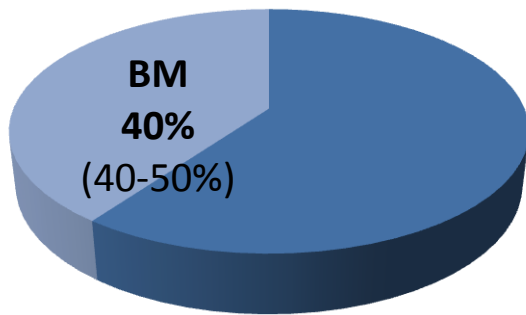
T790M inhibitor as first line

- 'Hitting harder' the EGFRm target

- Better tolerability profile versus available EGFR TKIs

- Optimising brain penetration
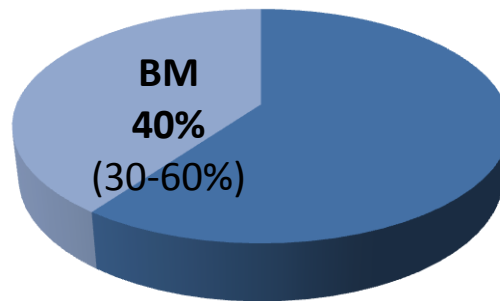
Optimising brain penetration

CNS involvement in NSCLC
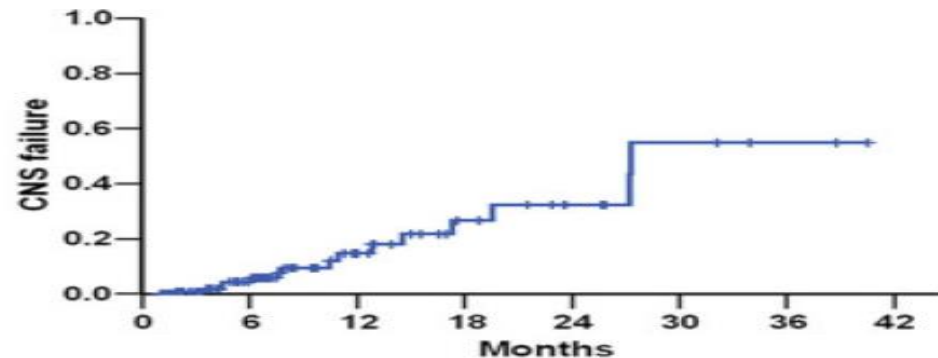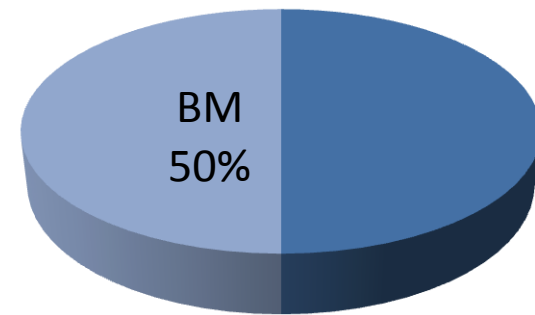
All comers incidence of BM

BM
40%
(40-50%)

Sorensen JB et al, J Clin Oncol.1988;6: 1474
Langer CJ et al, J Clin Oncol 2005, 23:6207

EGFR + patients treated with 1st generation TKI

BM
40%
(30-60%)

Homuro et al , Cancer.2005: 3, 2344
Hoen S et al, Clin Cancer Res 2010: 16, 5873
Lee YJ et al, Cancer 2010: 116, 1336

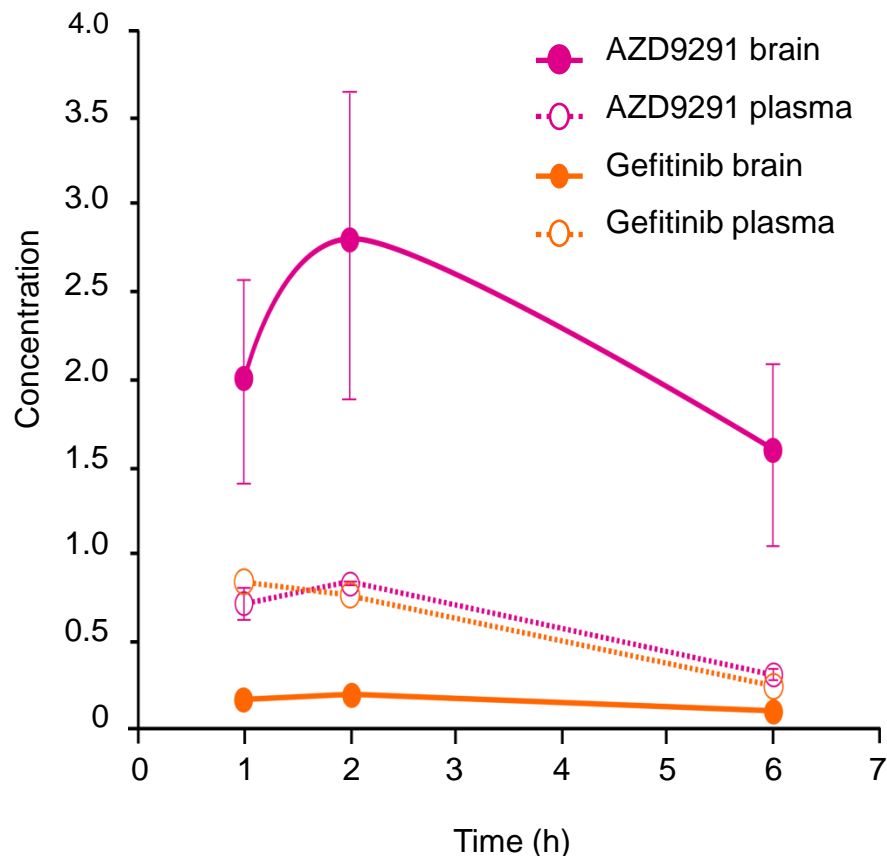**ALK+ patients treated with crizotinib**

BM
50%

Figure 1. The actuarial incidence of isolated central nervous system failure, measured by the Kaplan-Meier method, in patients with clinical benefit from epidermal growth factor tyrosine kinase inhibitors.

Osimertinib is distributed to mouse brain to a greater extent than gefitinib, CO-1686, or afatinib

AZD9291 and gefitinib p.o.

AZD9291 25 mg/kg and gefitinib 6.25 mg/kg mouse brain and plasma concentrations

- AZD9291 brain
- AZD9291 plasma
- Gefitinib brain
- Gefitinib plasma

AZD9291, gefitinib, CO-1686, and afatinib p.o. plasma and brain C_{max}

	AZD9291	Gefitinib	CO-1686	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (µM)	0.82	0.82	3.3	0.14
Brain C_{max} (µM)	2.8	0.17	BLQ	BLQ
Brain/plasma ratio	3.4	0.21	NC	NC

BLQ, below limit of quantification (CO-1686 0.25 µM, afatinib 0.05 µM); C_{max}, maximum concentration; NC, not calculated; p.o., orally. Doses are equivalent to clinical doses or reported previously for preclinical studies.

At clinically relevant doses, AZD9291 distribution to the brain is ~10-fold higher than gefitinib

[^{11}C]AZD9291 is distributed to cynomolgus monkey brain

Head/neck

Abdomen

[^{11}C]AZD9291

[^{11}C]CO-1686

Brain

Radioactivity (kBq/cc)

Radioactivity (kBq/cc)
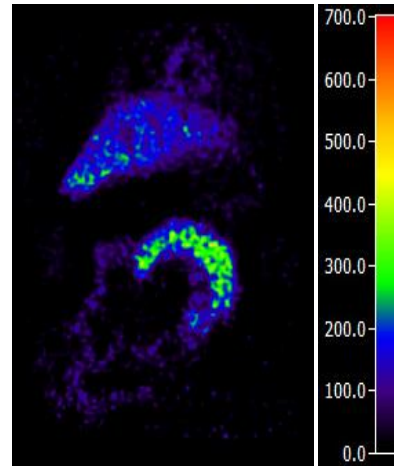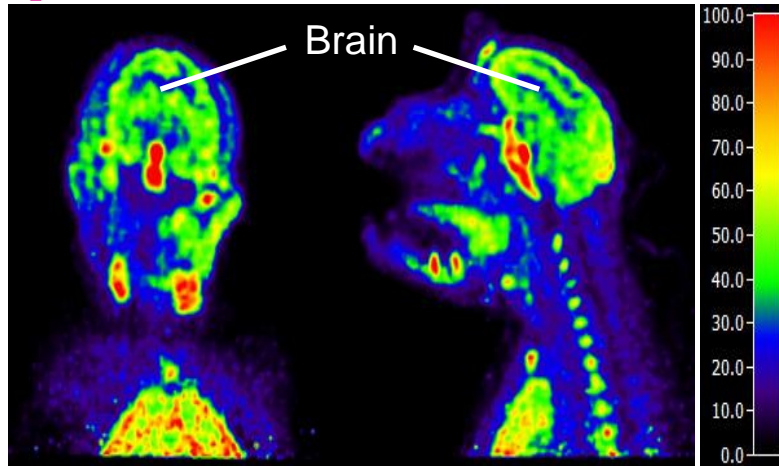
Radiolabeled imaging

	Brain to blood ratio AUC$_{0-90}$ min
[^{11}C]AZD9291	2.6 ± 1.4*
[^{11}C]CO-1686	0.025†
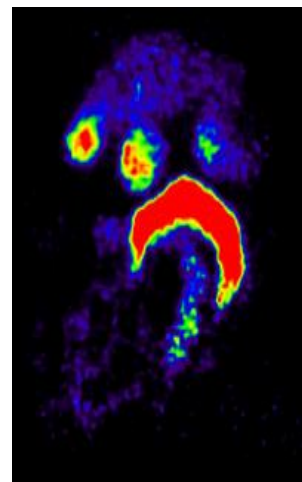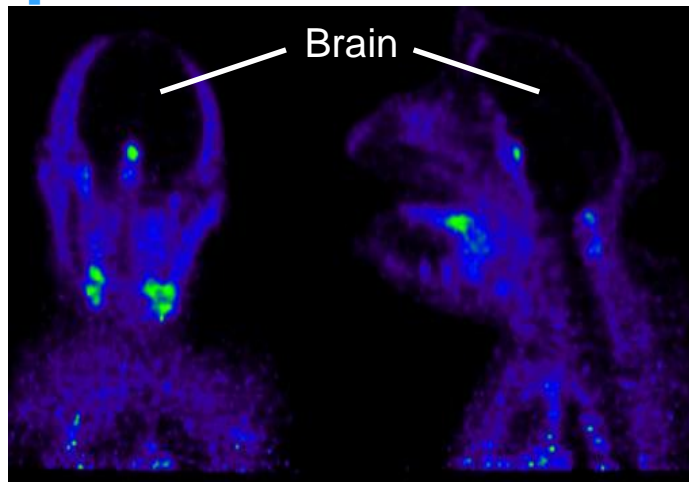
Summation images acquired 5 min up to 2 h after intravenous microdose (<3 µg) injection

Summation images acquired 1.5 h up to 2 h after intravenous microdose (<3 µg) injection

Brain metastases – Case Study 2

- Sixty-year-old Taiwanese female diagnosed with advanced NSCLC (L858R) in January 2011

- Prior therapy: erlotinib January 2011–October 2012 (PR), pemetrexed/cisplatin/ carboplatin October 2012–January 2013 (SD), erlotinib January 2013– March 2013 (NE), docetaxel April 2013–June 2013 (SD), gemcitabine June 2013–July 2013 (NE). T790M detected in August 2013

- AZD9291 80 mg daily started 2 September 2013 in expansion cohort, best response PR. A single brain met target lesion decreased from 13 mm at baseline to 12 mm at Week 6, 8 mm at Week 12–18 (38% shrinkage). NTLs including brain mets had non-CR/non-PD reported for 4 months between 8 October 2013 to 2 January 2014, but progressed in the brain met NTLs on 13 February 2014

Brain MRI
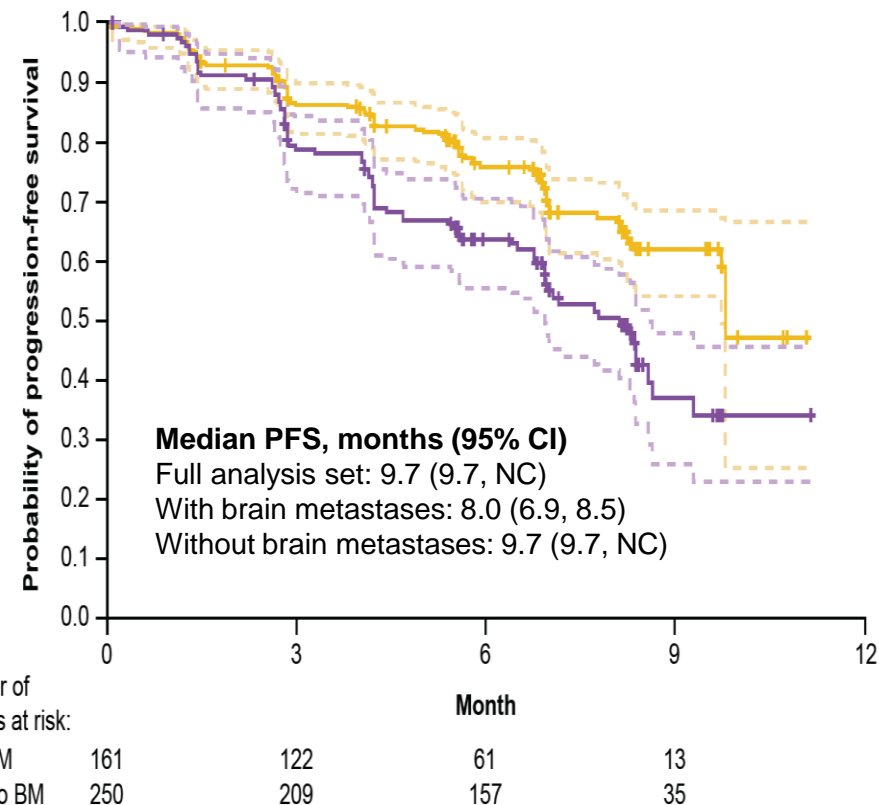**A) Baseline on 9 August 2013. B) 8 October 2013**

Kim et al. Ann Oncol 2014;25(Suppl 4): Poster 456P
NE, not evaluable
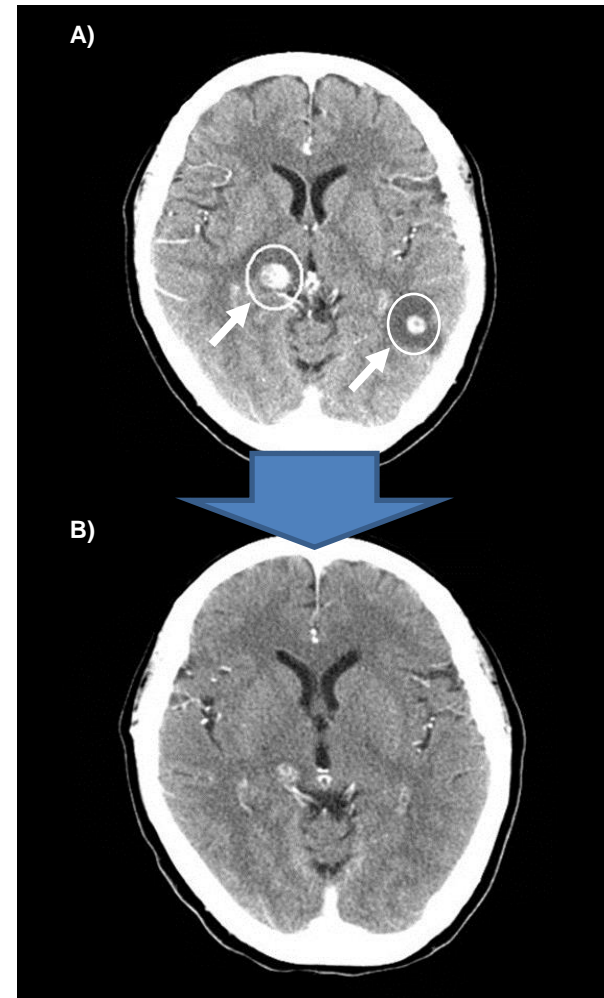
ORR by medical history of brain metastases AZD9291 data from phase II studies

	ORR in pooled dataset (evaluable for response)
BICR evaluable set	66.1% (263/398) 95% CI 61.2, 70.7%
With brain metastases	62.0% (98/158) 95% CI 54.0, 69.6%
Without brain metastases	68.8% (165/240) 95% CI 62.5, 74.6%

BICR, blinded independent central review; CI, confidence interval; ORR, objective response rate

Median PFS, months (95% CI)
Full analysis set: 9.7 (9.7, NC)
With brain metastases: 8.0 (6.9, 8.5)
Without brain metastases: 9.7 (9.7, NC)

Number of patients at risk:

BM	161	122	61	13
No BM	250	209	157	35

Month

Myung-ju Ahn et al, ECCO 2015

T790M inhibitor as first line

- 'Hitting harder' the EGFRm target

- Better tolerability profile versus available EGFR TKIs

- Optimising brain penetration

- Exposure of the entire EGFR-mut population (T790M false -)

Rate in T790M negative cohorts (central test)

Best percentage change from baseline in target lesion

Legend:
- 20 mg
- 40 mg
- 80 mg
- 160 mg
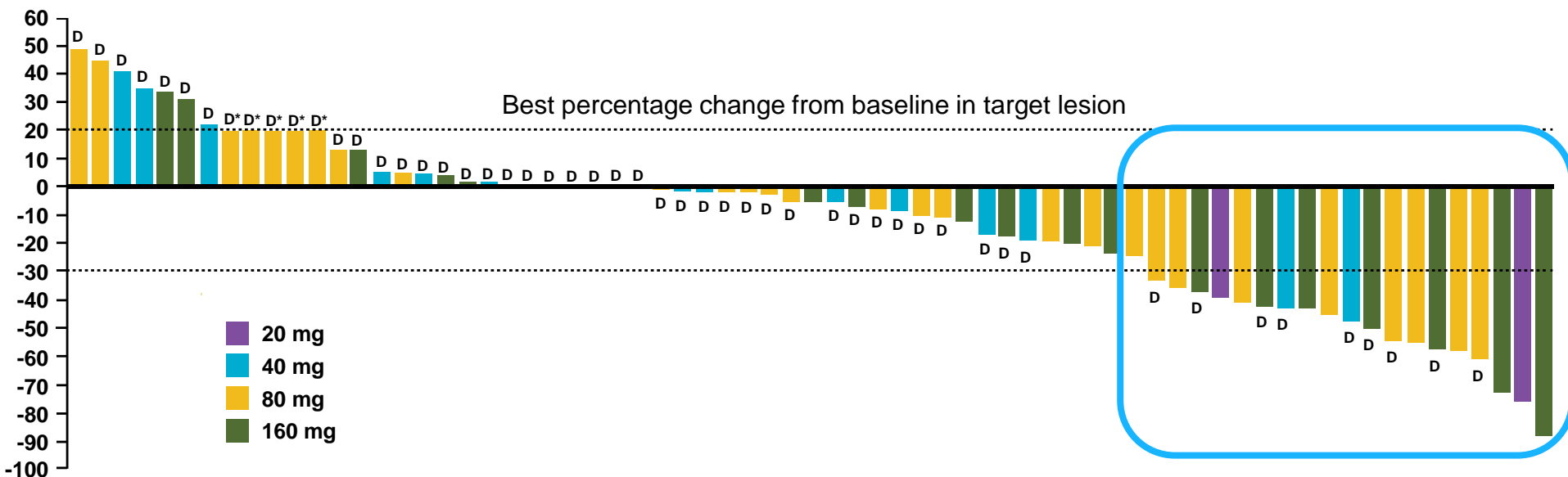
DCR (CR+PR+SD) in patients with centrally tested T790M negative tumours was 64% (44 / 69; 95% CI 51, 75)

	20 mg	40 mg	80 mg	160 mg	Total
N (69)	3	17	29	20	69
ORR (95% CI)	67% (9, 99)	12% (2, 36)	21% (8, 40)	30% (12, 54)	23% (14, 35)

*Imputed values for patients who died within 14 weeks (98 days) of start of treatment and had no evaluable target lesion assessments
Patients are evaluable for response if they were dosed and had a baseline RECIST assessment. Data cut-off 2 Dec 2014

Striking Activity in T790M-negative Patients

Best Response for Target Lesions
Centrally Confirmed T790M Negative 1686-008 Pts at 500 or 625mg BID
(Clinical Dose Group)

- RECIST ORR = 42% overall
- mPFS = 7.5mo

+ = Ongoing
T = Last Prior Therapy was TKI

Change from Baseline (%)

500 BID HBr
625 BID HBr
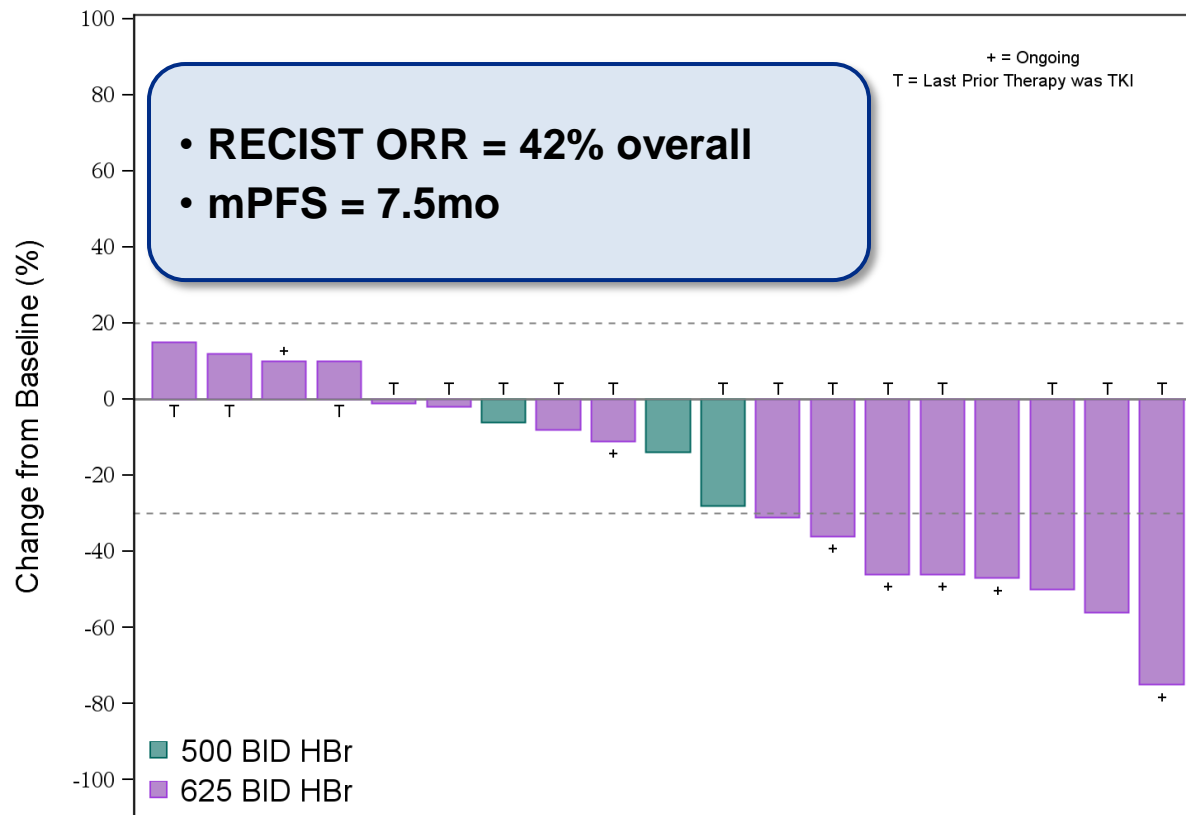
-False negative ?
-Real tumor heterogeneity ?
-Specific mechanism of action of the compound ?

JC. Soria et al

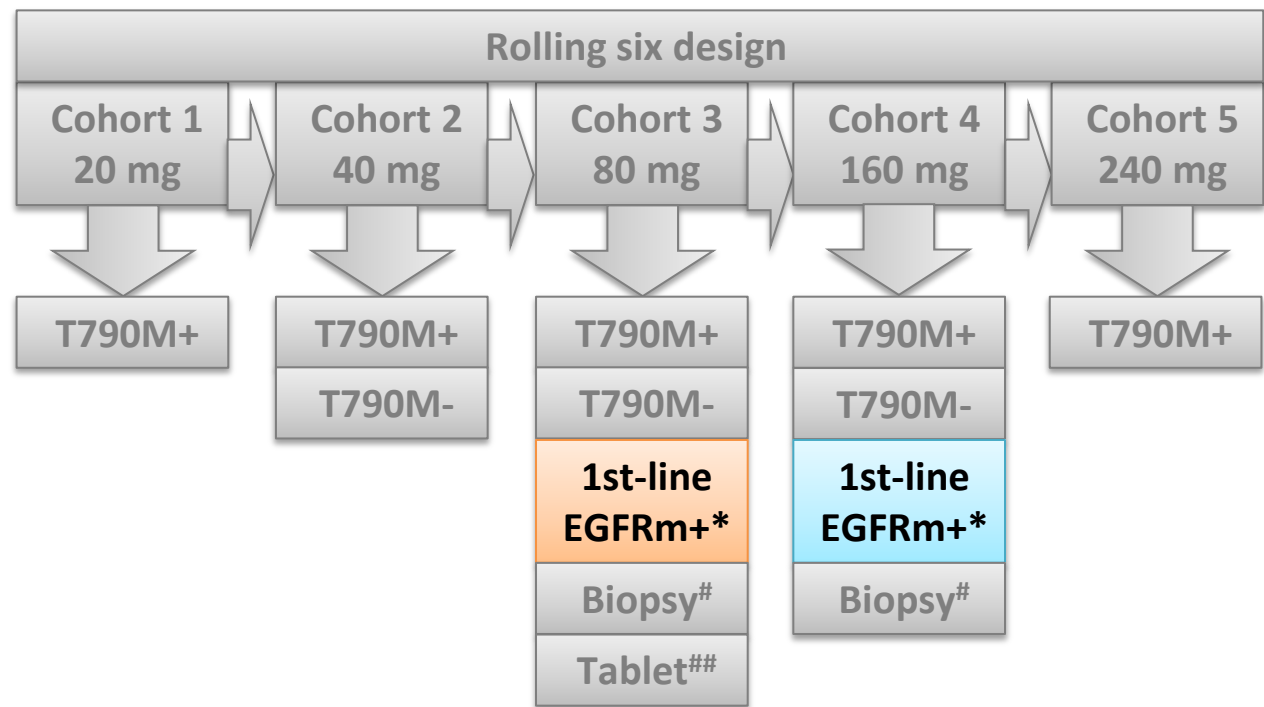# Phase I dose escalation/expansion study design (NCT01802632)

- For the first-line cohorts, patients with a documented EGFR-TKI-sensitising mutation and who have received no prior therapy for advanced stage NSCLC were enrolled
- Patients received AZD9291 once daily as an 80 mg or 160 mg capsule

Escalation
Not preselected by T790M status

Expansion
Enrollment by local testing followed by central laboratory confirmation (cobas EGFR Mutation Test) of T790M status or by central laboratory testing alone

Rolling six design				
Cohort 1 20 mg	Cohort 2 40 mg	Cohort 3 80 mg	Cohort 4 160 mg	Cohort 5 240 mg
T790M+	T790M+	T790M+	T790M+	T790M+
	T790M-	T790M-	T790M-	
		1st-line EGFRm+*	1st-line EGFRm+*	
		Biopsy#	Biopsy#	
		Tablet##		

*Prior therapy not permissible in this cohort. #Paired biopsy cohort patients with T790M+ tumours. ##Not selected by mutation status, US only.

Suresh S. Ramalingam et al, IASLC 2015

Tumor response in AZD9291 first-line cohorts by dose

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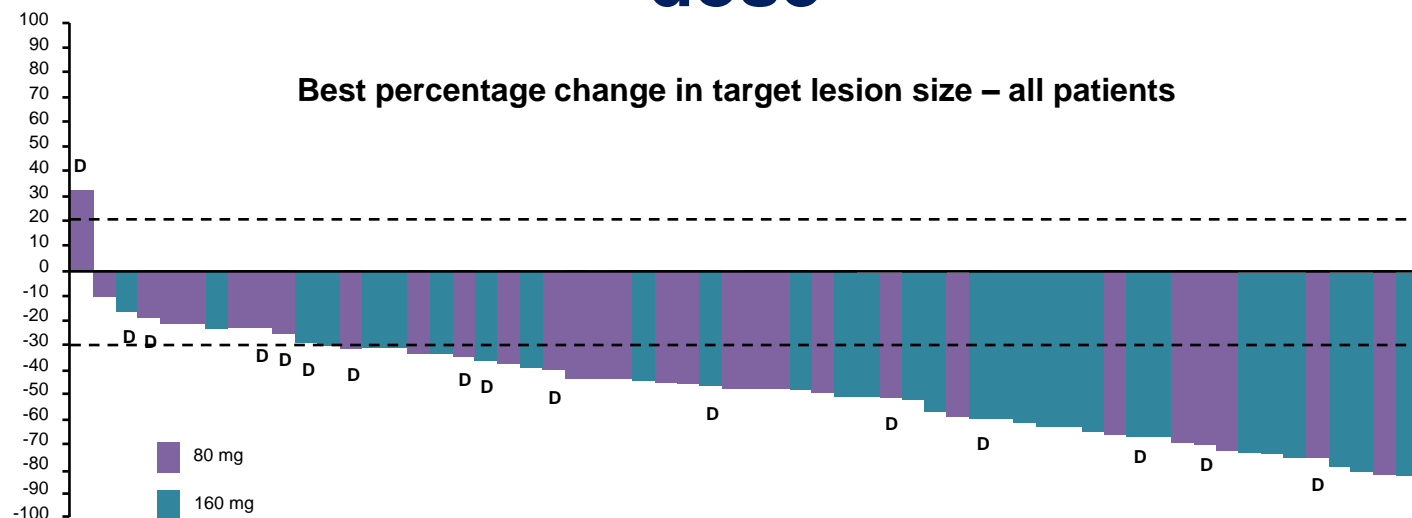
	80 mg N=30	160 mg N=30	Total N=60
Confirmed objective response rate	67% (95% CI 47, 83)	83% (95% CI 65, 94)	75% (95% CI 62, 85)
Disease control rate	93% (95% CI, 78, 99)	100% (95% CI 88, 100)	97% (95% CI 89, 100)
Best objective response			
Complete response	0	2*	2*
Partial response	20	23	43
Stable disease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

Suresh S. Ramalingam et al, IASLC 2015

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

Duration of response

Probability of response (y-axis: 0.0–1.0)
Month (x-axis: 0, 3, 6, 9, 12, 15, 18)

- AZD9291 80 mg
- AZD9291 160 mg
- Censored observation
- Censored observation

Number of patients at month:

	0	3	6	9	12	15	18
80 mg	20	20	17	14	10	5	0
160 mg	25	25	21	18	8	0	0

Progression-free survival

Probability of response (y-axis: 0.0–1.0)
Month (x-axis: 0, 3, 6, 9, 12, 15, 18)

- AZD9291 80 mg
- AZD9291 160 mg
- Censored observation
- Censored observation

Number of patients at risk:

	0	3	6	9	12	15	18
80 mg	30	26	23	22	19	12	3
160 mg	30	29	27	23	17	0	0

	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+

	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,	19.2+	13.8+	19.2+

LBA1_PR - Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC: updated efficacy and safety results from two Phase I expansion cohorts

S. Ramalingam[1], J. Yang[2], C. Lee[3], T. Kurata[4], D.-W. Kim[5], T. John[6], N. Nogami[4], Y. Ohe[4], P. Jänne[7]; [1]GA/US, [2]TW, [3]NSW/AU, [4]JP, [5]KR, [6]VIC/AU, [7]MA/US

Population: all
Progression eve
†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

Suresh S. Ramalingam et al, IASLC 2015

Adverse events (all causality) in AZD9291 first-line cohorts

AEs by preferred term (all grade) occurring in ≥25% of patients overall	All patients					
	80 mg N=30 n (%)		160 mg N=30 n (%)		Total N=60 n (%)	
	Any grade	Gr ≥3	Any grade	Gr ≥3	Any grade	Gr ≥3
Rash (grouped terms)	21 (70)	0	25 (83)	1 (3)	46 (77)	1 (2)
Diarrhea	18 (60)	0	26 (87)	2 (7)	44 (73)	2 (3)
Dry skin	12 (40)	0	12 (40)	0	24 (40)	0
Paronychia	9 (30)	0	15 (50)	2 (7)	24 (40)	2 (3)
Stomatitis	10 (33)	0	13 (43)	1 (3)	23 (38)	1 (2)
Fatigue	8 (27)	0	8 (27)	0	16 (27)	0
Decreased appetite	8 (27)	0	7 (23)	0	15 (25)	0
Nausea	7 (23)	1 (3)	8 (27)	0	15 (25)	1 (2)
Pruritus	8 (27)	0	7 (23)	0	15 (25)	0
Select AEs of interest						
ILD (grouped terms)	3 (10)	0	0 (0)	0	3 (5)	0
Hyperglycemia	1 (3)	0	2 (7)	0	3 (5)	0
QT prolongation	2 (7)	0	3 (10)	0	5 (8)	0

six Grade 2, 18 Grade ≥3, two currently ungraded. Of these, a total of four patients are reported to have died due to ILD (Grade 5)
Population: all dosed patients, data cut-off August 1, 2015
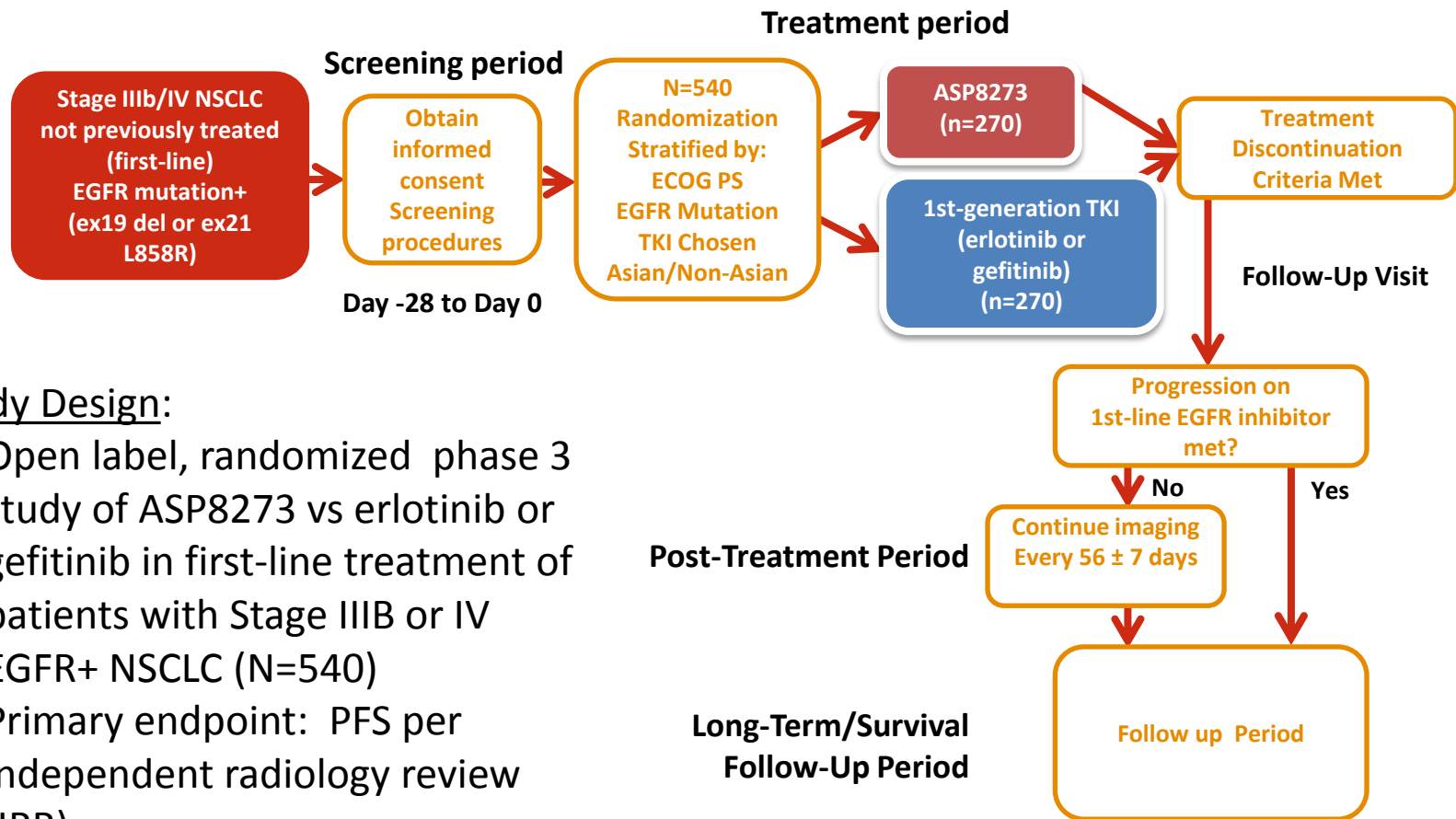AE, adverse event

FLAURA Study Design

Enrollment by local* or central# _EGFR_ mutation testing of biopsy sample

Stratified by:

Asian / non-Asian

Ex19del / L858R

Randomize patients 1:1

AZD9291 (80 mg p.o. qd)

EGFR-TKI standard of care##: gefitinib (250 mg p.o. qd) or erlotinib (150 mg p.o. qd)

RECIST 1.1 assessment every 6 weeks until objective progressive disease

Patients randomized to standard of care may receive AZD9291 after progression§

Primary objective: efficacy by PFS

*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
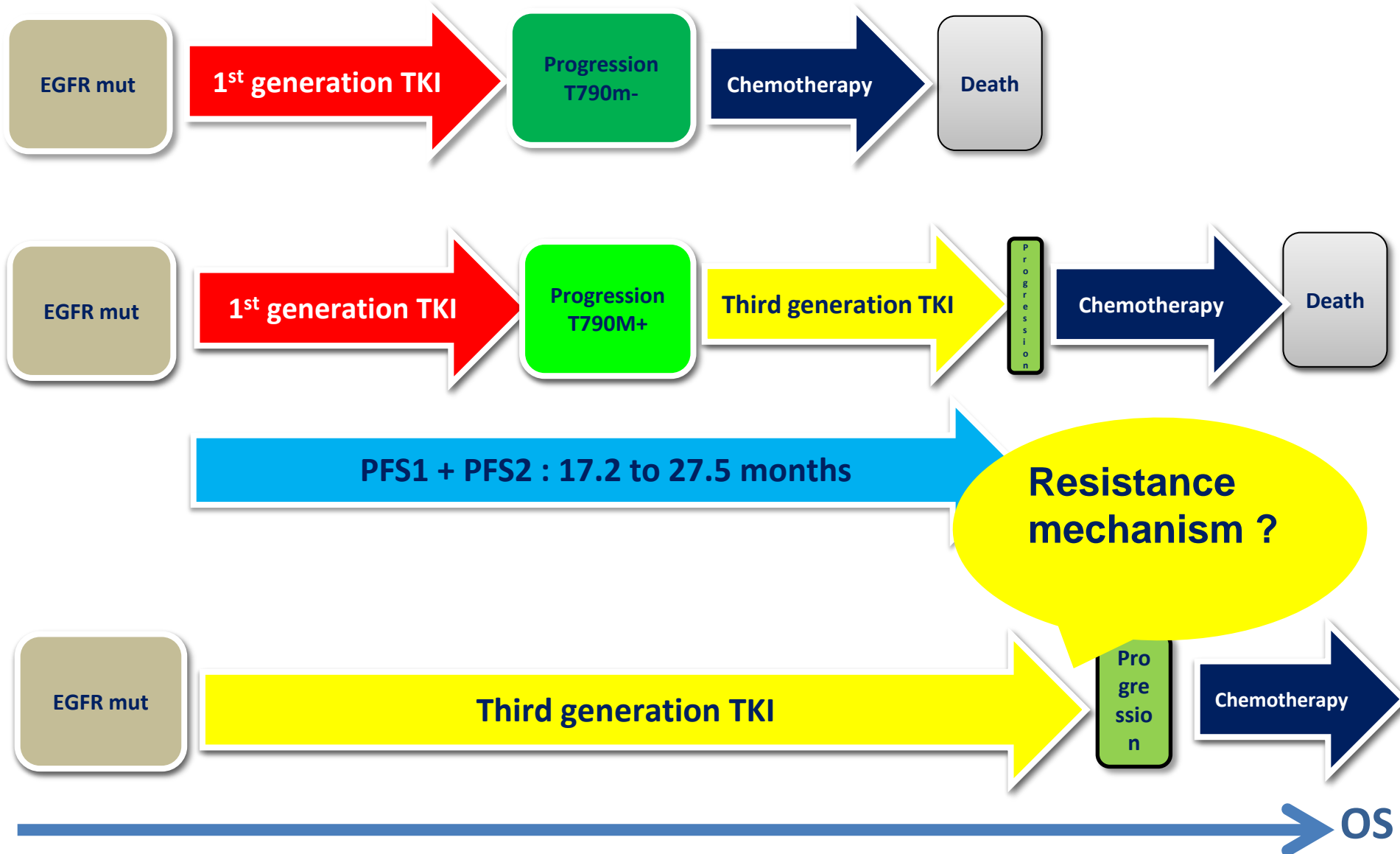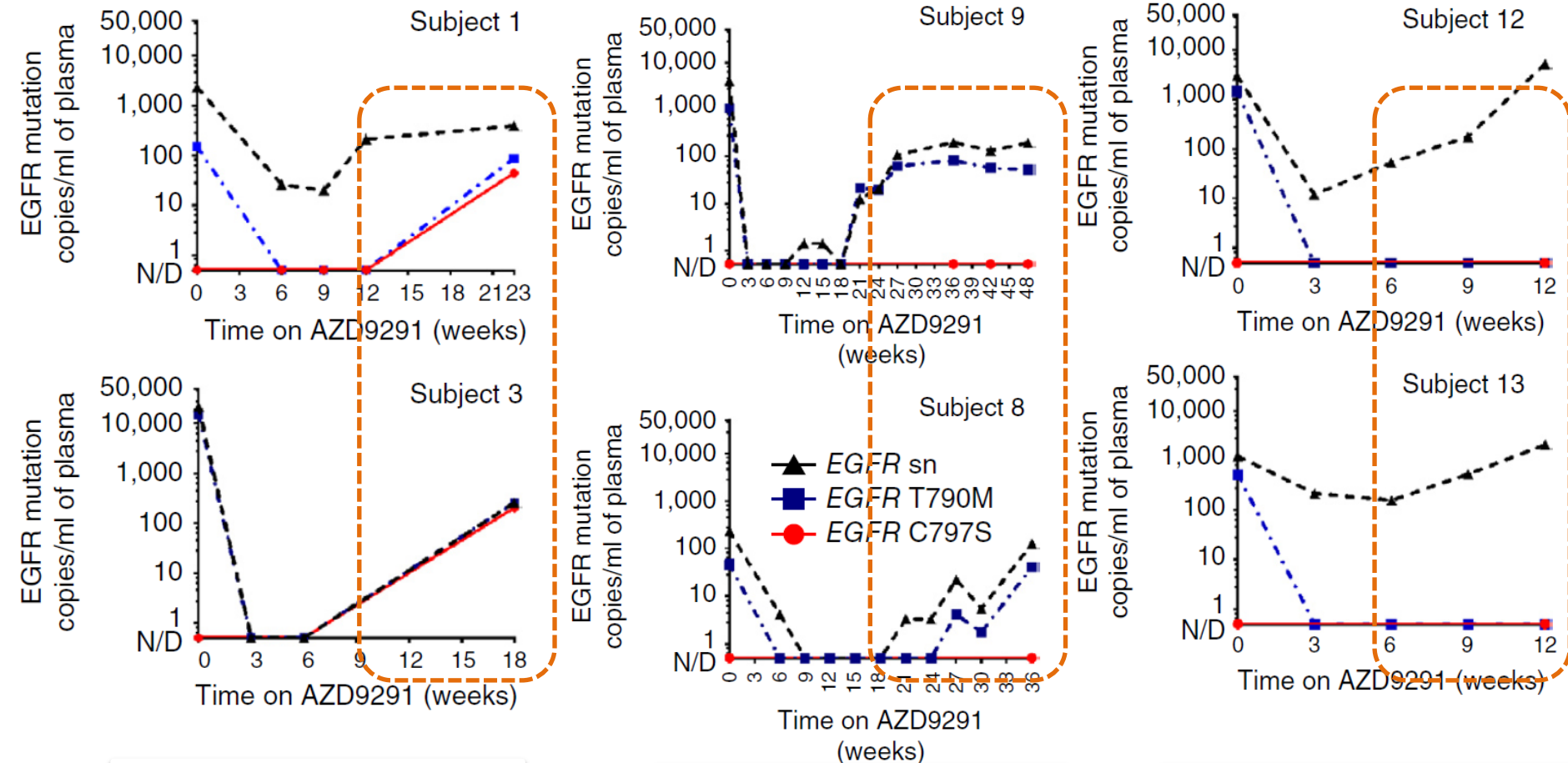
Phase 3 SOLAR Study Schematic (NCT02588261)

Treatment period

Screening period

Stage IIIb/IV NSCLC not previously treated (first-line) EGFR mutation+ (ex19 del or ex21 L858R)

Obtain informed consent Screening procedures

Day -28 to Day 0

N=540 Randomization Stratified by: ECOG PS EGFR Mutation TKI Chosen Asian/Non-Asian

ASP8273 (n=270)

1st-generation TKI (erlotinib or gefitinib) (n=270)

Treatment Discontinuation Criteria Met

Follow-Up Visit

Progression on 1st-line EGFR inhibitor met?

No **Yes**

Post-Treatment Period

Continue imaging Every 56 ± 7 days

Long-Term/Survival Follow-Up Period

Follow up Period

Study Design:

- Open label, randomized phase 3 study of ASP8273 vs erlotinib or gefitinib in first-line treatment of patients with Stage IIIB or IV EGFR+ NSCLC (N=540)
- Primary endpoint: PFS per independent radiology review (IRR)
- Key secondary endpoints: OS, ORR per IRR, PFS (inv), DCR

Astellas Pharma

What will be the magnitude of the PFS T790M inhibitor 1st line and resistence ?

EGFR mut → 1st generation TKI → Progression T790m- → Chemotherapy → Death

EGFR mut → 1st generation TKI → Progression T790M+ → Third generation TKI → Progression → Chemotherapy → Death

PFS1 + PFS2 : 17.2 to 27.5 months

Resistance mechanism ?

EGFR mut → Third generation TKI → Progression → Chemotherapy

OS

Tumor heterogeneity has important clinical implications

Kenneth S Thress et al, nature 2015

Allelic Context of C797S Mutation Acquired Impacts Sensitivity to Subsequent Treatment Strategies

Matthew J. Niederst et al, CCR 2015
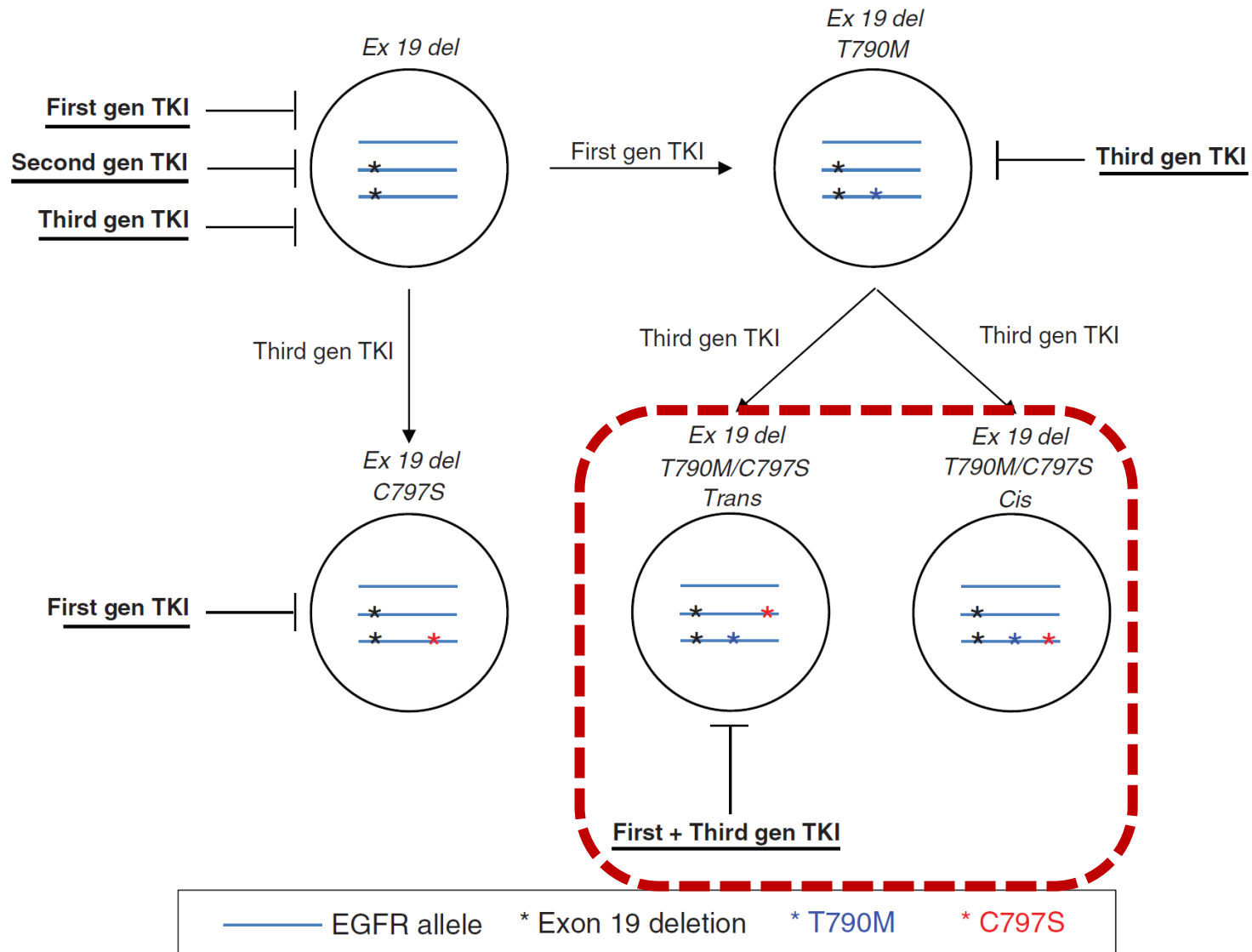
Phase I of AZD9291 in combinaition or alternating with gefitinib in EGFR inhinitor naive EGFR mutant lung cancer

Patients

- ECOG PS 0-2
- Histologically confirmed Stage IV NSCLC with activating *EGFR* mutation (L858R or exon 19 del)
- EGFR TKI naïve
- No untreated or uncontrolled CNS disease
- Any lines of prior systemic therapy
- Eligible for repeat biopsy at resistance

→

AZD9291 & Gefitinib X 28 days

→

AZD9291 x 28 days alternating with gefitinib X 28 days

→

Objectives

Primary
- Feasibility of combination or alternating therapy for 6 cycles

Secondary
- Rate of grade 3/4 events
- ORR
- PFS
- Rate of change of plasma EGFR mutation(s) over time
- Proportion of patients who become plasma "negative" for EGFR activation mutation
- Tumor cfDNA burden resistance over time and correlation with PFS
- Evaluation of resistance mechanisms

Amanda Redig - DFCI

Inhibitor of anti-apoptotic factors BCL-xL and BCL-2 enhances apoptotic response of late-resistant EGFRT790M cells

% Tumor response
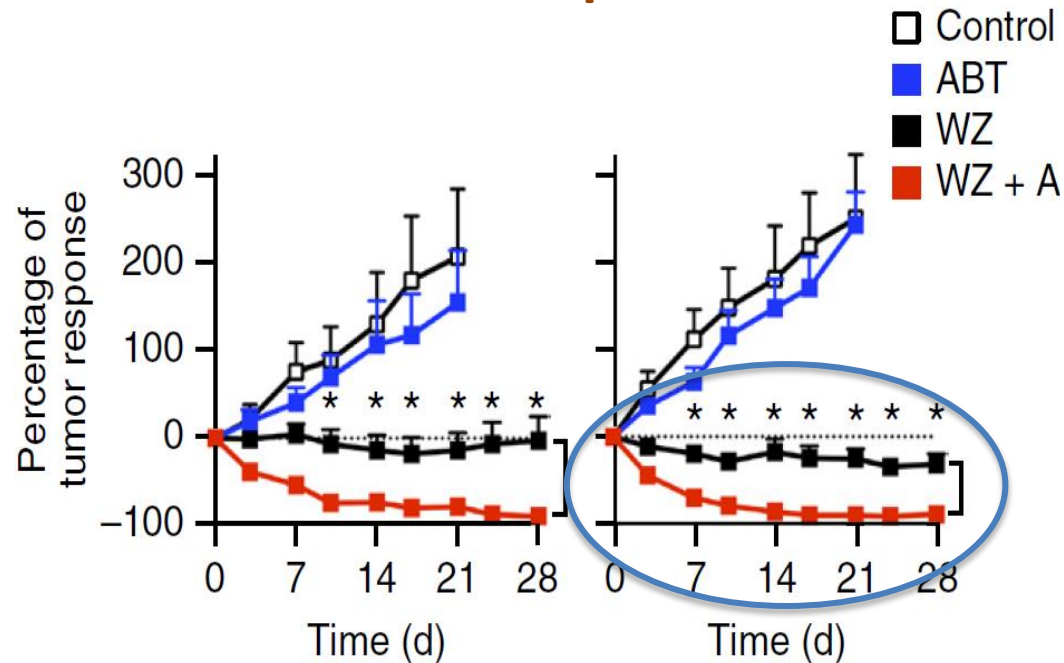
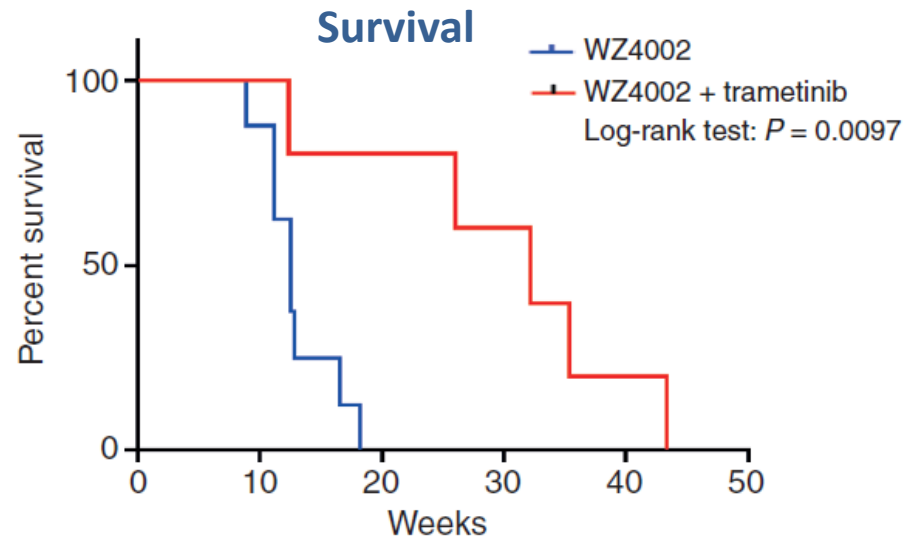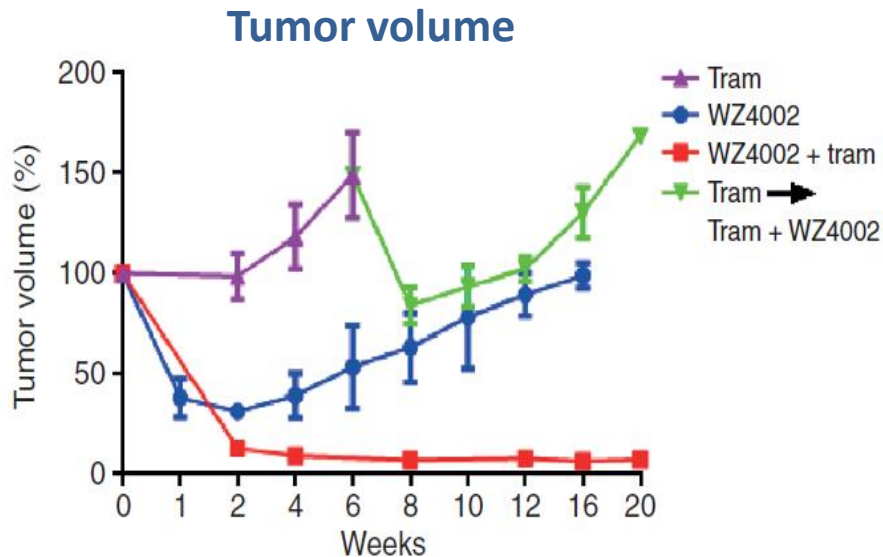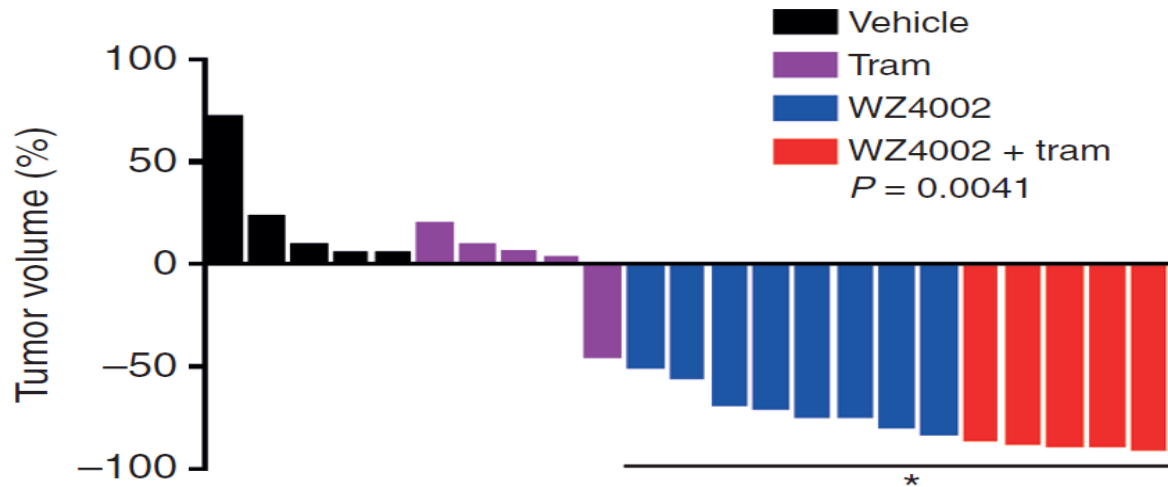**% Apoptosis**
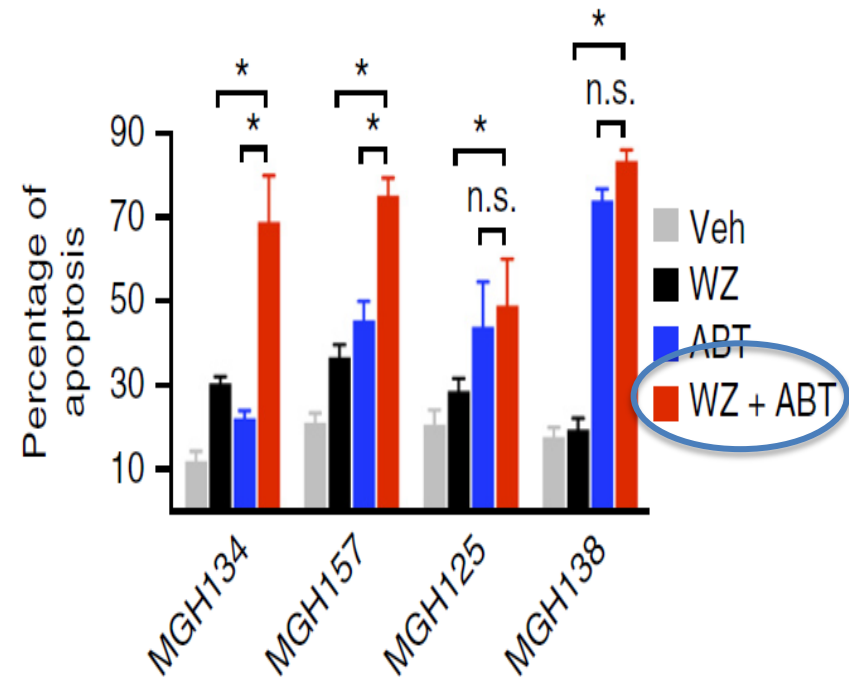
Cotargeting EGFR and MEK
prolongs effective treatment duration in EGFR L858R/T790M genetically engineered mice

Erin M. Tricker et al, cancer discovery 2015

Osimertinib + Durvalumab: Toxicity (TATTON study)

- AZD9291 + durvalumab combination regimens have demonstrated a comparable safety profile with AZD9291 and durvalumab in patients with advanced NSCLC

AEs*	3 mg/kg (Asia) n=6		3 mg/kg (ROW) n=7		10 mg/kg (Asia) n=4		10 mg/kg (ROW) n=6	
Number of events, n	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhoea	4					0	0	0
Vomiting	6					0	0	0
Anaemia	3					0	2	0
Constipation	3					0	1	0
Cough	1					0	3	0
Nausea	3					0	3	0
WBC count decreased	4					1	0	0

3 cases of pneumonitis reported at ASCO in 23 patients

136O - Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: Results from the TATTON phase Ib trial

M.-J. Ahn[1], J. Yang[2], H. Yu[3], H. Saka[4], S. Ramalingam[5], K. Goto[4], S.-W. Kim[1], L. Yang[6], A. Walding[7], G. Oxnard[8]; [1]KR, [2]TW, [3]NY/US, [4]JP, [5]GA/US, [6]CN, [7]GB, [8]MA/US

*Occurring in ≥3 instances at any dose
Oxnard GR, et al. J Clin Oncol 2015;33:(suppl abstract 2509).

Rociletinib Clinical Development Program

Front-line

TIGER-1 (Phase 2)
- Randomized rociletinib vs erlotinib
- Includes front-line, treatment-naïve patients
- Enrollment complete

NCT02630186 (Phase 1b/2)
- Rociletinib in combination with MPDL3280A (atezolizumab)
- First and later line patients
- Enrollment open in USA; enrollment in France opens soon

TIGER-2 (Phase 2)
- Single-arm, single-agent rociletinib
- 2nd-line EGFR mutant NSCLC
- Enrollment complete

Late-line

TIGER-X (Phase 1/2)
- Single-arm, single-agent rociletinib
- ≥2nd-line patients who have received ≥1 prior EGFR-directed therapy
- Enrollment complete

TIGER-3 (Phase 3)
- Randomized rociletinib vs single-agent chemotherapy
- >2nd-line EGFR mutant NSCLC; T790M-positive and negative patients
- Enrollment open

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Conclusion

- **Drug resistance** limits the long term sucess of even the most effective targeted therapies

- **Prevention** may be a better stategy than treatment of resistance

- Best treatment strategy needs to be both effective and tolerable

- **In treatment-naïve patients with EGFRm positive** advanced NSCLC, Osimertinib demonstrates encouraging clinical activity and a manageable tolerability profile

- **Role of tumor heterogeneity** with EGFR T790M + and - cancer cells can both pre-exist and evolve from drug-tolerant cells

- To further improve outcomes, combination regimens that prevent or overcome resistance might be needed in first line

THANK YOU!

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Thierry Le Chevalier

david.planchard@gustaveroussy.fr