Targeting T790M

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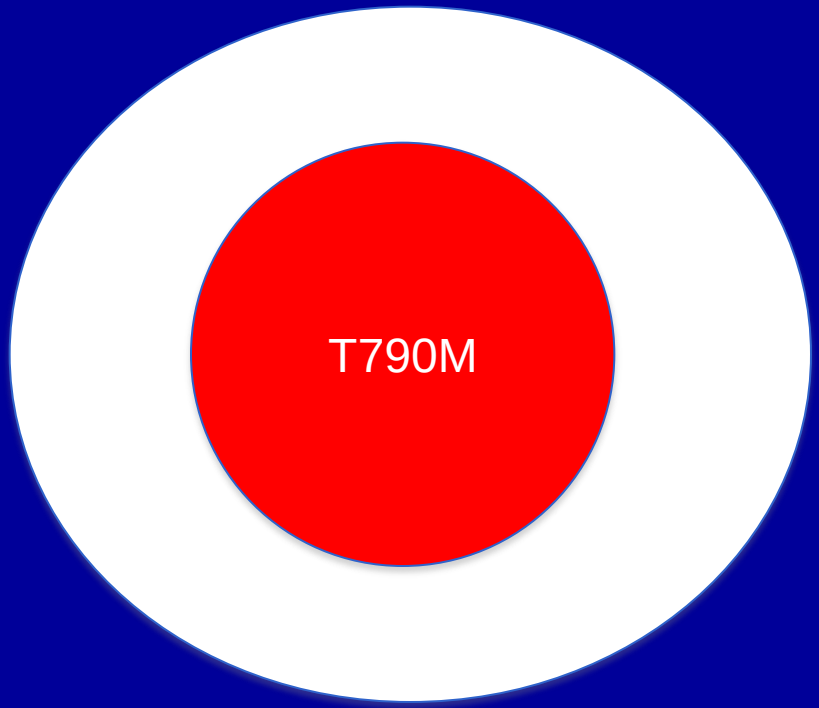
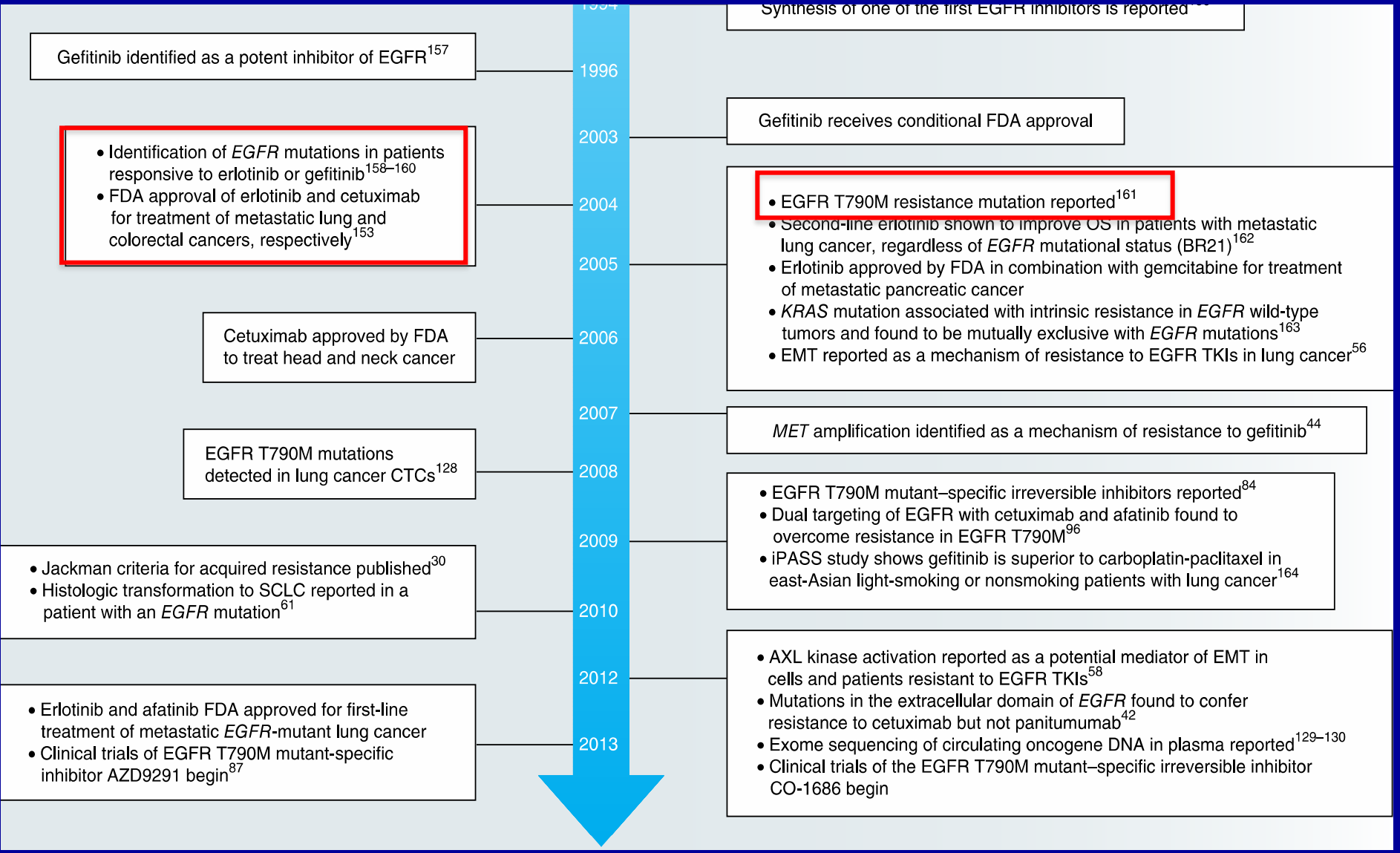

T790M

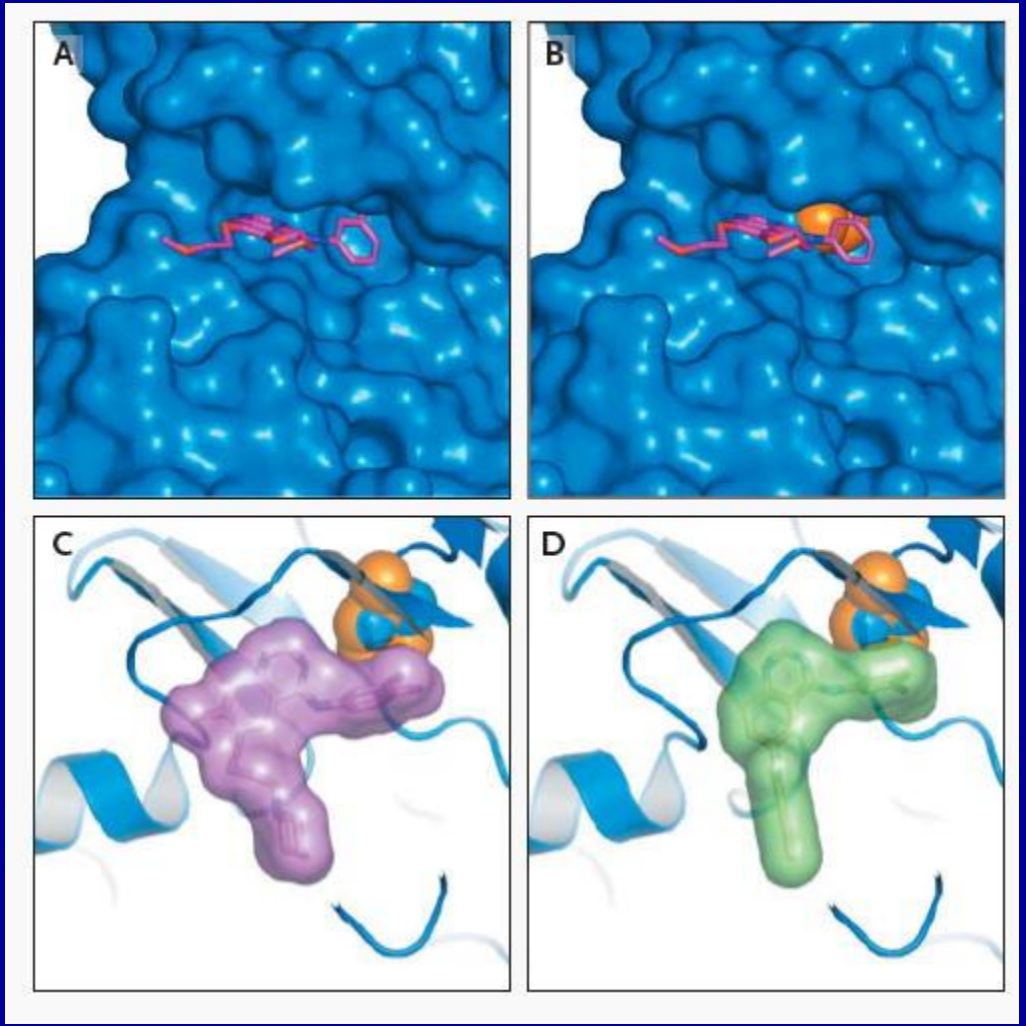
Historic Time Line of EGFR mutations



Chong and Janne Nature Medicine 2013

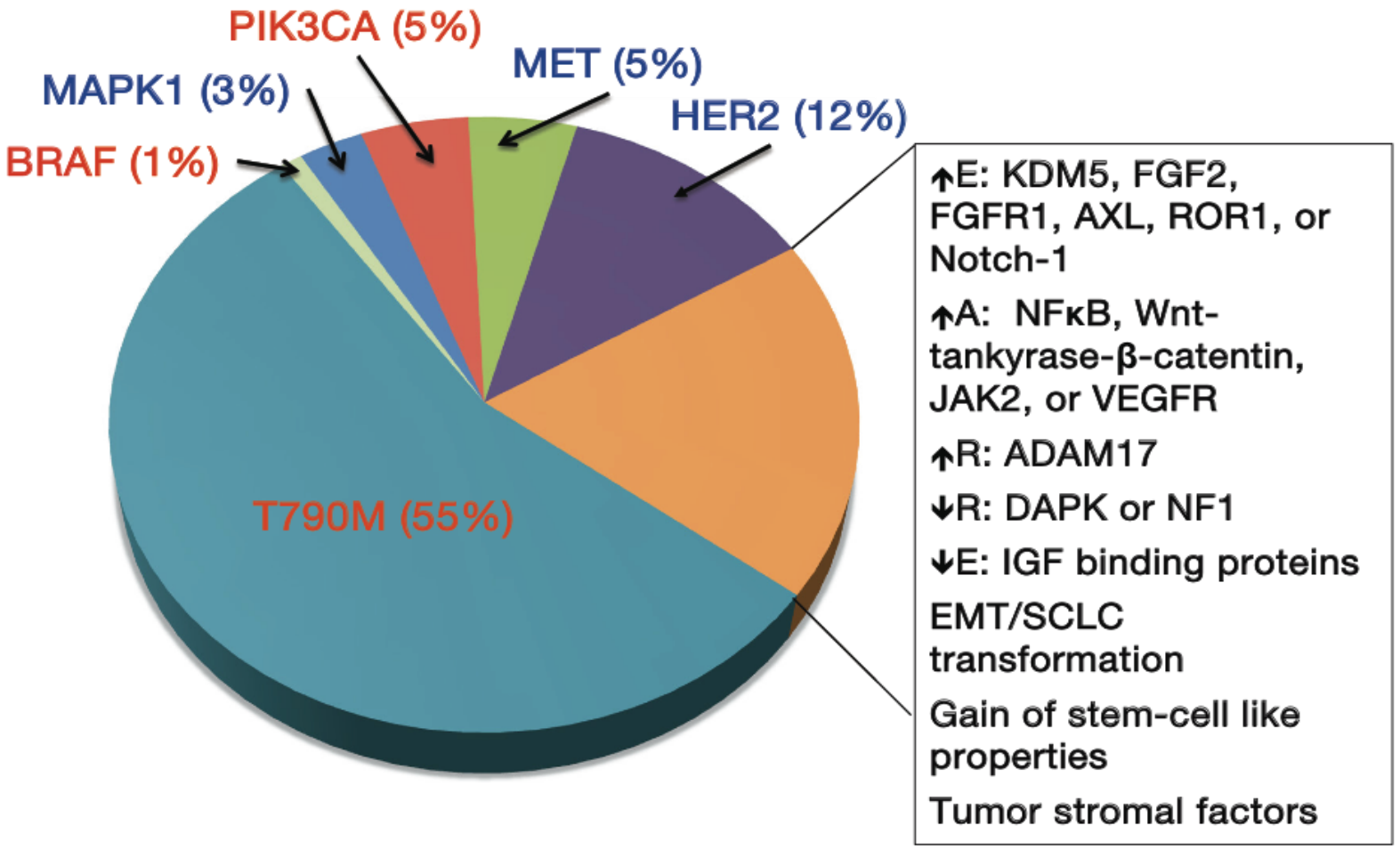
Gatekeeper Mutation: T790M

- Acquired point mutation resulting in threonine-to-methioine amino acid change at position 790
- Restore the TKI binding capacity to wild type level
- T790M may lower the growth kinetic of cancer cell



Kobayashi S NEJM 352:786, 2006

Mechanism of resistance



Oxnard et al CCR 17:5530, 2011
Sequist et al Sci Trans Med, 2011
Stewart et al Translational Lung Cancer 2015

de-Novo T790M may exist at presentation

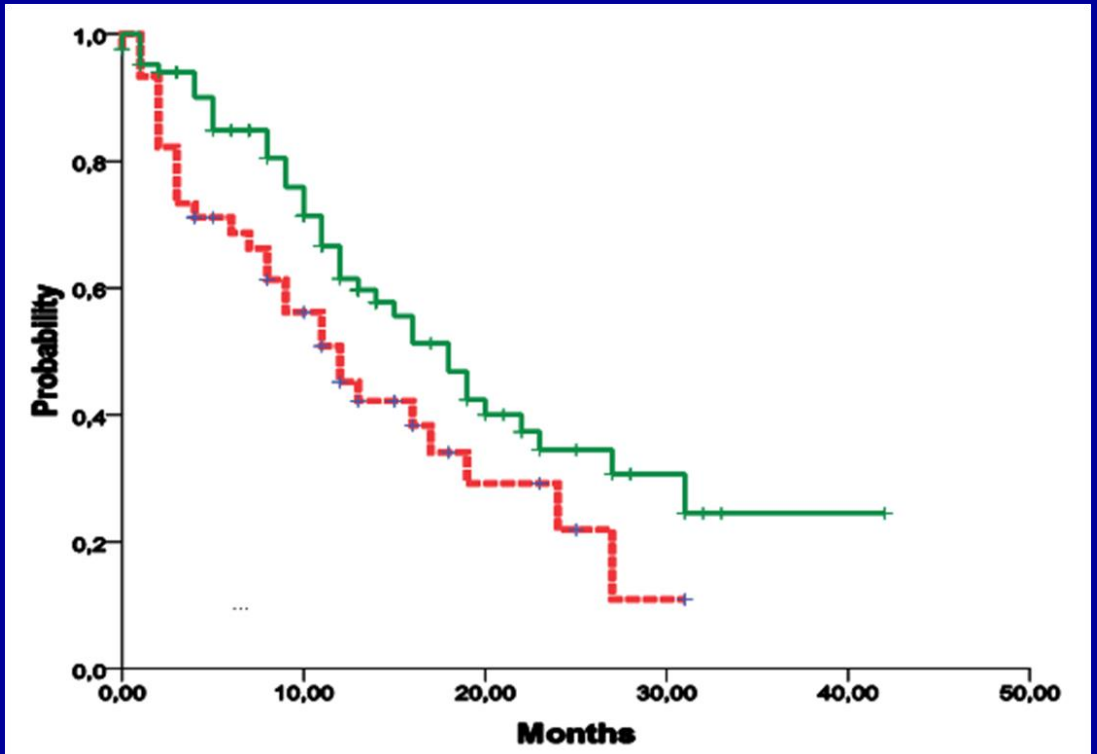
EXON 18	EXON 19	EXON 20	EXON 21
G719X (3%)	LREA deletion (45%)	V765A (<1%)	L858R (40%)
	VAIKEL insertion (1%)	T783A (<1%)	L861X (2%)
	L747S (<1%)	V774A (<1%)	T854A (<1%)
	D761Y (<1%)	S784P (<1%)	A871E (<1%)
		T790M *	
		Exon 20 insertion (4%)	
		V769M (<1%)	
		V769M (<1%)	

De-novo T790M mutation

Mutation	Frequency in *EGFR*-mutant lung adenocarcinoma (%)	Clinical properties			
		Response rate to EGFR TKIs		Median PFS	
		%	Reference	Months	Reference
Exon 19 deletions	45	82.8	13	11.5	13
		84.8	170	9.0	14
		63	171	11	12
		64	172	14.6	171
		70	173	12	174
				9.3	172
				9.8	173
L858R (exon 21)	40	67.3	13	10.8	13
		60.9	170	9.6	14
		50[a]	171	8.4[b]	12
		62	172	9.7	171
				5	174
				6.9	172
Exon 20 insertions	2–9	The variable response to EGFR TKIs is thought to be related to the effect of varyi pocket[175]. Median OS of 16 months[176] in one series and 4 years in another[177]			
G719X	3	~50	178	8.1	179
L861X	2	60	179	6	
Exon 19 insertions	1	Case series report responsiveness to erlotinib[180]			
T790M	0.5–3 (in some case series)	Associated with lack of response to EGFR TKIs in patients with *EGFR*-activating m			

[a]*P* = 0.39 compared to exon 19 deletions in this series. [b]*P* = 0.075 compared to exon 19 deletions in this series. [c]*P* = 0.65 compar

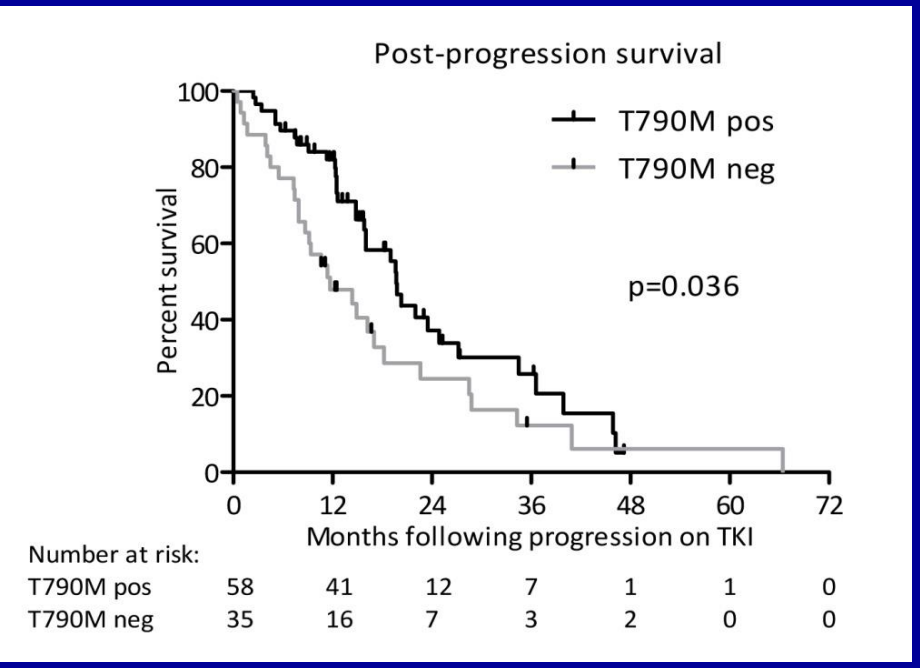
SLCG: Implication of de-novo T790M



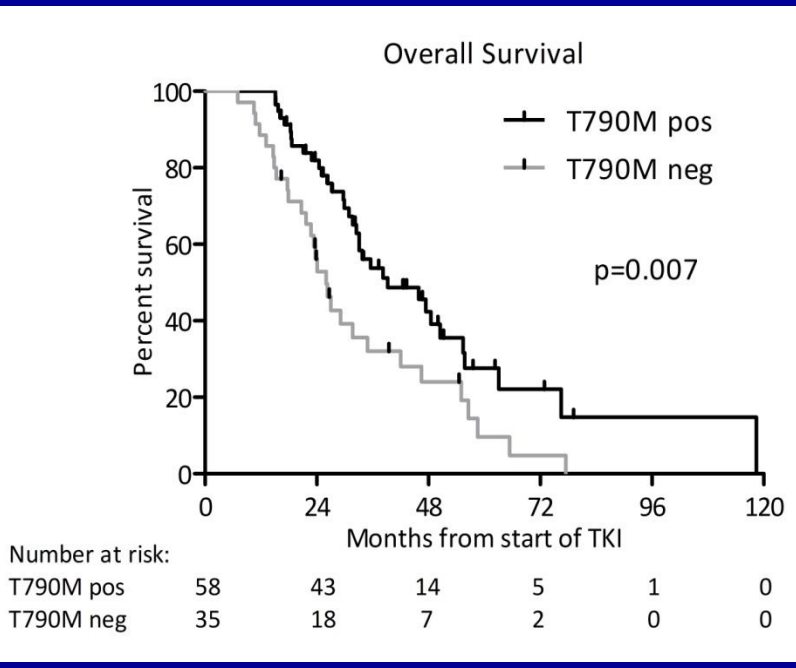
	N	Median	95% CI	P Value
T790M positive	45	12	7.6-16.4	0.05(*)
T790M negative	84	18	14.1-21.9	

Rosell et al ASCO 2010

Implication of “acquired T790M”



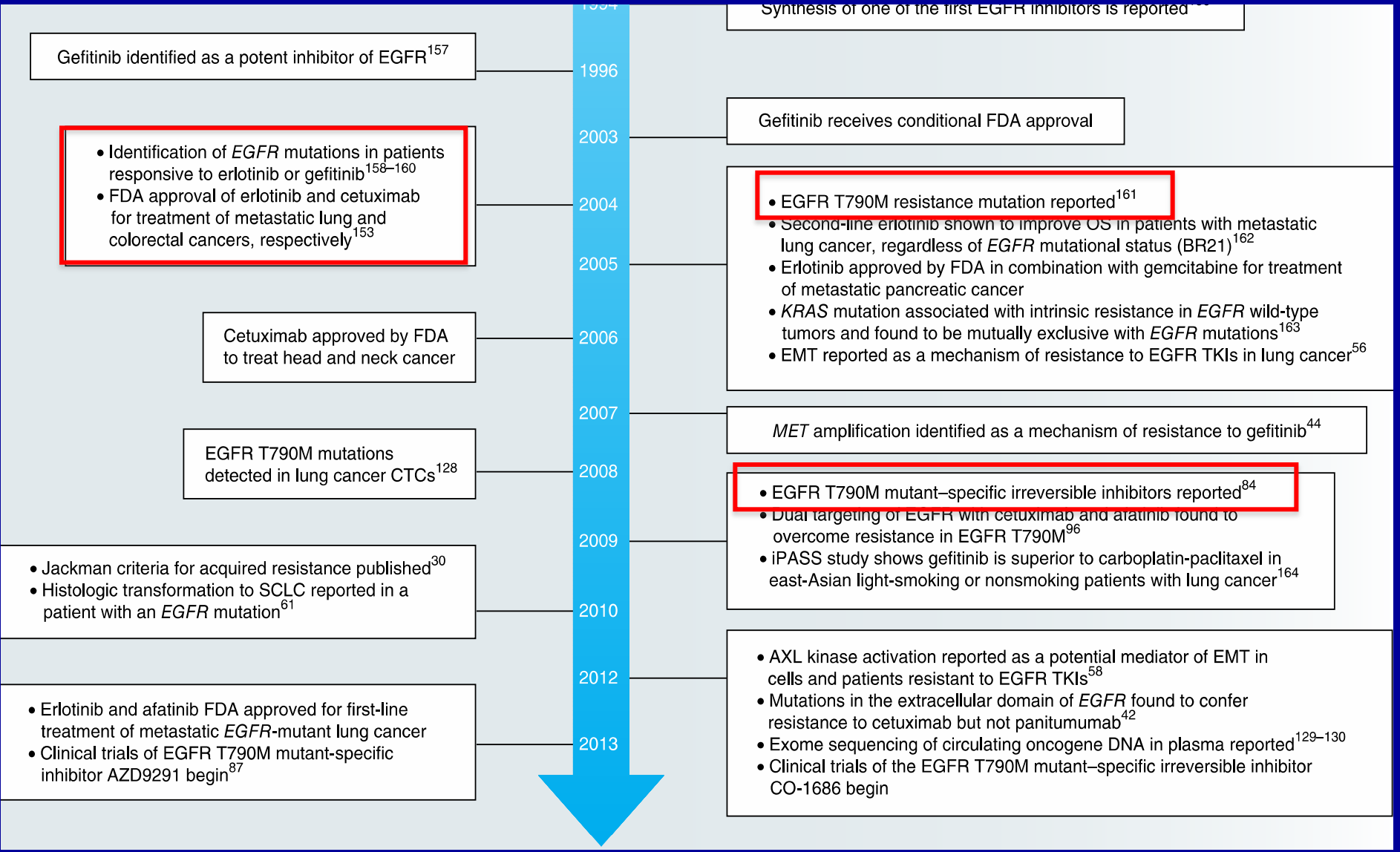
Median T790M pos = 19 months
Median T790M neg = 12 months



Median T790M pos = 39 months
Median T790M neg = 26 months

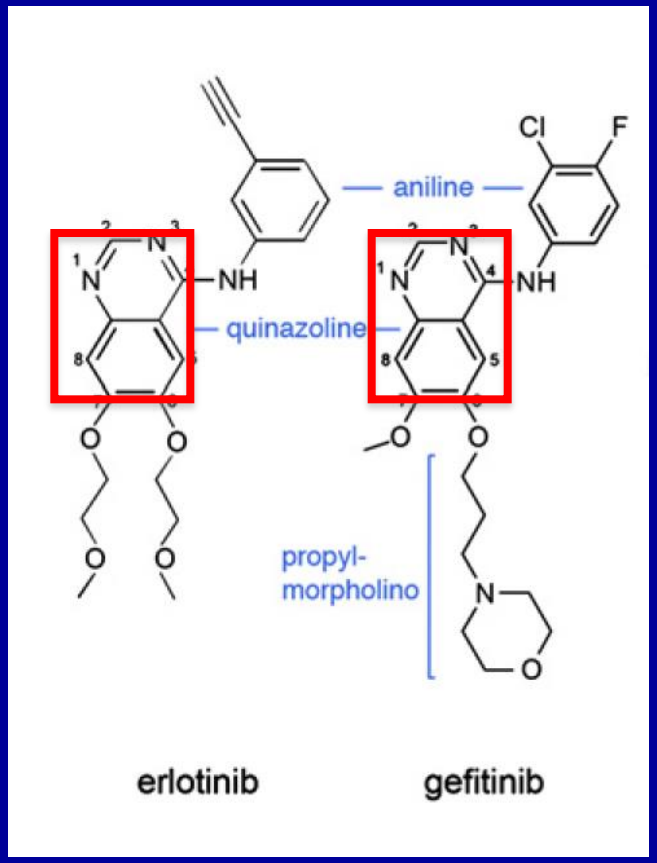
Oxnard et al CCR 17:1616, 2011

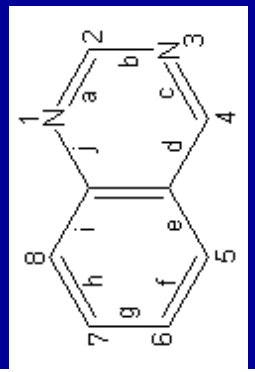
Historic Time Line of EGFR mutations



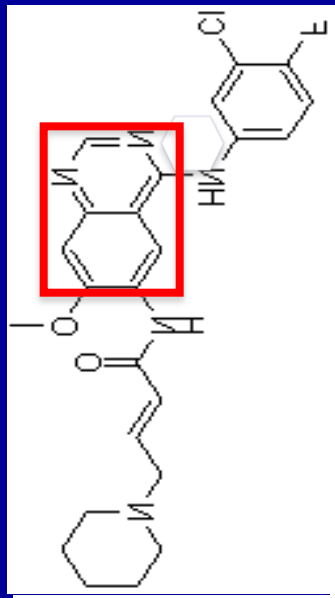
Chong and Janne Nature Medicine 2013

Quinazoline-based TKI

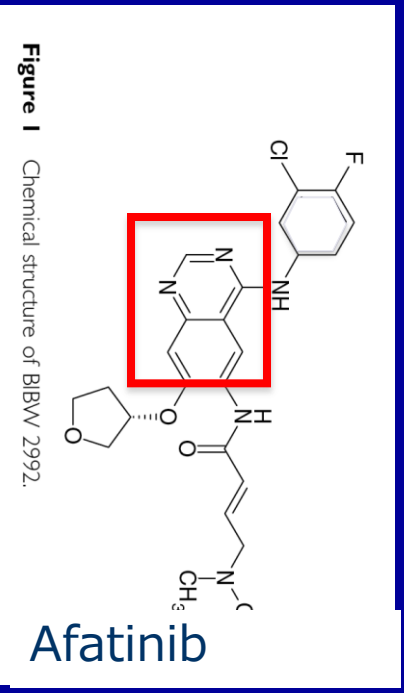




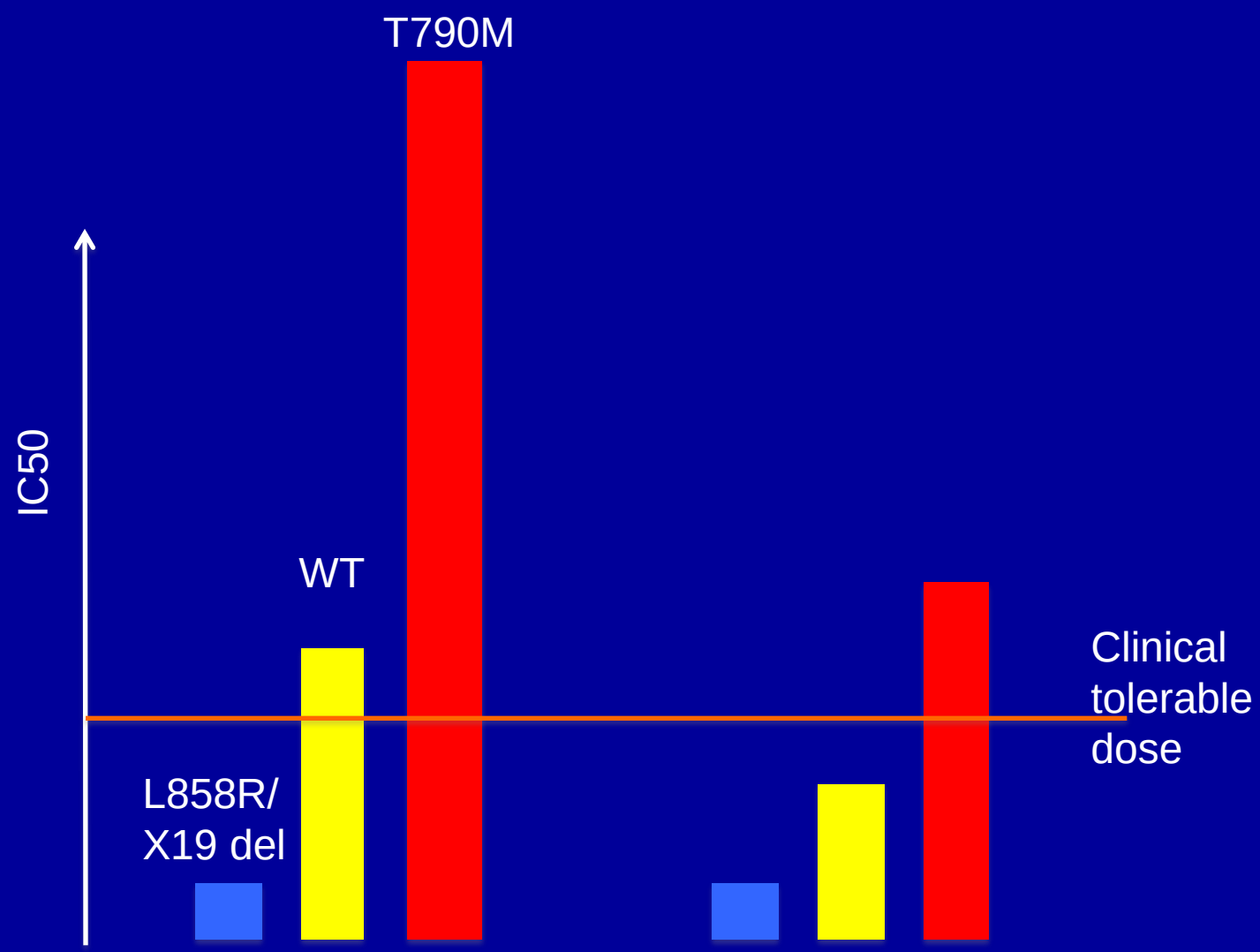
quinazoline



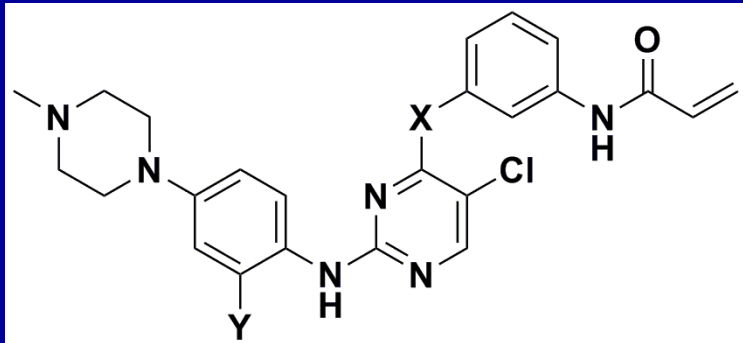
Dacomitinib



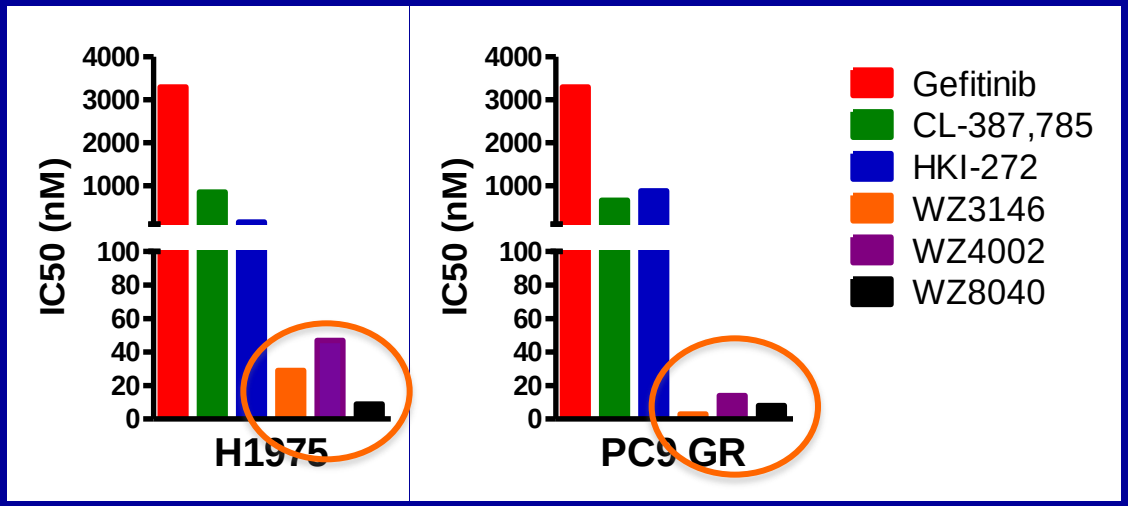
Afatinib


1st generation
gefitinib, erlotinib
2nd generation
Afatinib, dacomitinib
T790M
IC50
WT
L858R/
X19 del
Clinical
tolerable
dose

Pyrimidine-based TKI

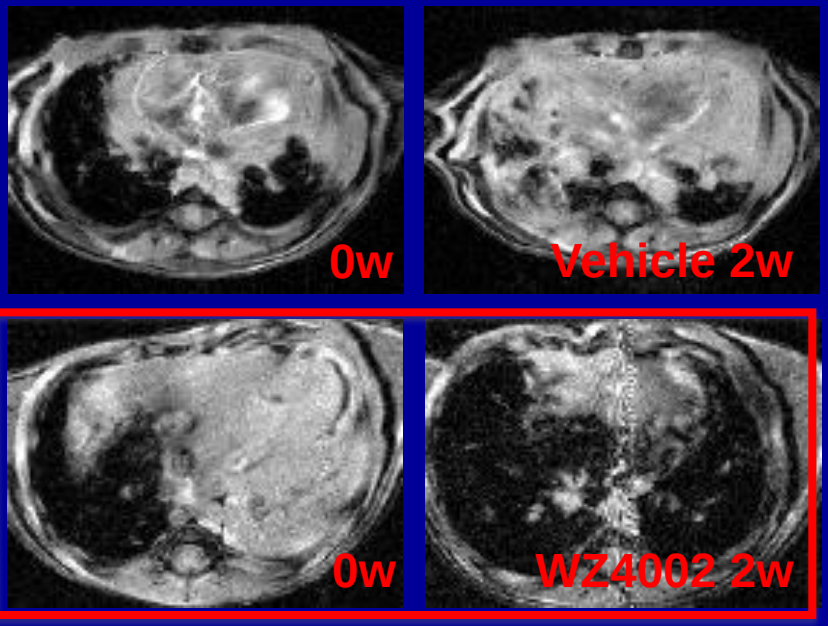


WZ3146 X=O, Y=H
WZ4002 X=O, Y=OMe
WZ8040 X=S, Y=H

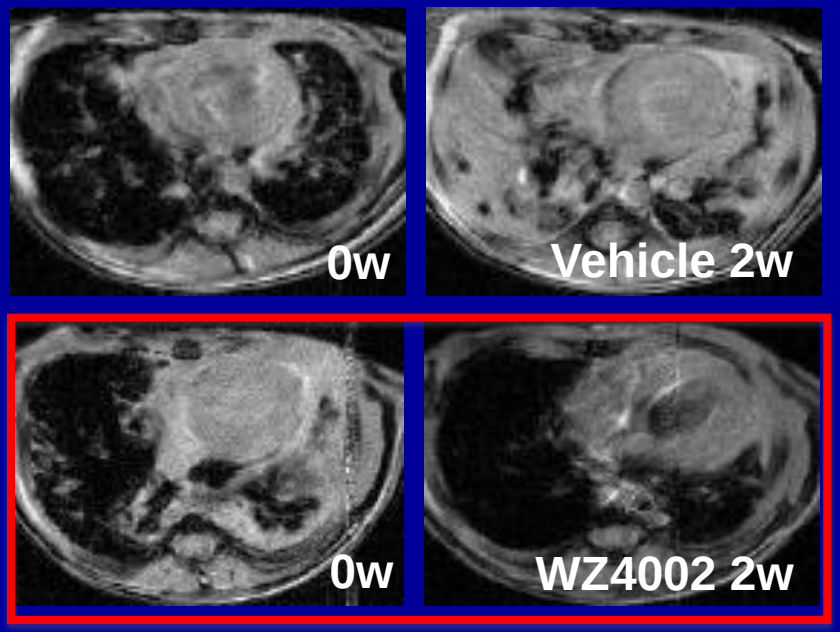


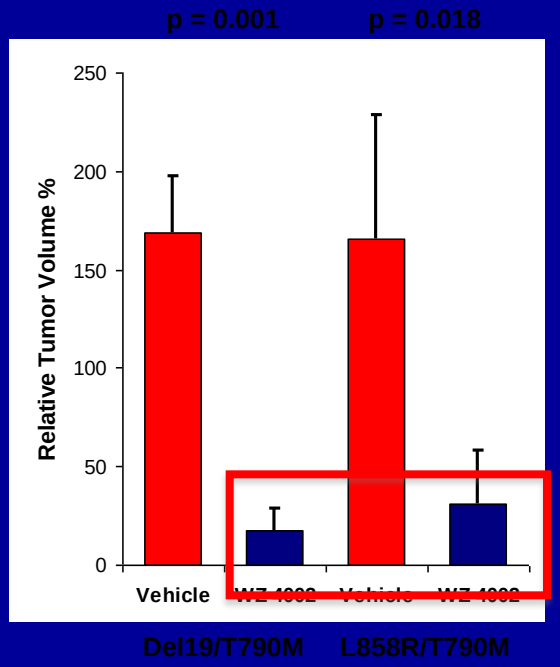
Zhou and Janne Nature 2009

L858R/T790M

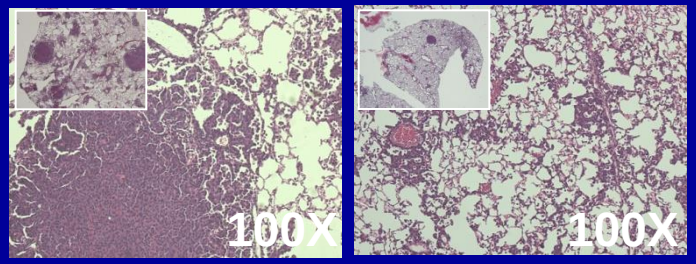


Del19/T790M

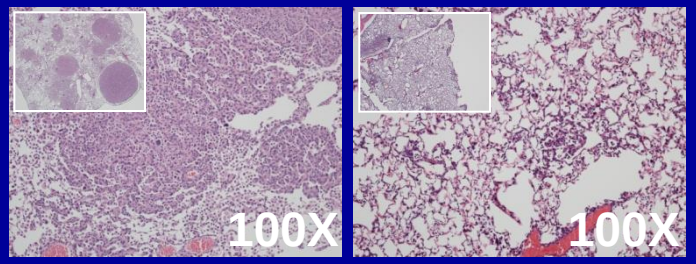




L858R/T790M



Del19/T790M

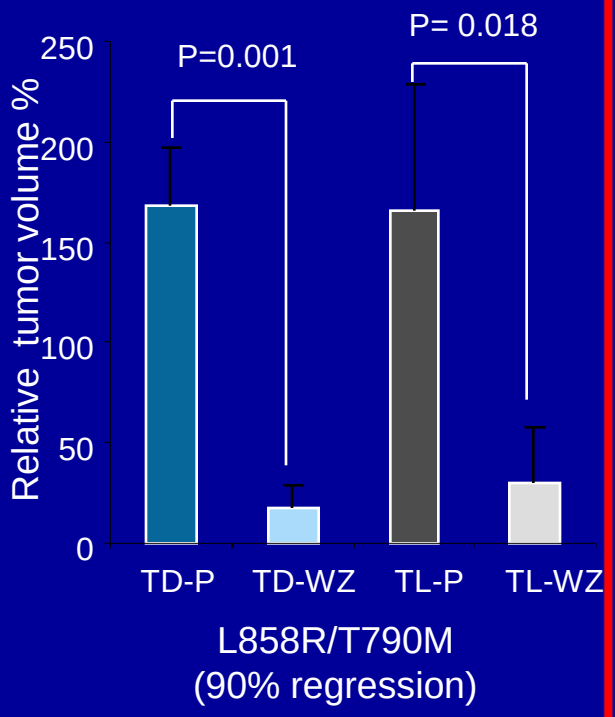


Vehicle WZ4002

Zhou et al. Nature 2009

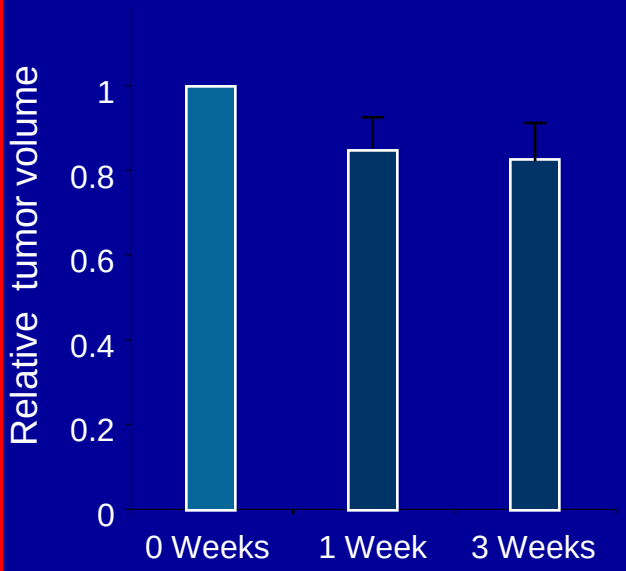
Superior to Efficacy Relative to Clinical Agents in Mouse Models

WZ4002



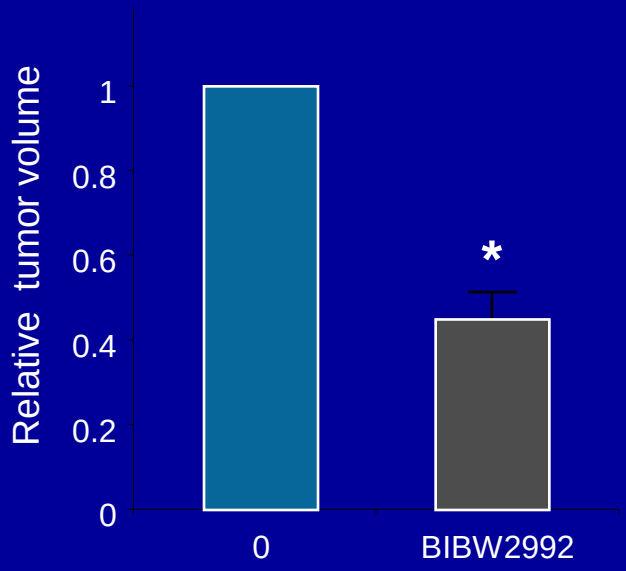
L858R/T790M
(90% regression)

HKI-272



L858R/T790M
(20% regression)

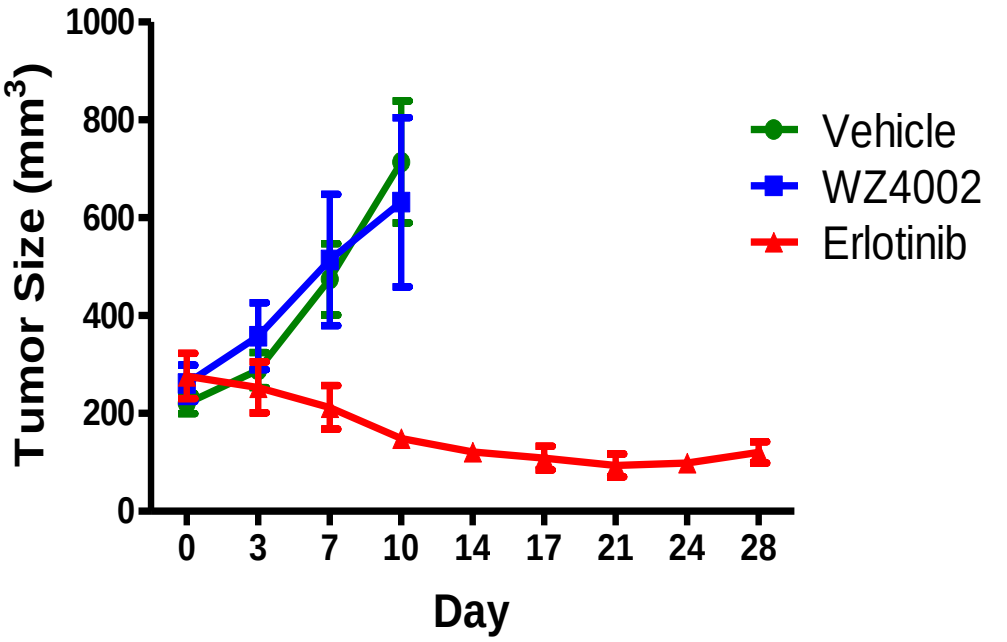
BIBW-2992



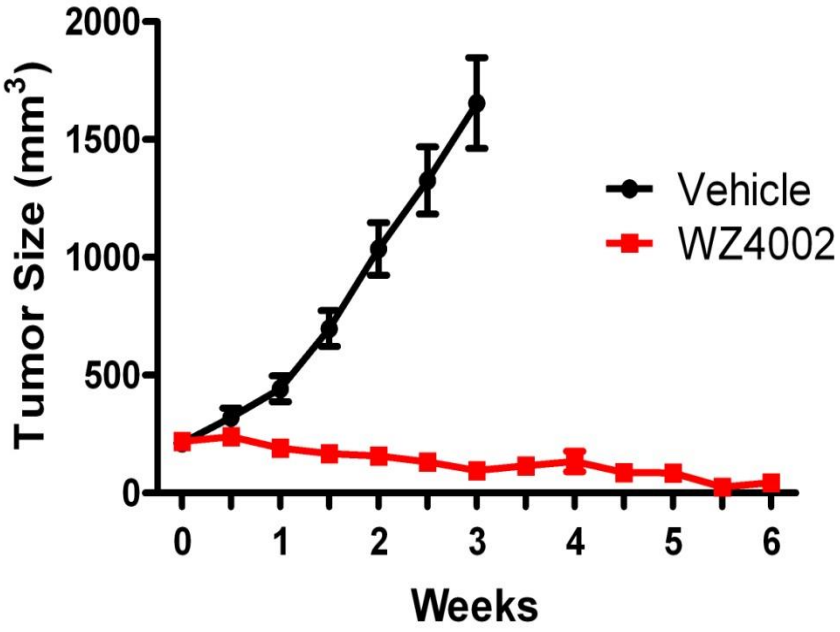
L858R/T790M
(50% regression)

Kwok-Kin Wong, Liang Chen

WZ4002 does not inhibit EGFR WT



A431 Cells
EGFR WT & amplified



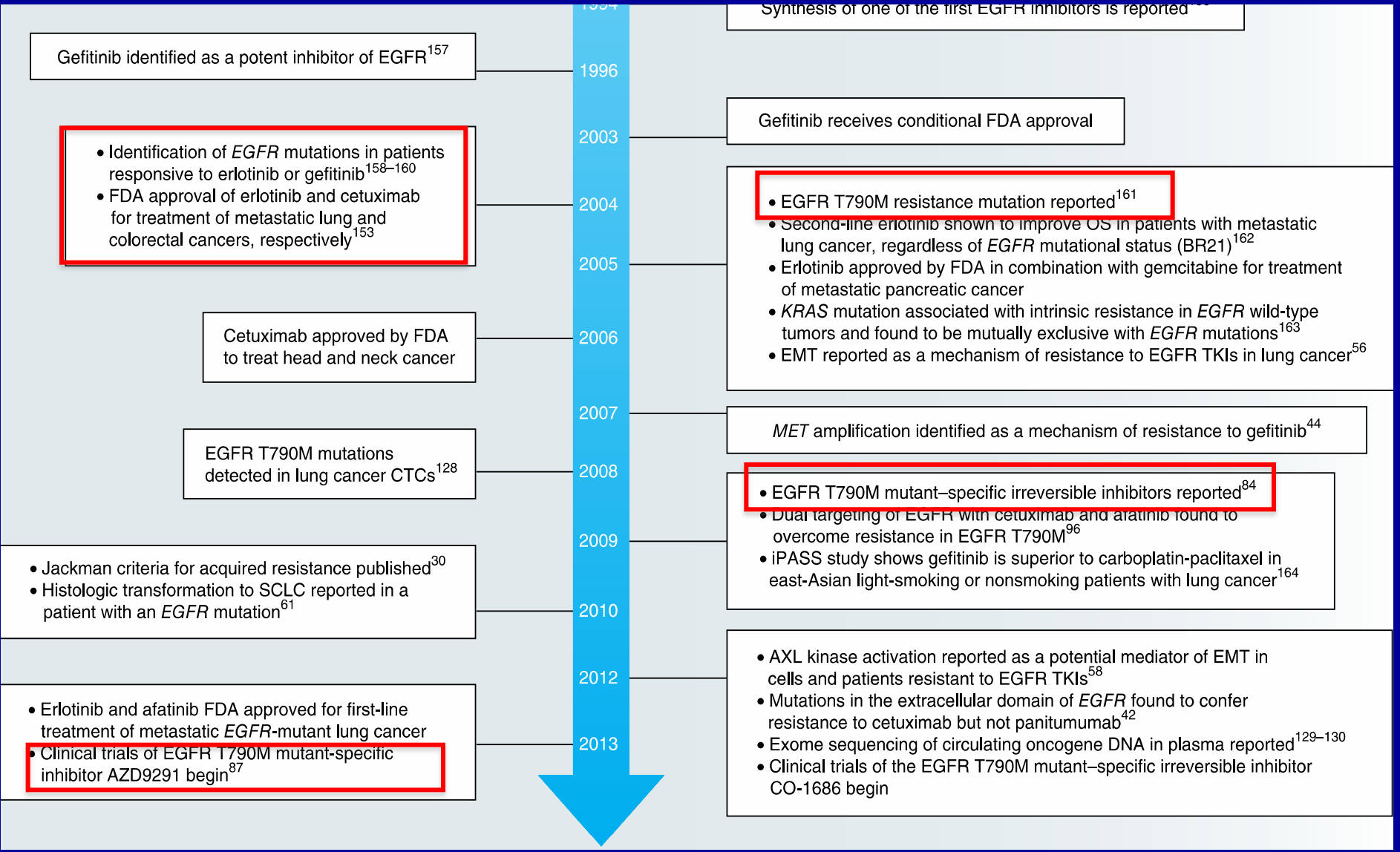
PC9 GR4 Cells
EGFR Del 19/T790M

Third Generation EGFR Inhibitors

Drug	Company	Clinical Stage	Covalent	Structure
WZ4002	DFCI	Tool compound	Yes	Pyrimidine
AP26113	Ariad	Phase I/II	No	Pyrimidine
CO-1686*	Clovis	Phase II/III	Yes	Pyrimidine
AZD9291*	Astra Zeneca	Phase II/III	Yes	Pyrimidine
HM61713	Hanmi	Phase I	Yes	Pyrimidine
ASP8273	Astellas	Phase I	Yes	Pyrimidine
EGF816	Novartis	Phase I	Yes	?
Avitinib	Acea Bio	Phase I	?	?
PF-06747775	Pfizer	Phase I	?	?

*FDA Breakthrough designation

Historic Time Line of EGFR mutations

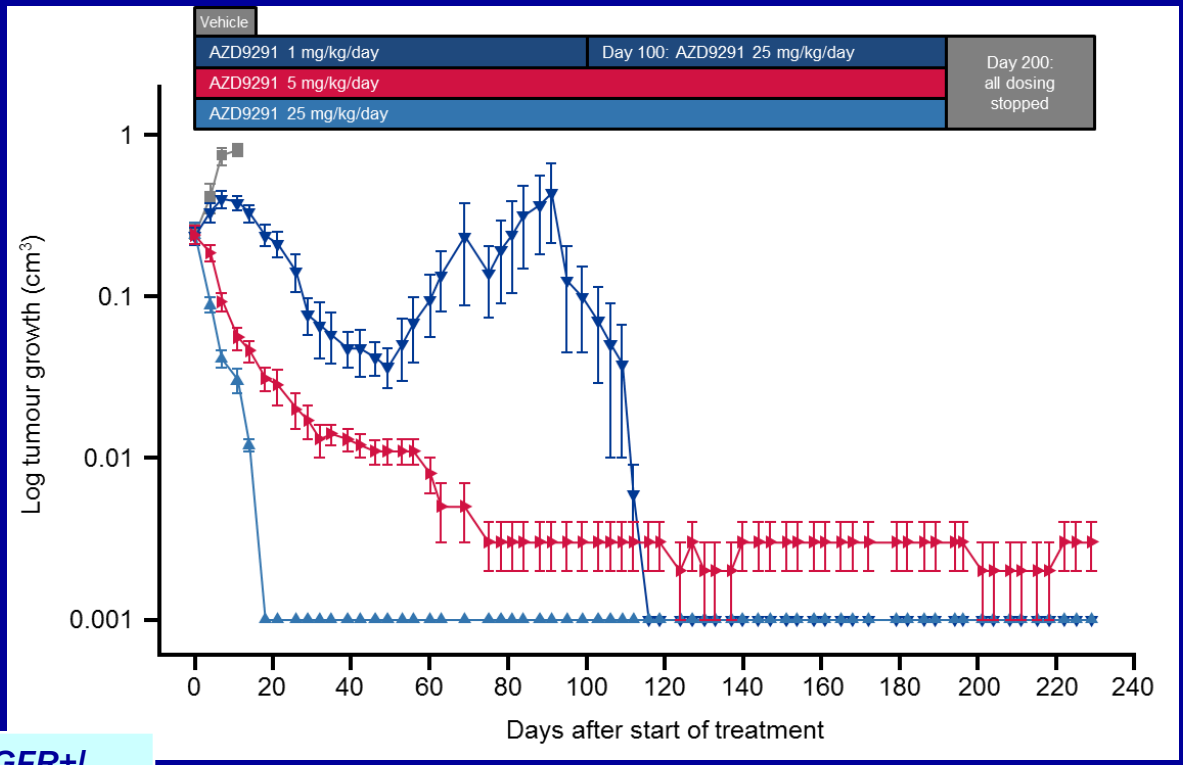


Chong and Janne Nature Medicine 2013

In vitro and *In vivo* activity of AZD9291

- AZD9291 is a potent oral, irreversible inhibitor of *EGFR* that contains EGFR-TKI-sensitising (*EGFR*+) and resistance mutations (T790M)
- Good potency and high selectivity demonstrated in enzymatic and cellular *in vitro* assays[1]

Updated long-term dosing of H1975 (L858R/T790M) xenograft with indicated doses of AZD9291



Model	Wild-type LoVo cells	*EGFR*+ PC9 cells	*EGFR*+/ T790M H1975 cells
AZD9291 phospho-EGFR IC_{50} nM	480	17	15

- Profound regression in EGFR-mutant tumour models, showing sustainable complete macroscopic tumour response out to at least 200 days

Ranson et al WCLC 2013

1. Cross et al. Abstract A109, AACR-EORTC-NCI conference, Boston, 2013

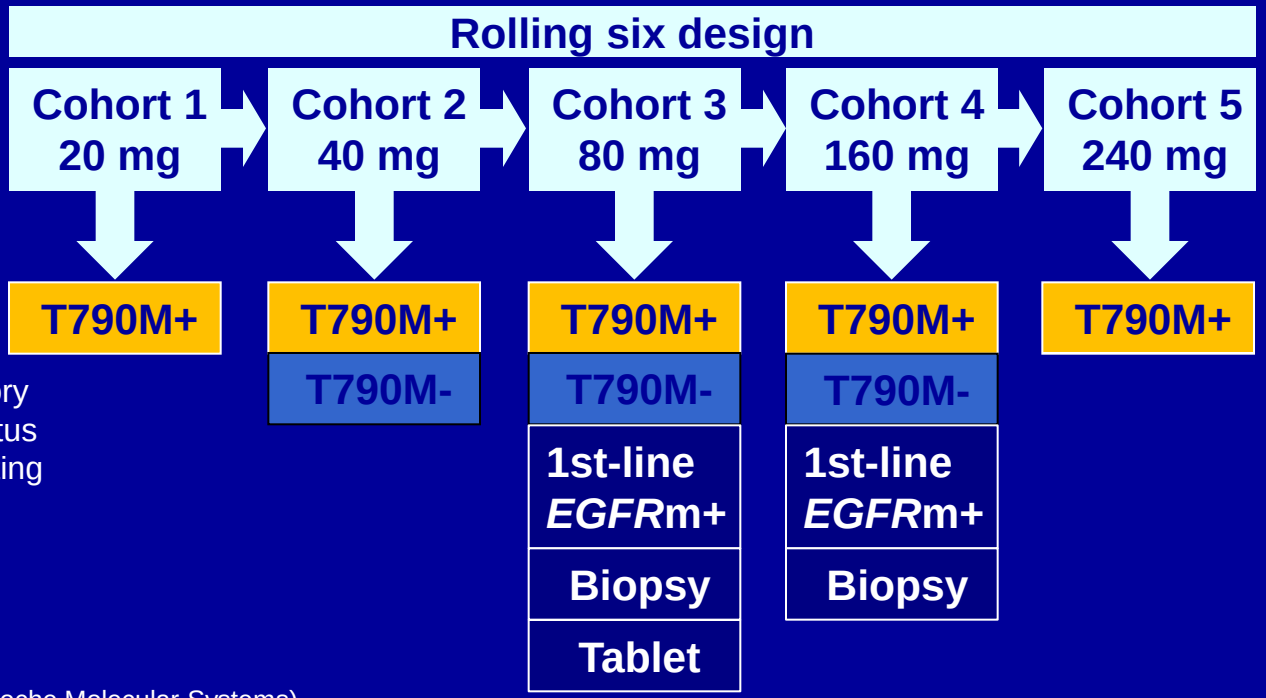
Phase I/II study on AZ9291

open-label, multicenter study of AZD9291 administered once daily in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI (AURA; NCT01802632)

Objectives

Primary: safety and tolerability in EGFR-TKI-refractory patients

Secondary include: define maximum tolerated dose, pharmacokinetics, preliminary efficacy

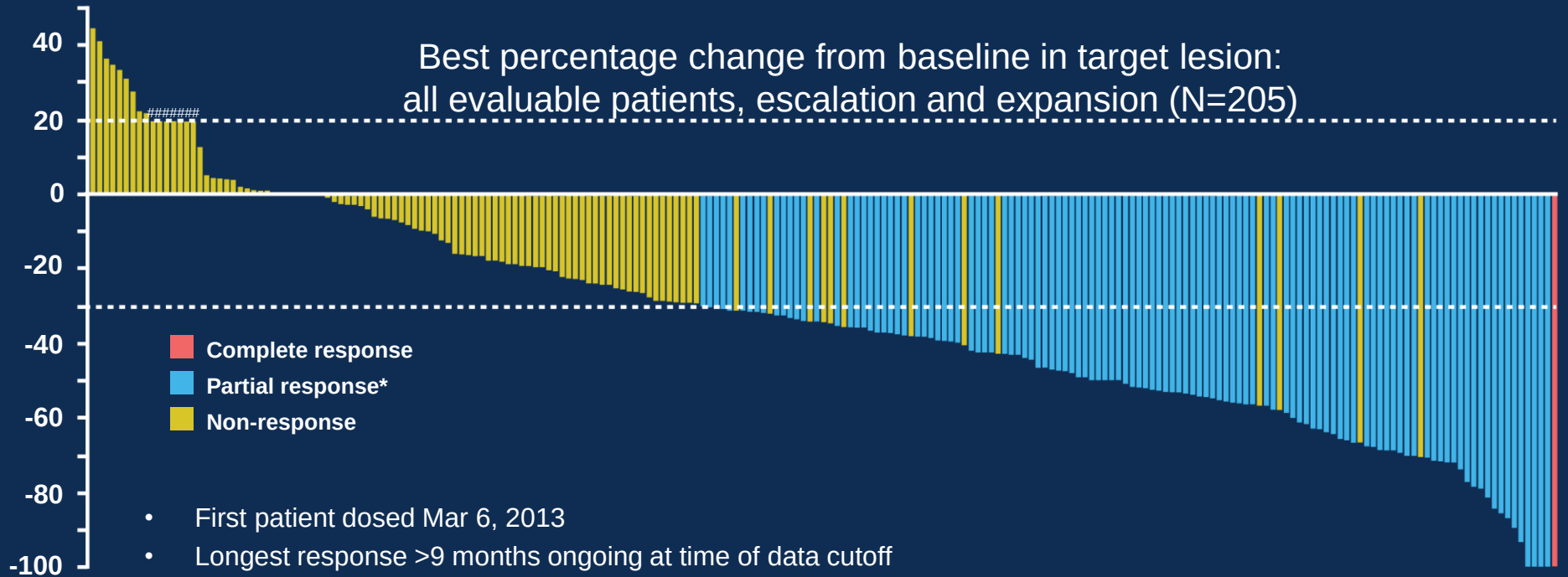


Expansion
Enrollment by local testing followed by central laboratory confirmation* of T790M status or by central laboratory testing alone

*cobas® EGFR Mutation Test (Roche Molecular Systems)

Janne ASCO 2014

Response rate* in overall population

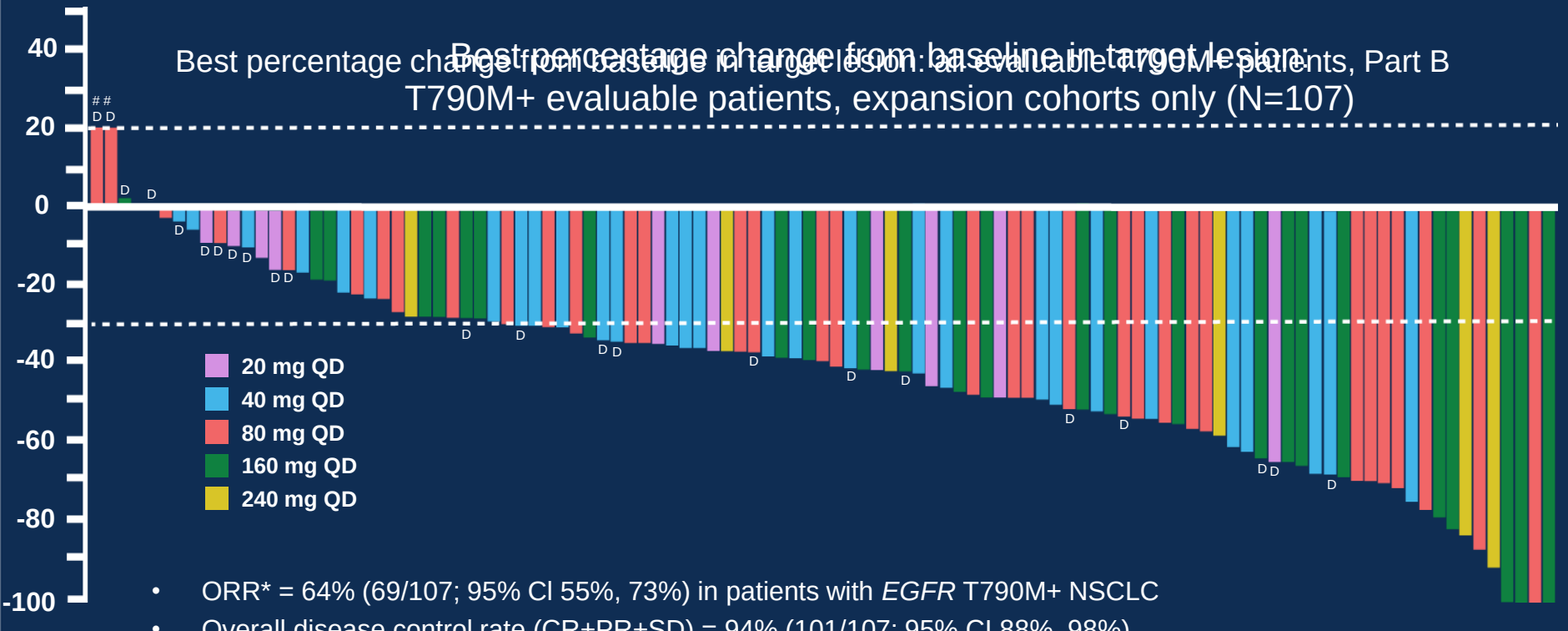


- First patient dosed Mar 6, 2013
- Longest response >9 months ongoing at time of data cutoff
- ORR* = 53% (109/205; 95% CI 46%, 60%); no difference in ORR by race
- Overall disease control rate (CR+PR+SD) = 83% (171/205; 95% CI 78%, 88%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (205)	20	57	61	55	12
ORR	55%	44%	54%	58%	67%

*Includes confirmed responses and responses awaiting confirmation; # represents imputed values. Population: all dosed patients with a baseline RECIST assessment and an evaluable response (CR, PR, SD or PD), N=205 (from 232 dosed patients, 27 patients with a current non-evaluable response are not included). CI, confidence interval; CR, confirmed complete response; ORR, overall response rate; PR, confirmed partial response; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Response rate* in central T790M+



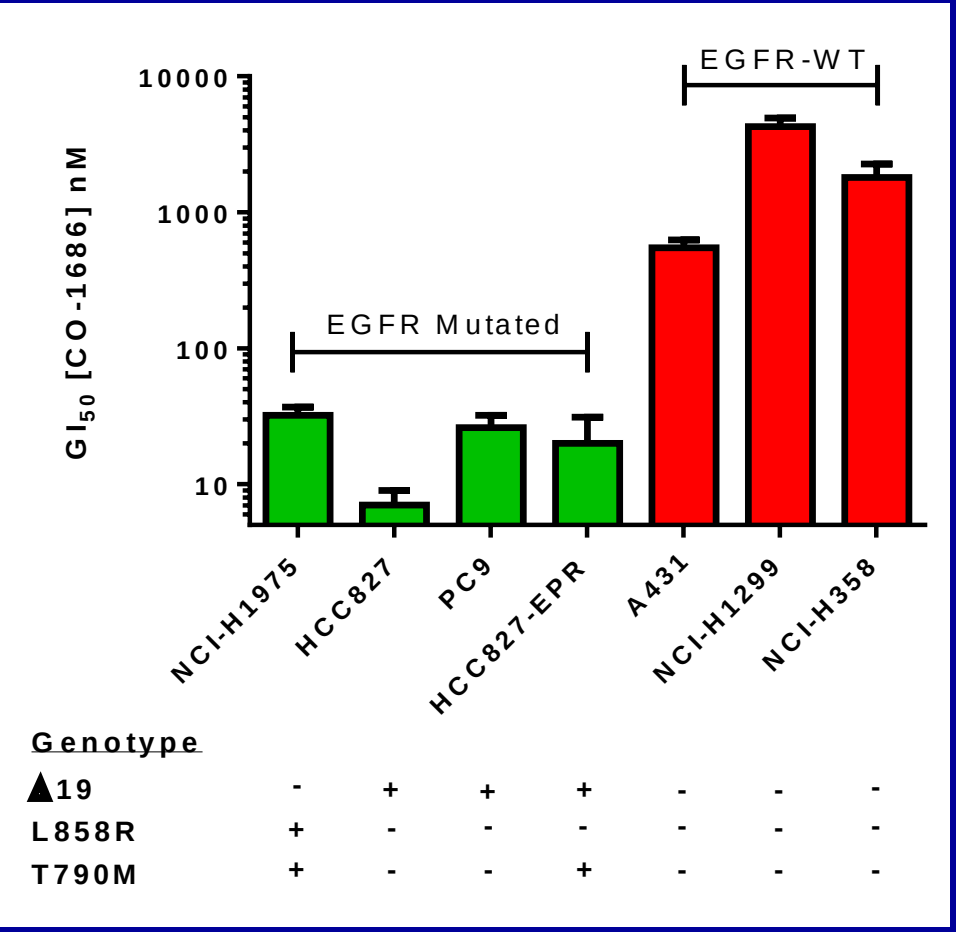
- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with *EGFR* T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

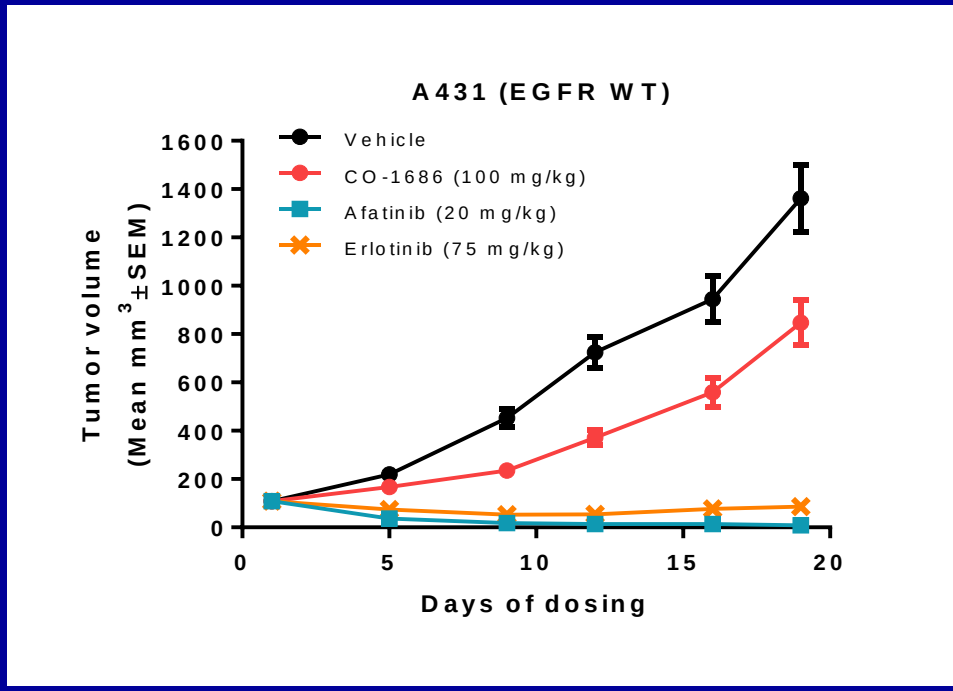
	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

*Includes confirmed responses and responses awaiting confirmation; # represents imputed values.
Population: all dosed central T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD or PD), N=107 (from 120 T790M+ patients, 13 patients with a current non-evaluable response are not included).
QD, once daily; central T790M+, T790M positive by central laboratory testing

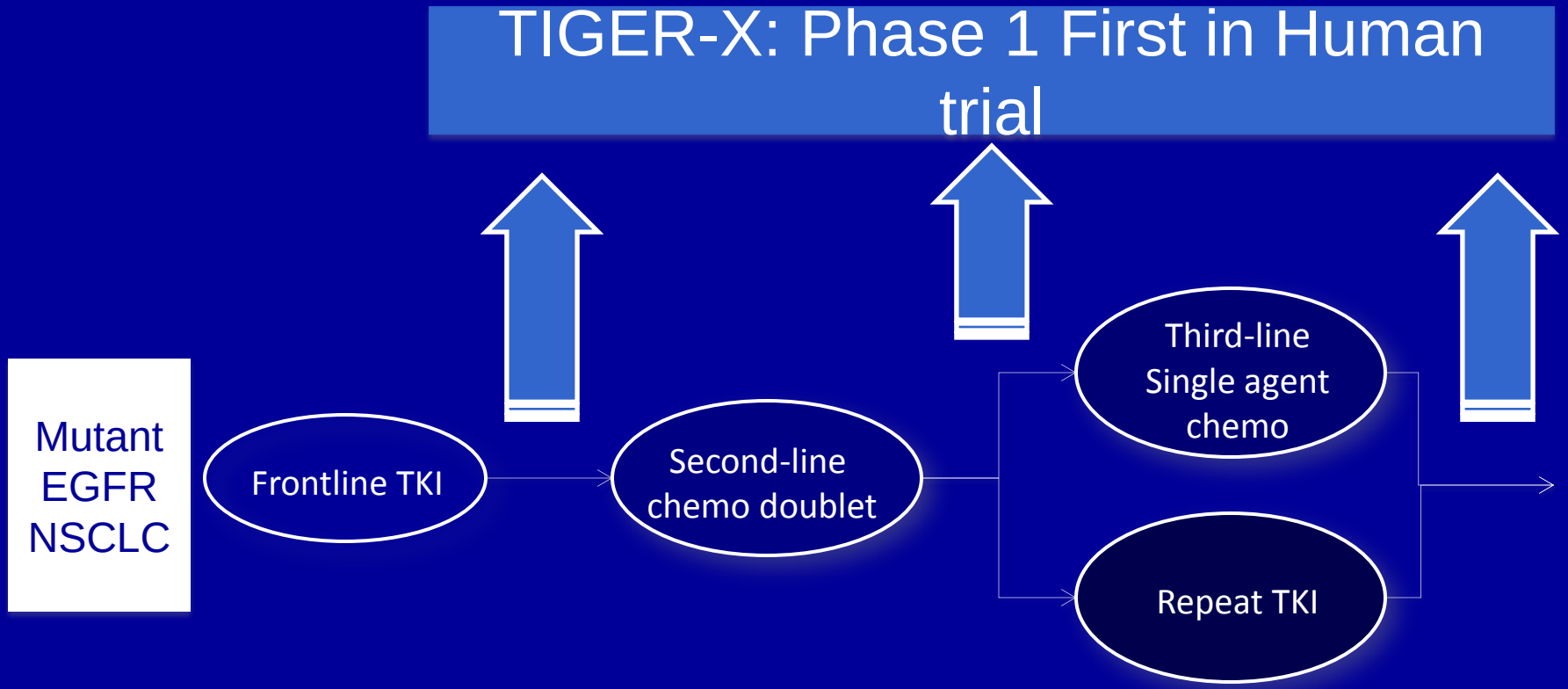
Rociletinib (CO-1686) inhibits mutant EGFR, including T790M, but spares wild-type EGFR

Growth inhibition of tumor cell lines with rociletinib (CO-1686)





TIGER-X Enrolls Broad Spectrum of Patients*

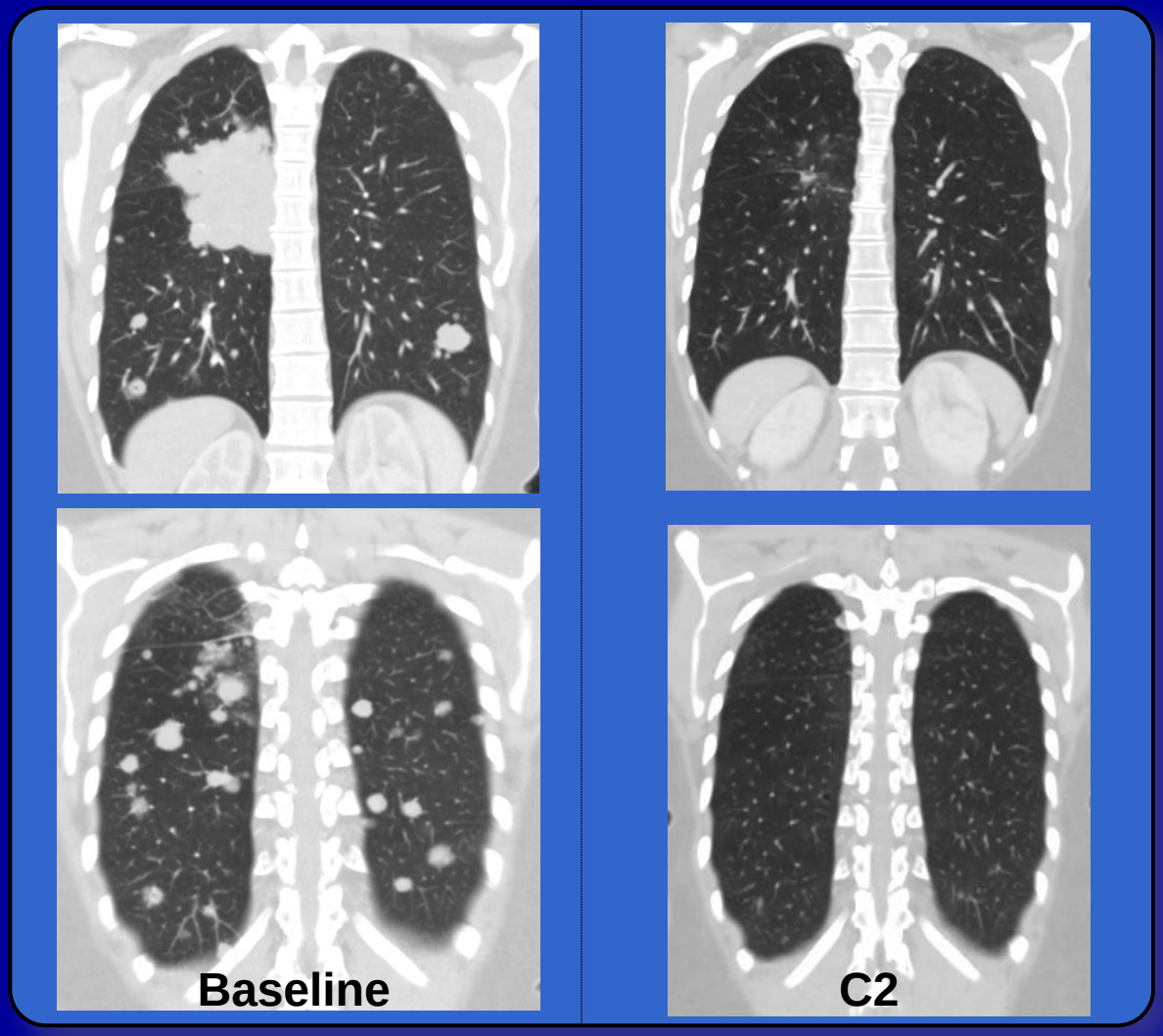


TIGER-X clinical dose group (T790M+): baseline characteristics

	625 mg BID	500 mg BID	Total
N	30	26	56
Median age, years	59	59	59
Female, %	63	77	70
Asian, %	7	15	11
ECOG PS grade 0, %	13	27	20
Median no. of prior Rx	3	3	3
No. of prior TKIs, %			
1	43	46	45
2	13	39	25
≥3	27	12	20
Immediate prior TKI, %	73	85	79
History of diabetes, %	3	12	7
History of cardiovascular disease, %	13	15	14

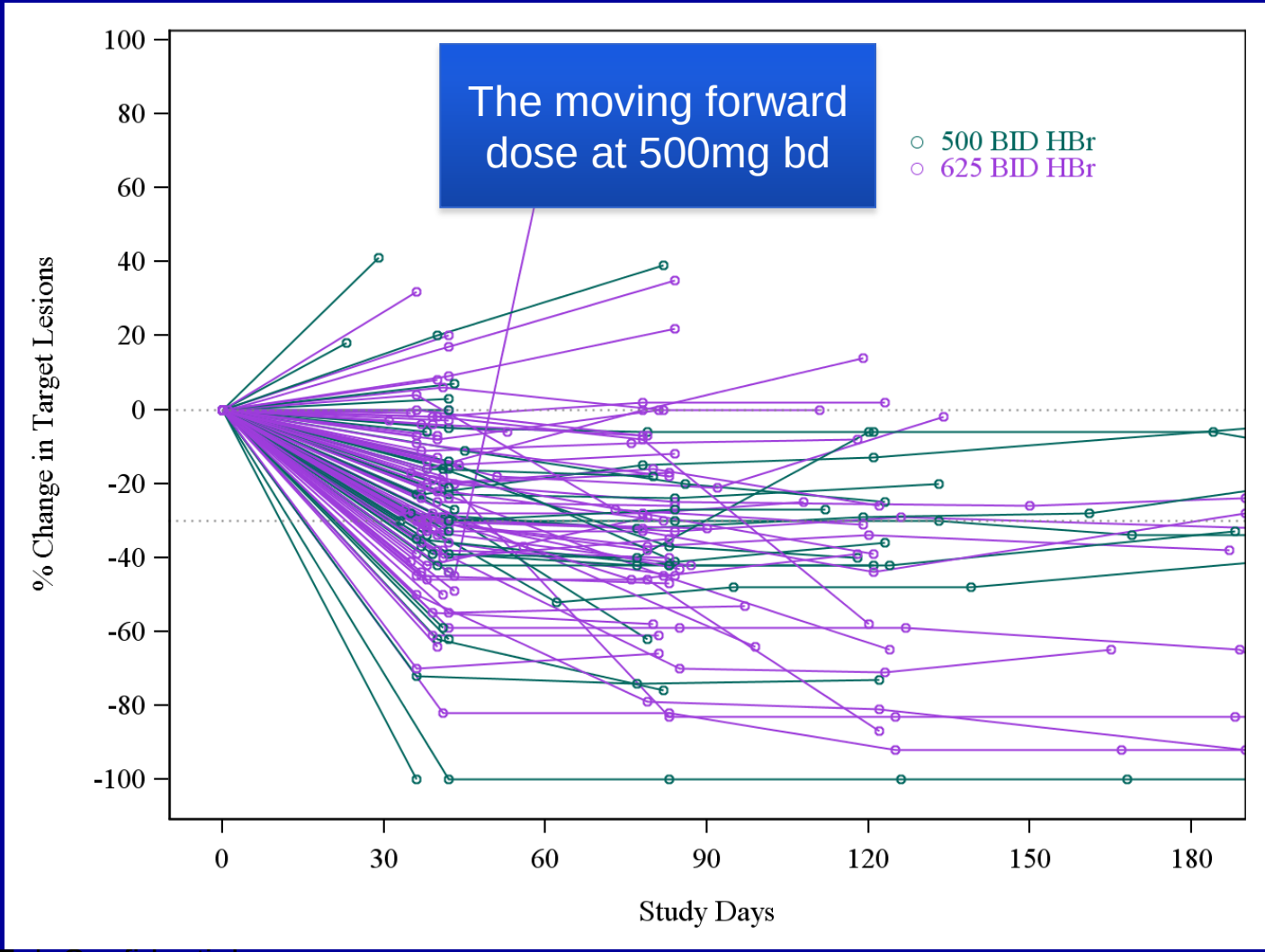
*7 patients started treatment with 900 mg BID free-base formulation and converted to 500 mg HBr salt tablet. The majority of their treatment was with HBr tablet and they are aggregated with the 500 mg BID HBr tablet group.
ECOG PS=Eastern Cooperative Oncology Group Performance Status.

T790M+ Patient Treated with rociletinib

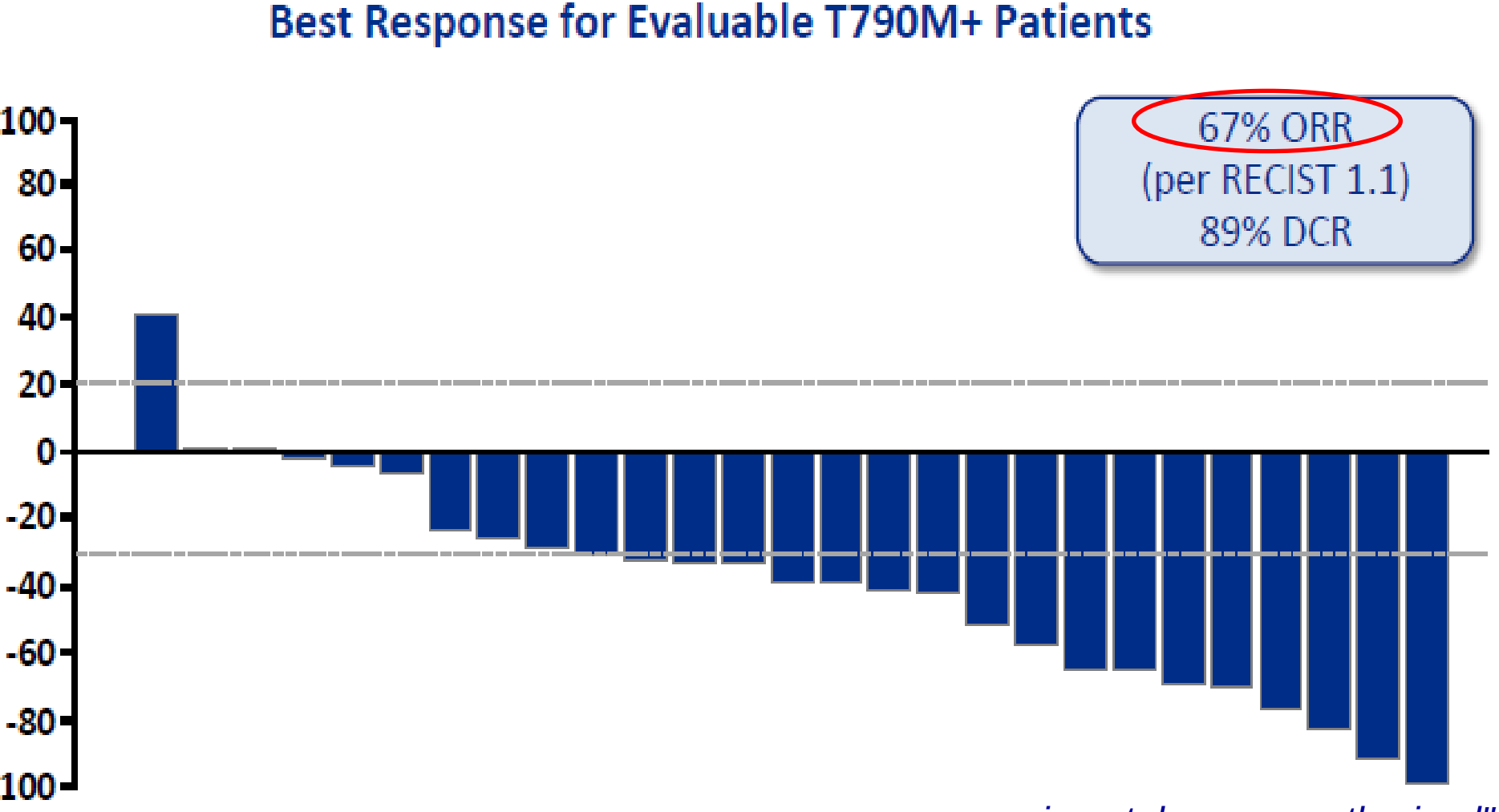


- Four prior lines:
  1. Erlotinib
     - 10 mo w/ response
  2. Afatinib
     - no response
  3. Chemotherapy
     - No response
  4. Erlotinib
     - Retreated for 2 mo immediately before rociletinib start
- Start on rociletinib at 500 BID

Response kinetics are similar at 500mg bid and 625mg bid

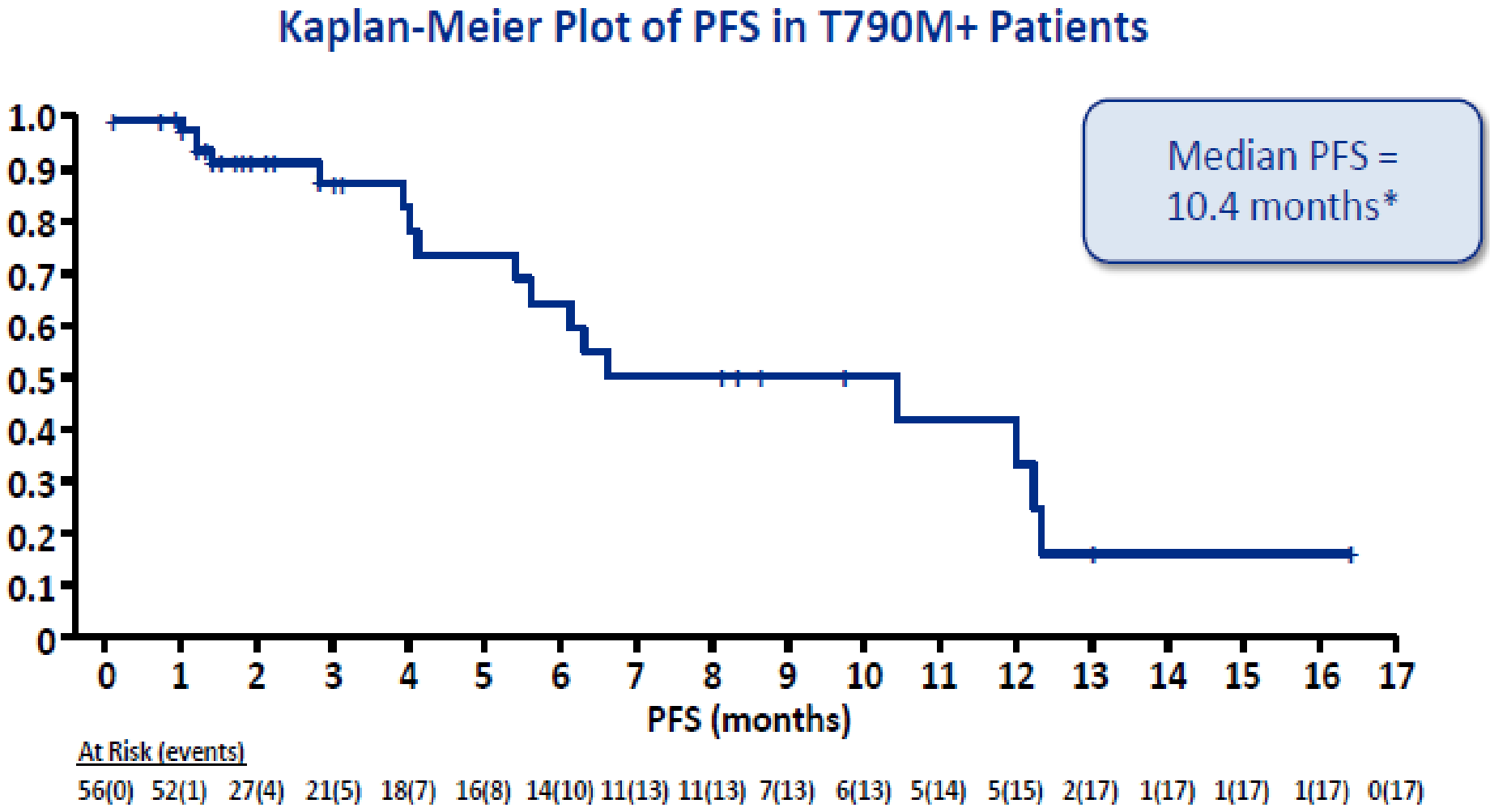


TIGER-X clinical dose group responses



experimental use, unauthorized"

TIGER-X clinical dose group: PFS



*Data as of 25 September 2014 reflecting 31% data maturity.
PFS=progression-free survival.

experimental use, unauthorized"

Adverse events were generally mild with hyperglycemia observed most commonly

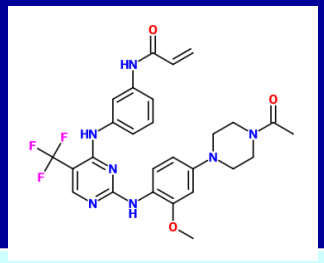
Treatment-related AEs occurring in ≥ 5% of CO-1686 patients (N=148) treated us doses, n (%)

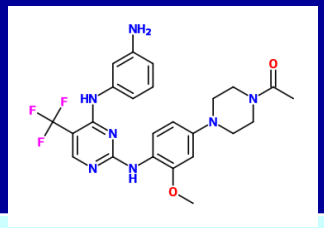
Preferred term	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	25 (16.9%)	15 (10.1%)	2 (1.4%)	0
Hyperglycemia and IGT	15 (10.1%)	8 (5.4%)	25 (16.9%)	0
Diarrhea	24 (16.2%)	4 (2.7%)	0	0
Vomiting	13 (8.8%)	2 (1.4%)	3 (2.0%)	0
Fatigue	13 (8.8%)	13 (8.8%)	3 (2.0%)	0
Decreased appetite	7 (10)	7 (10)	1 (1)	0
Myalgia	9 (6.1%)	2 (1.4%)	0	0
QTc prolonged	4 (2.7%)	3 (2.0%)	5 (3.4%)	0

2 (1.4%) patients with any form of rash all Grade 1

Observed hyperglycemia relates to metabolite of rociletinib*

- Rociletinib metabolite M502 is an inhibitor of IGF1R and accumulates in humans causing hyperglycemia
  - No hyperglycemia observed in toxicology studies of rociletinib
- Like rociletinib, M502 is wild-type EGFR sparing





Assay	Rociletinib	M502
A431 (IC_{50}, nM) Cellular (wild-type EGFR)	903	907
NCI-H1975 (IC_{50}, nM) Cellular (T790M EGFR)	36	961
IGF1R (IC_{50}, nM) Kinase	477	57
IGF1R (IC_{50}, nM) Cellular	458	58

IC_{50}=half maximal inhibitory concentration; IGF1R=insulin-like growth factor 1 receptor.

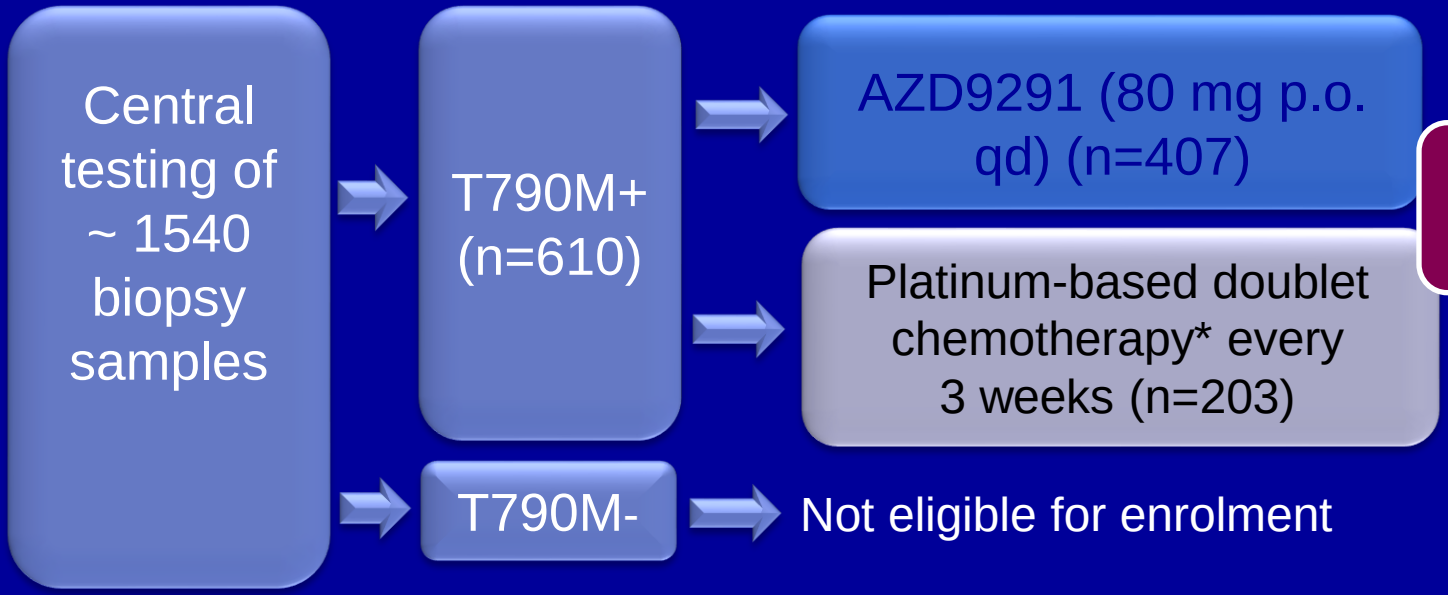
Adapted from Soria et al 2015

Both AZ9291 and CO1686 are on fast track approval by FDA

- TIGER 2 study: Single arm phase II study of CO1686 for patient with T790M resistant mutation after first TKI failure
- AURA 2 study: Single arm phase II study of AZ 9291 for patient with T790M resistant mutation after first line TKI failure

AURA 3 Study Design

Randomise ~610 patients 2:1



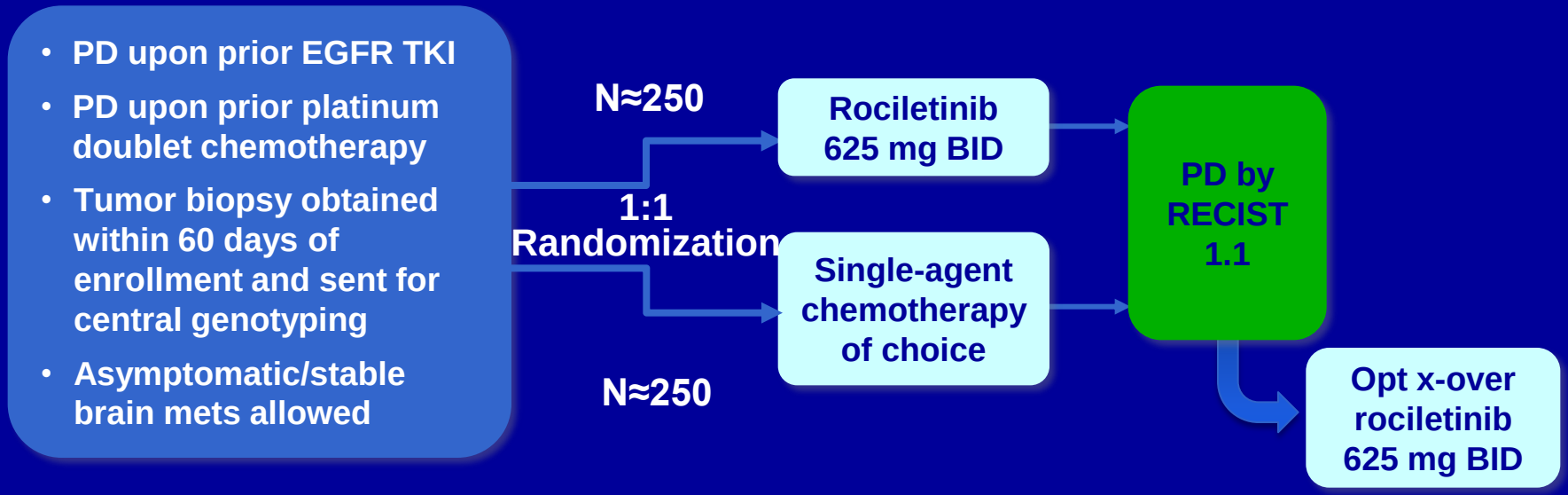
*Pemetrexed 500 mg/m^2 + carboplatin AUC5 or Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2

AUC5, area under the plasma concentration–time curve 5 mg/mL^{-1} per minute; *EGFR*m+, *EGFR* mutation-positive; EGFR-TKI, EGFR tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; p.o., orally; qd, once daily; T790M+, T790M mutation-positive; T790M-, T790M mutation-negative

PI: T Mok YL Wu

TIGER 3: Second line phase III study (T790M+ and T790M–)

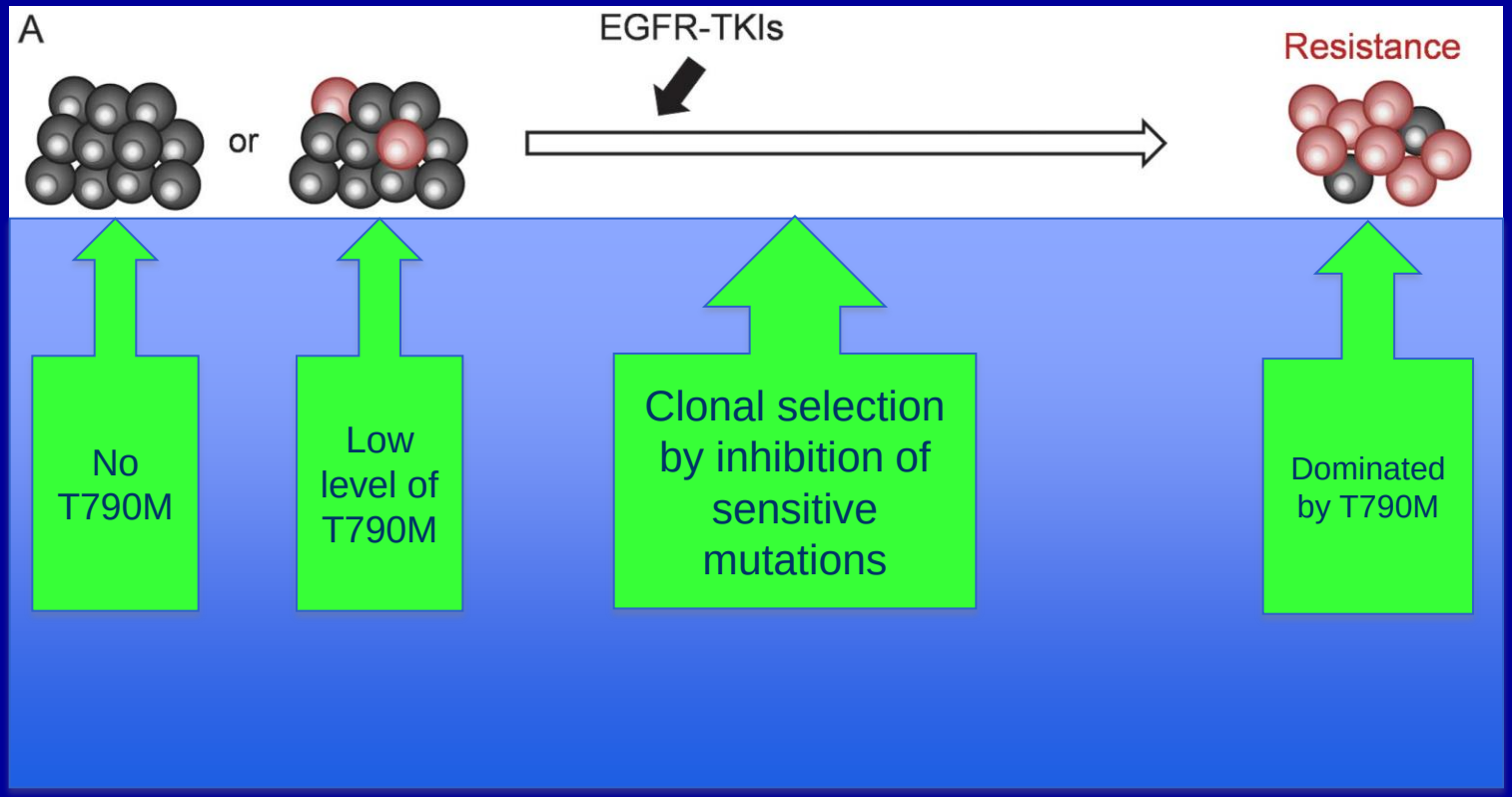
TIGER-3: International, randomized, phase 3 study in ≥3rd line mutant EGFR NSCLC, both T790M+ and T790M–



Primary endpoint is PFS; step-down primary efficacy analysis – initially in central T790M+ patients, then all-comers

Mets=metastases; PD=progressive disease.

Best timing of T790M inhibition?



Detection of T790M

cfDNA for T790M

- Digital PCR (Rui Chen et al):
  - Studied 135 patients with acquired resistance to TKI

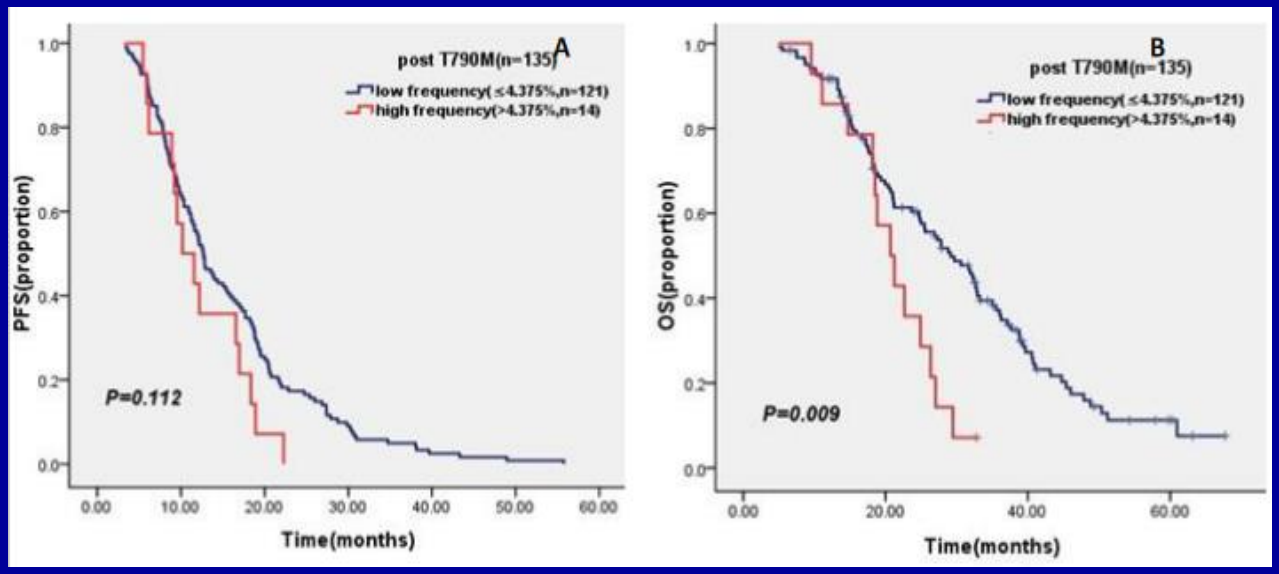
	ARMS	Digital PCR
Pre-TKI (N=109)	5% T790M pos	30% T790M pos
Post-TKI (N=135)	25% T790M pos	43% T790M pos

No corresponding rebiopsy tumor for T790M

Chen et al, WCLC, 2013

Low frequency of T790M in plasma is predictive of OS

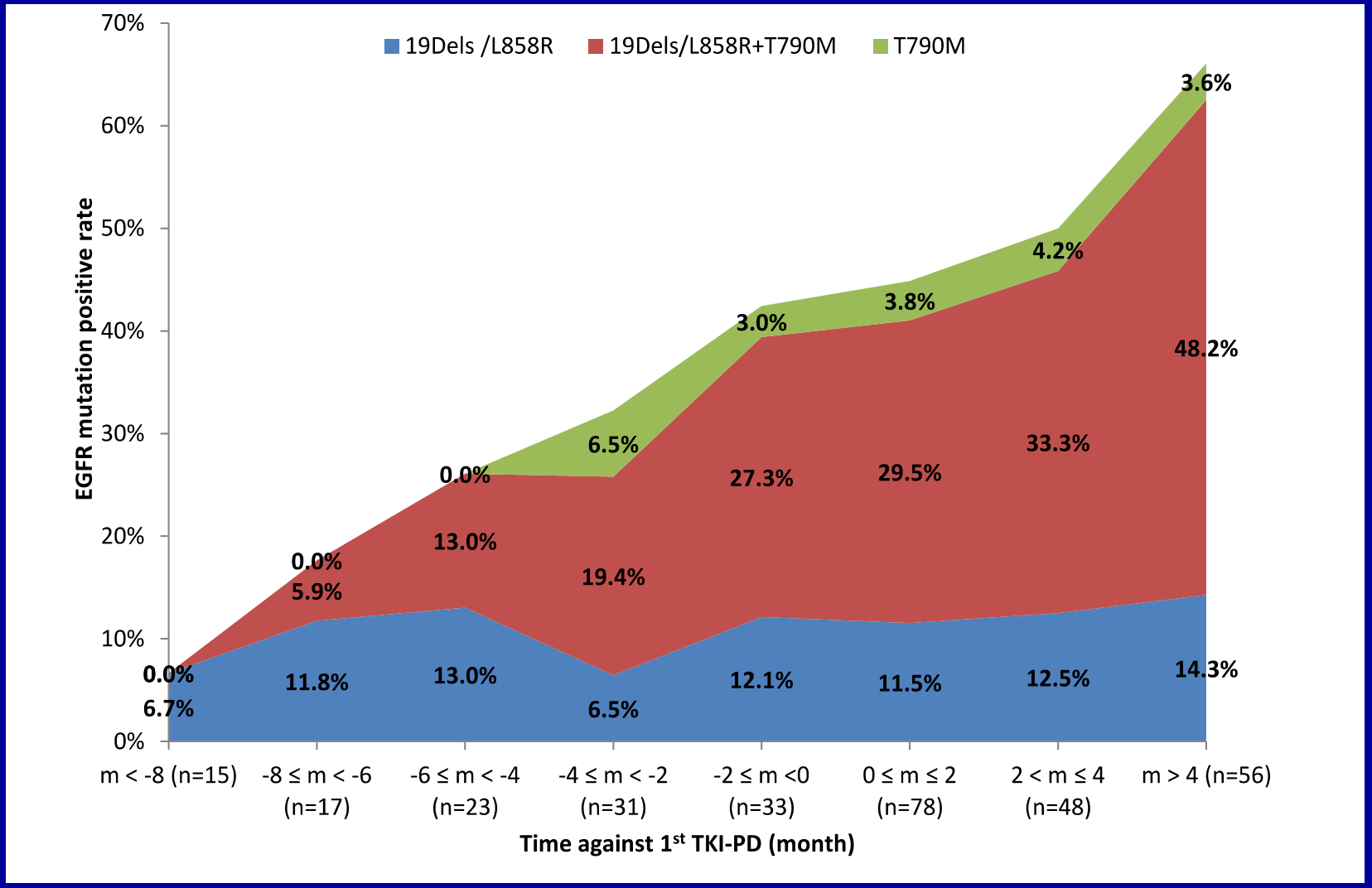
- Digital PCR (Rui Chen et al):
  - Much greater power as a quantitative assay



  - These exploratory findings are in contrast to reports suggesting acquired T790M lends a better prognosis*

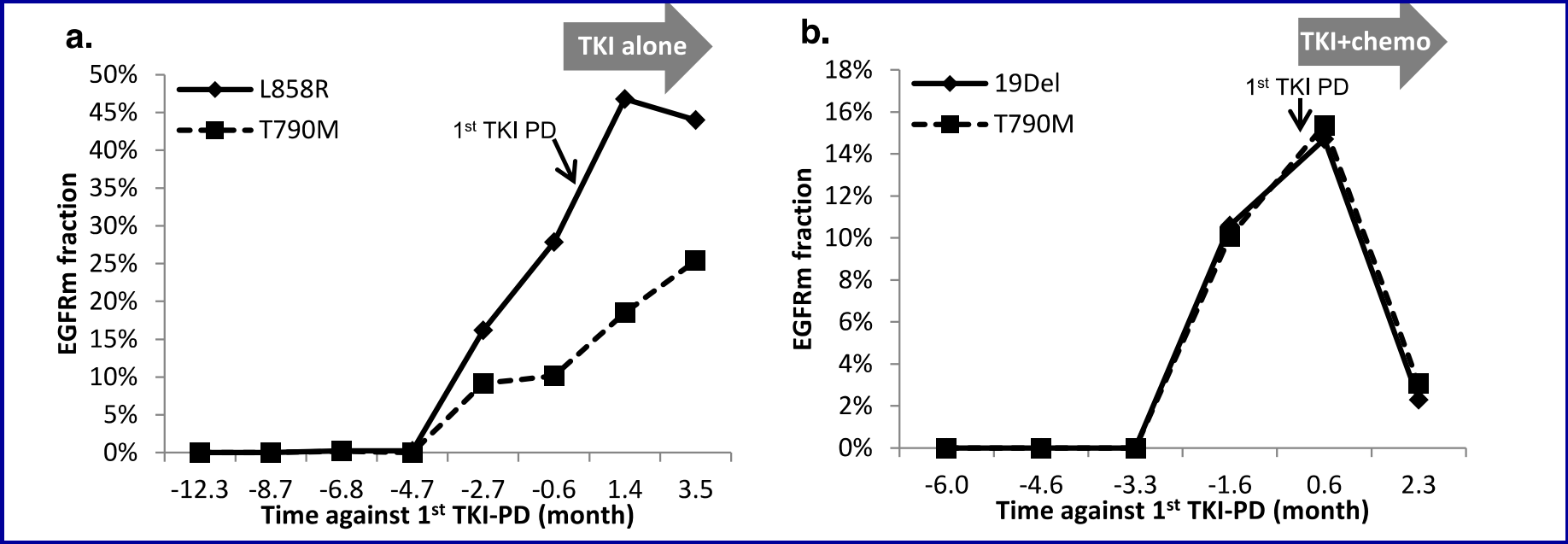
*Oxnard et al, CCR, 2011; Hata et al, Cancer, 2013

Serial change in T790M by ddPCR

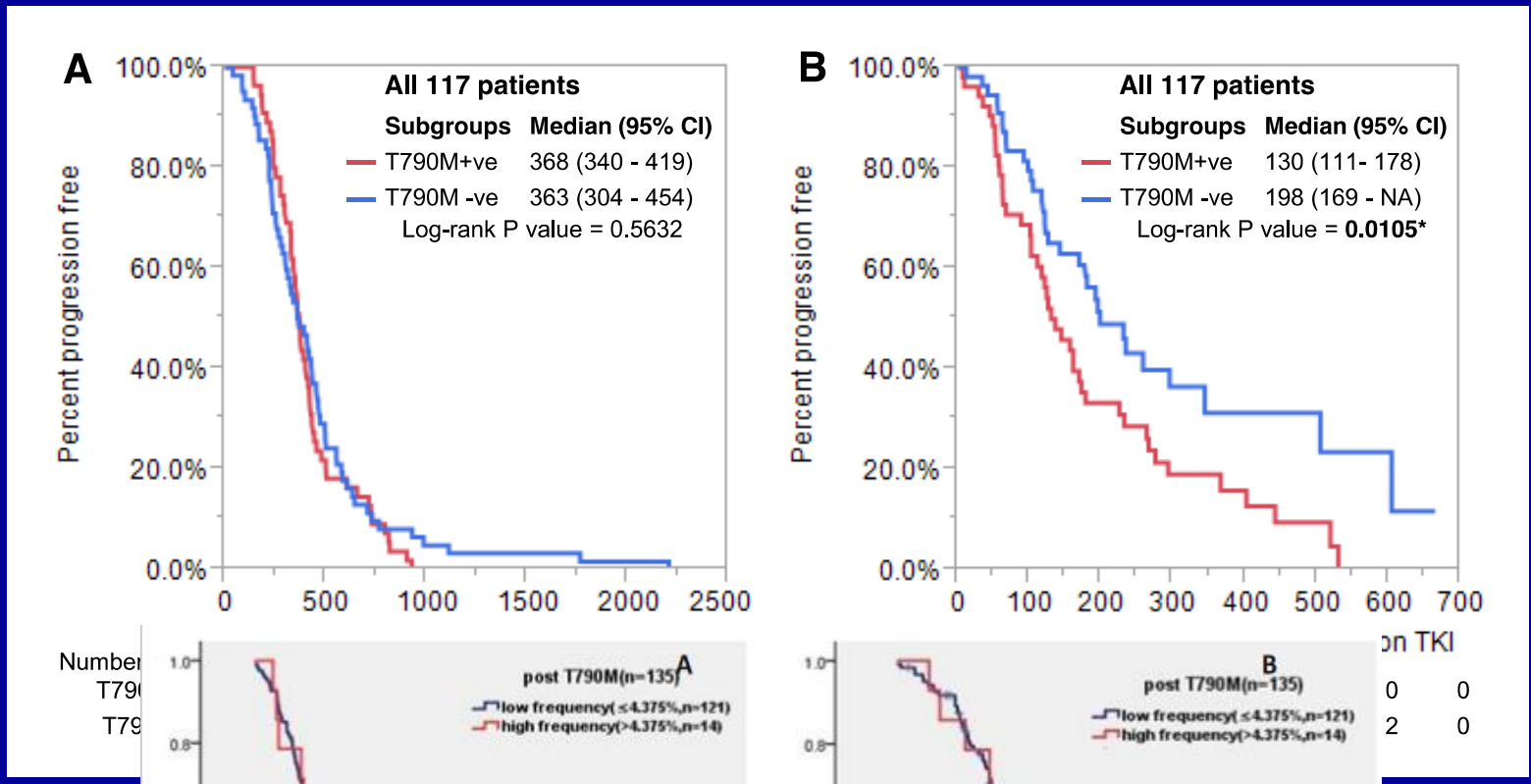


Zhang et al ASCO 2014

Impact of post-PD treatment on plasma DNA for T790M

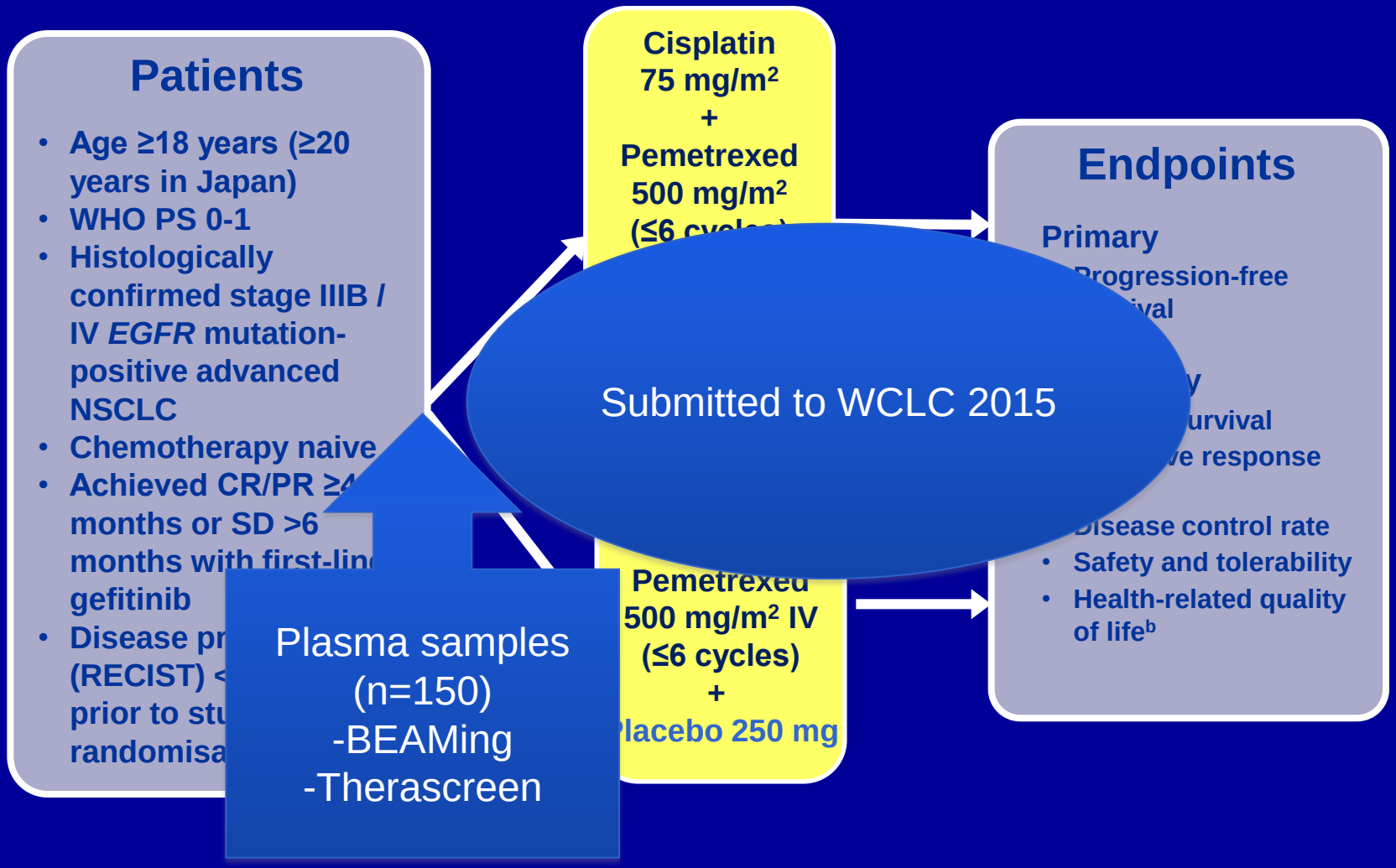


Prognostic value of plasma T790M



IMPRESS: Study Design

Enrollment period: March 2012-December 2013



Mok et al EMSO 2014

Summary

- T790M accounts for over 50% of TKI resistance
- Quinlazoline-based TKI cannot inhibit T790M at clinical tolerable dose
- Third generation pyrimidine-based TKIs are highly potent in T790M inhibition
- WZ4002 is the first pyrimidine-based TKI with high pre-clinical efficacy
- AZ9291 and CO1686 are associated with high tumor response rate and both are undergoing intensive clinical investigation.
- Plasma DNAis potentially the most effective way to detect presence of T790M

Mok T, Myanmar 2014