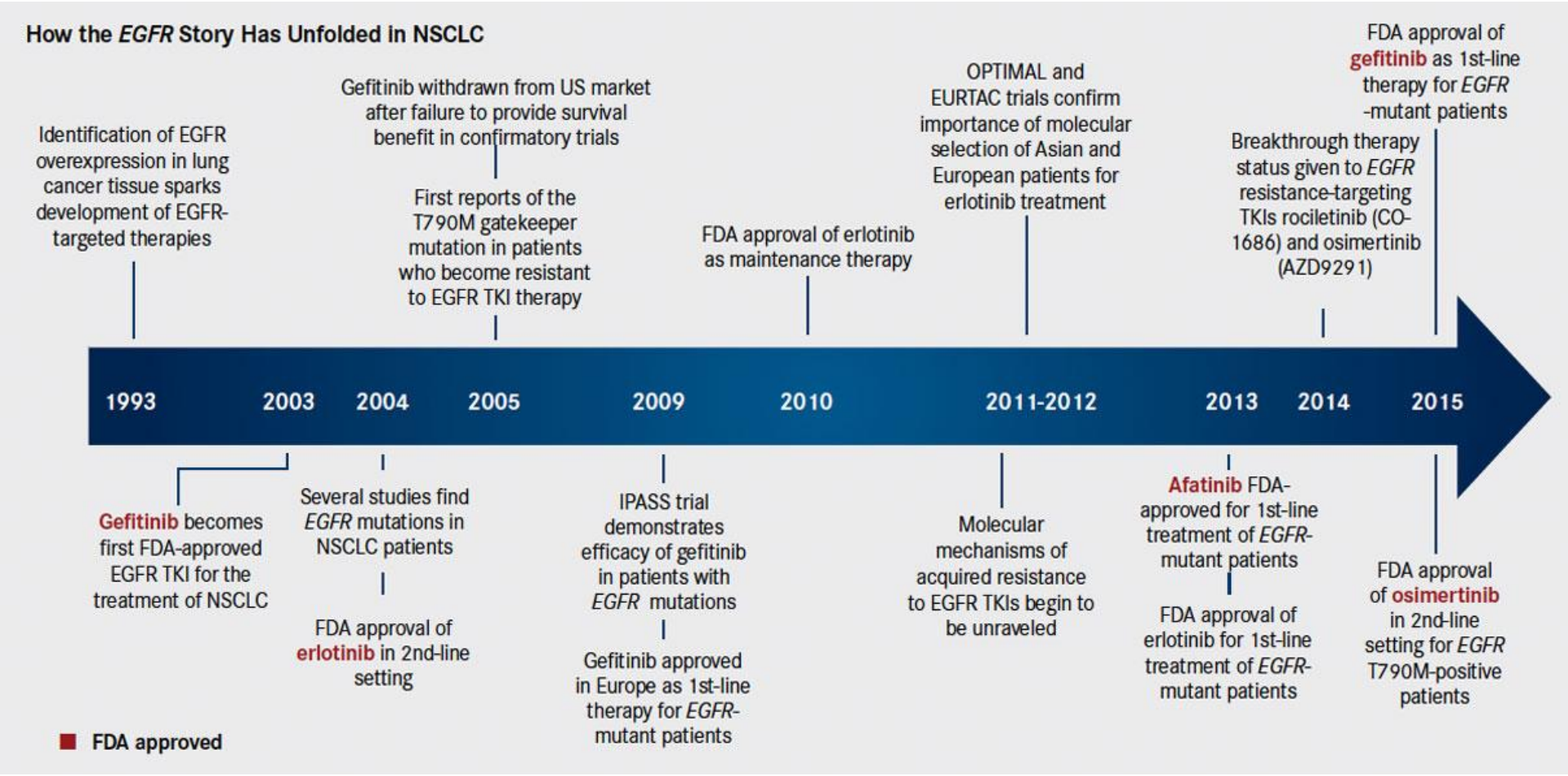
Treatment Options for Patients with EGFRm NSCLC

Giorgio V. Scagliotti
University of Torino
Department of Oncology
giorgio.scgliotti@unito.it

Discussion

- *Abstract 130O – Efficacy and safety of BI 1482694 (HM61713), an EGFR mutant-specific inhibitor, in T790M-positive NSCLC at the recommended phase II dose – Keunchil Park et al*
- *131O - Combination of chemotherapy and gefitinib as first-line treatment of patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomised controlled trial - Baohui Han et al*

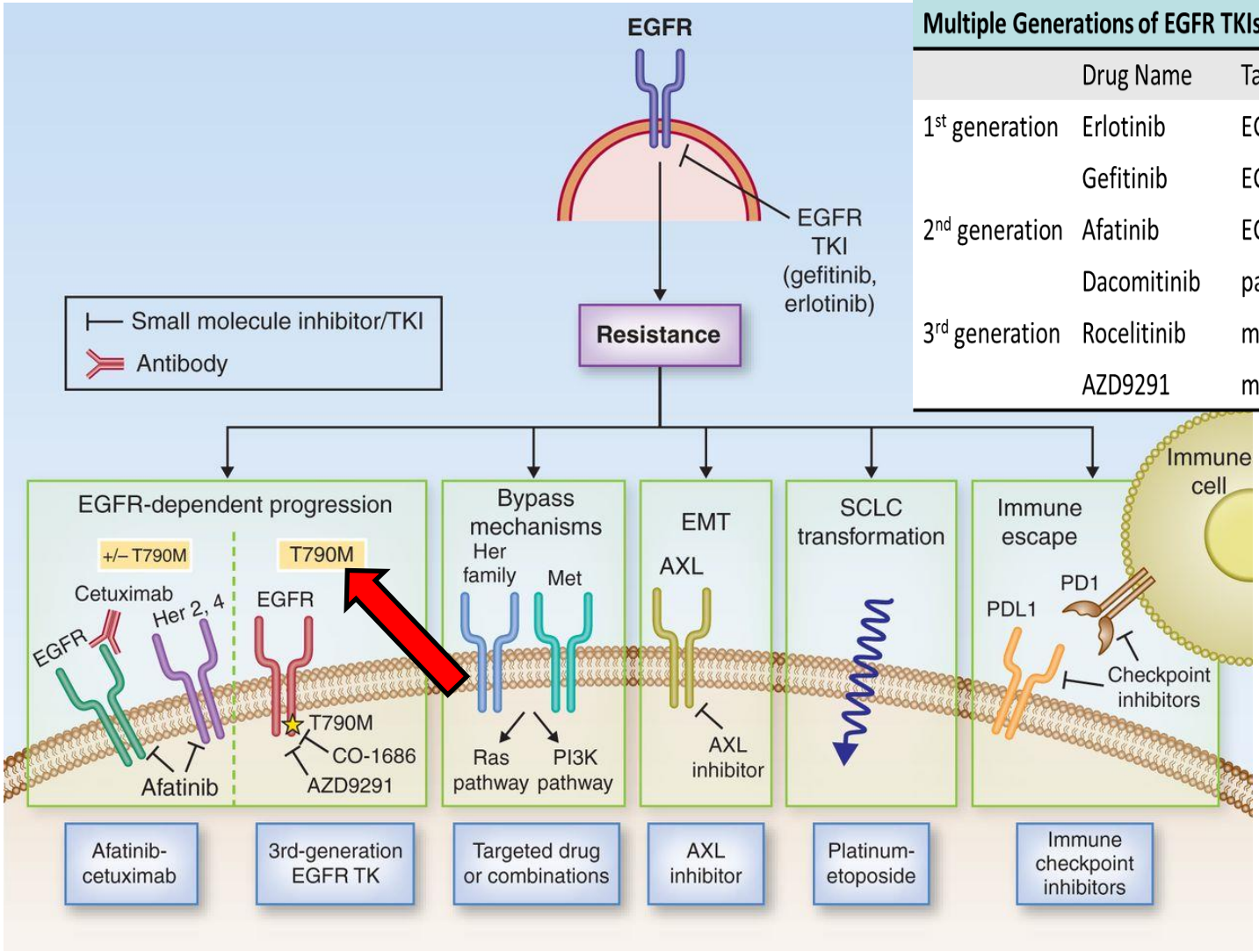
How the *EGFR* Story Has Unfold in NSCLC



Discussion

- *Abstract 130O – Efficacy and safety of BI 1482694 (HM61713), an EGFR mutant-specific inhibitor, in T790M-positive NSCLC at the recommended phase II dose – Keunchil Park et al*
- *131O - Combination of chemotherapy and gefitinib as first-line treatment of patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomised controlled trial - Baohui Han et al*

Acquired Resistance to 1st and 2nd generation EGFR TKIs



Multiple Generations of EGFR TKIs

	Drug Name	Target(s)	MOA
1st generation	Erlotinib	EGFR	reversible
	Gefitinib	EGFR	reversible
2nd generation	Afatinib	EGFR/HER2	irreversible
	Dacomitinib	panHER	irreversible
3rd generation	Rocelitinib	mutEGFR	irreversible
	AZD9291	mutEGFR	irreversible

Adapted from: Gibbons and Byers et al, *Cancer Discov*, 2014
Yu, H.A. et al, *Clin Cancer Res*, 2014

Third Generation EGFR-TKIs Agents

AZD9291 mono-anilino-pyrimidine compound, irreversible mutant selective EGFR-TKI

Rociletinib (CO-1686) a 2,4-disubstituted pyrimidine molecule, irreversible mutant-selective EGFR-TKI

HM61713 selective inhibitor for activating EGFR and T790M mutations

EGF816: Covalent, irreversible, EGFR-TKI for EGFR and T790M mutations

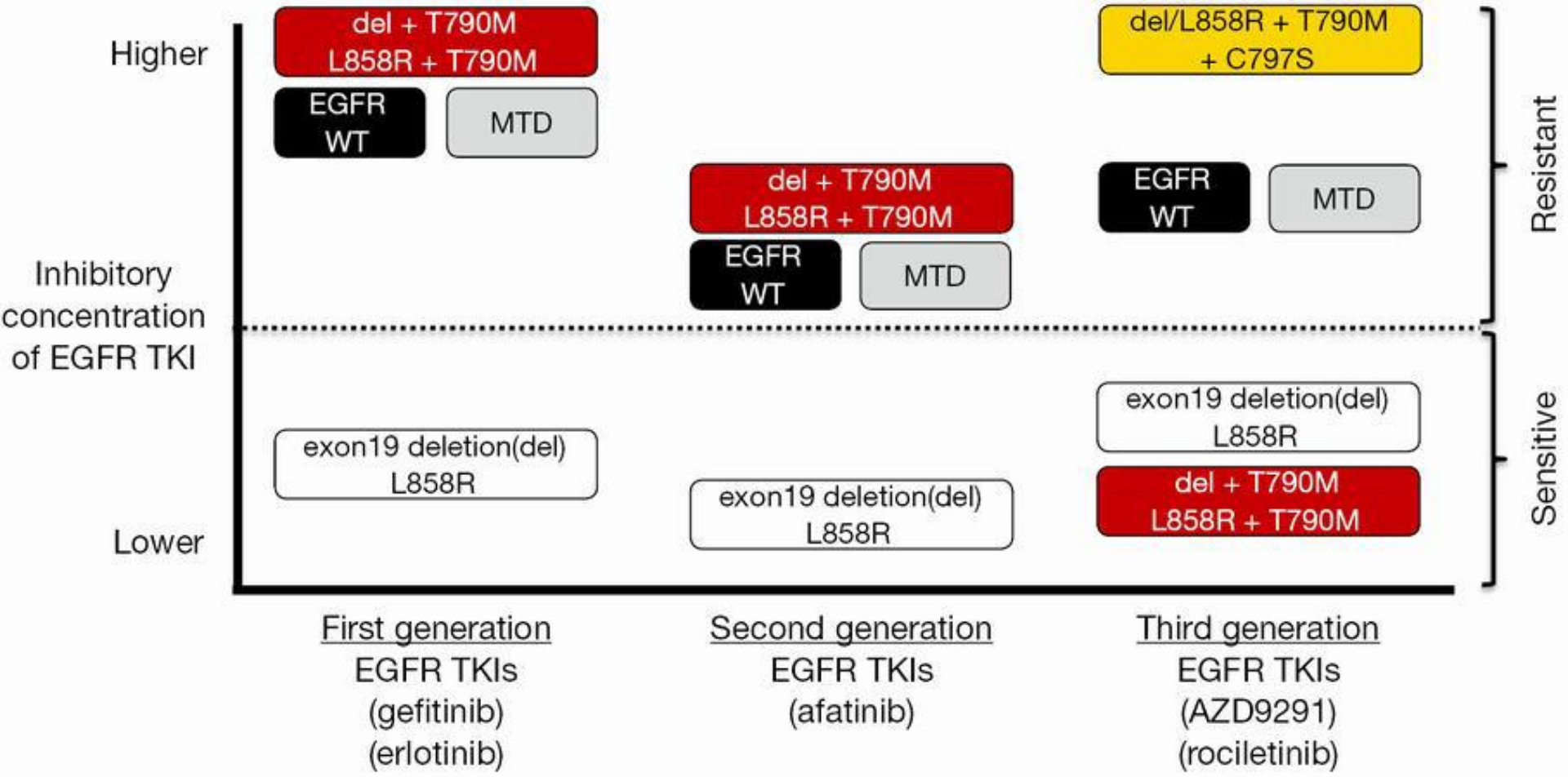
ASP8273 Mutant selective irreversible of EGFR and T790M mutations

BI 1482694 (HM61713) - *In vitro* cell growth inhibition in NSCLC

	Inhibition concentration (IC_{50}, nM)		
	H358	HCC827	H1975
	EGFR WT	$EGFR^{Del19}$	$EGFR^{L858R/T790M}$
Erlotinib	449	3.2	2,253
Afatinib	31	1.8	53
BI1482694	2,225	9.2	10

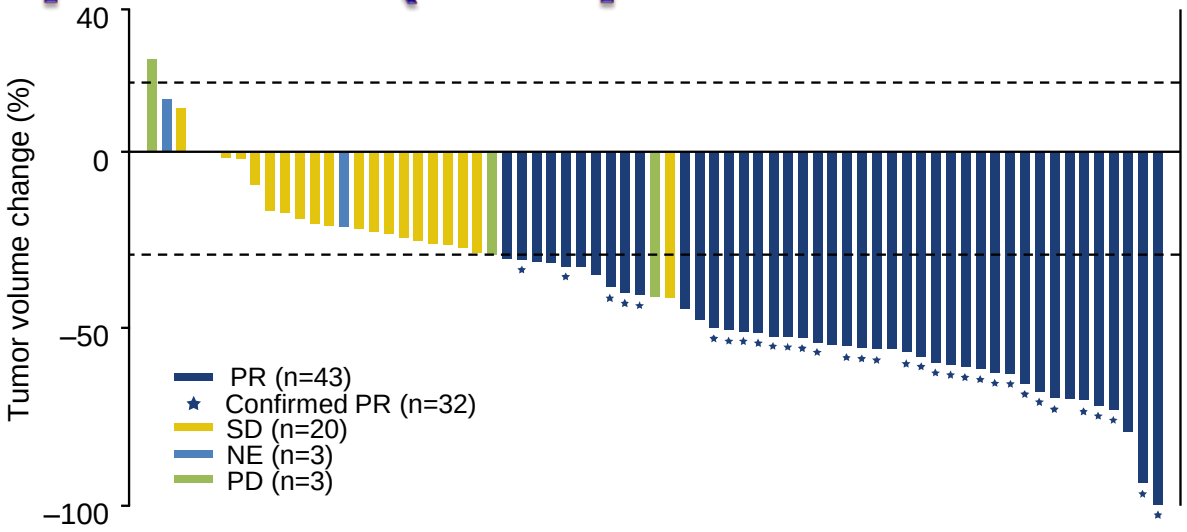
- Oral EGFR mutant-specific TKI
  - Potent and irreversible inhibition of sensitizing (Del19, L858R) and resistance (T790M) EGFR mutations
  - More than 200-fold selectivity over wild-type EGFR

In vitro inhibitory concentrations of EGFR-TKIs



Costa DB et al. TLCR 2015;4:809-15

ORR and tumor shrinkage in T790M+ patients (independent review)



	Evaluable patients (n=69)
OR (confirmed and unconfirmed), n (%)	43 (62)
Disease control, n (%) Confirmed OR, n (%) SD, n (%)	63 (91) 32 (46) 31 (45)
PD, n (%)	3 (4)
NE, n (%)	3 (4)

- DoR is immature; in patients with confirmed OR, response duration ranged between 6 and 31 weeks at data cut-off

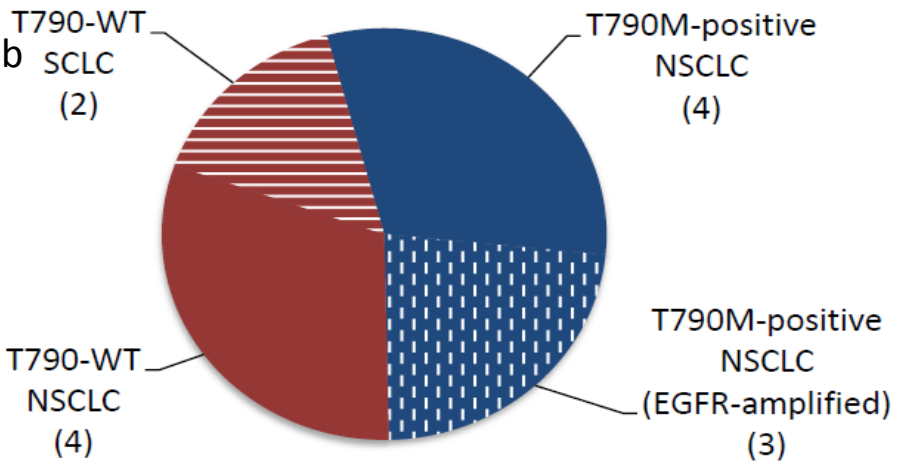
Third-generation EGFR TKIs

Drug Name	DLT	Recommended dose	RR	Toxicity	Status
AZD9291	-	80 mg QD	61%	Diarrhea, rash, nausea, ILD, QTc prolongation, decreased appetite	Phase III
CO-1686	hyperglicemia	500 mg BID	53%	Hyperglicemia, nausea, diarrea, QTc prolongation, fatigue	Phase III
EGF816	Rash, acute kidney injury	320 mg once per day (than 240 within trial)	60%	Rash, diarrhea, stomatitis, pruritus	Phase II
BI1482694/HM 61713	Abdominal pain, diarrhea	800 mg QD	62%	Diarrhea, nausea, dry skin, rash, pruritus	Phase II
ASP 8273	Diarrhea, nausea, malaise, colitis, biliary tract infection	300 mg QD (MTD 400 mg QD)	67%	Diarrhea, nausea, vomiting, rash (few), ILD, hyponatremia, QTc prolongation	Phase II

Acquired resistance to 3rd generation EGFR inhibitors

Acquired resistance to rocelitinib

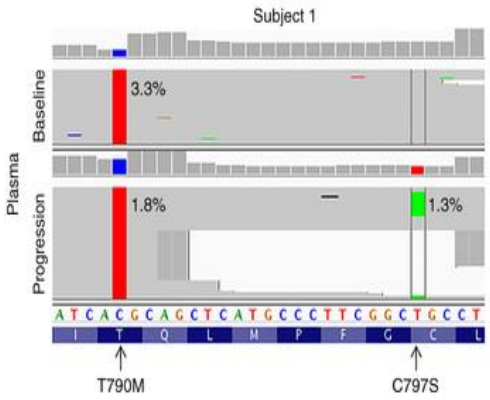
- 12 patients with T790M+ tumors at start of rocelitinib
- 13 biopsy samples
- 7 tumors retained T790M at the time of rocelitinib resistance
  - 3 tumors gained *EGFR* amplification
- 6 had loss of T790M at the time of rocelitinib resistance
  - Tumors became T790 wild type
  - 2 T790 wild-type tumors has conversion to SCLC histology

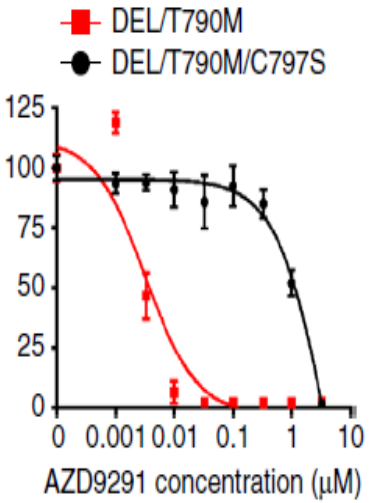


Piotrowska et al Cancer Discov 2015

Acquired resistance to AZD9291

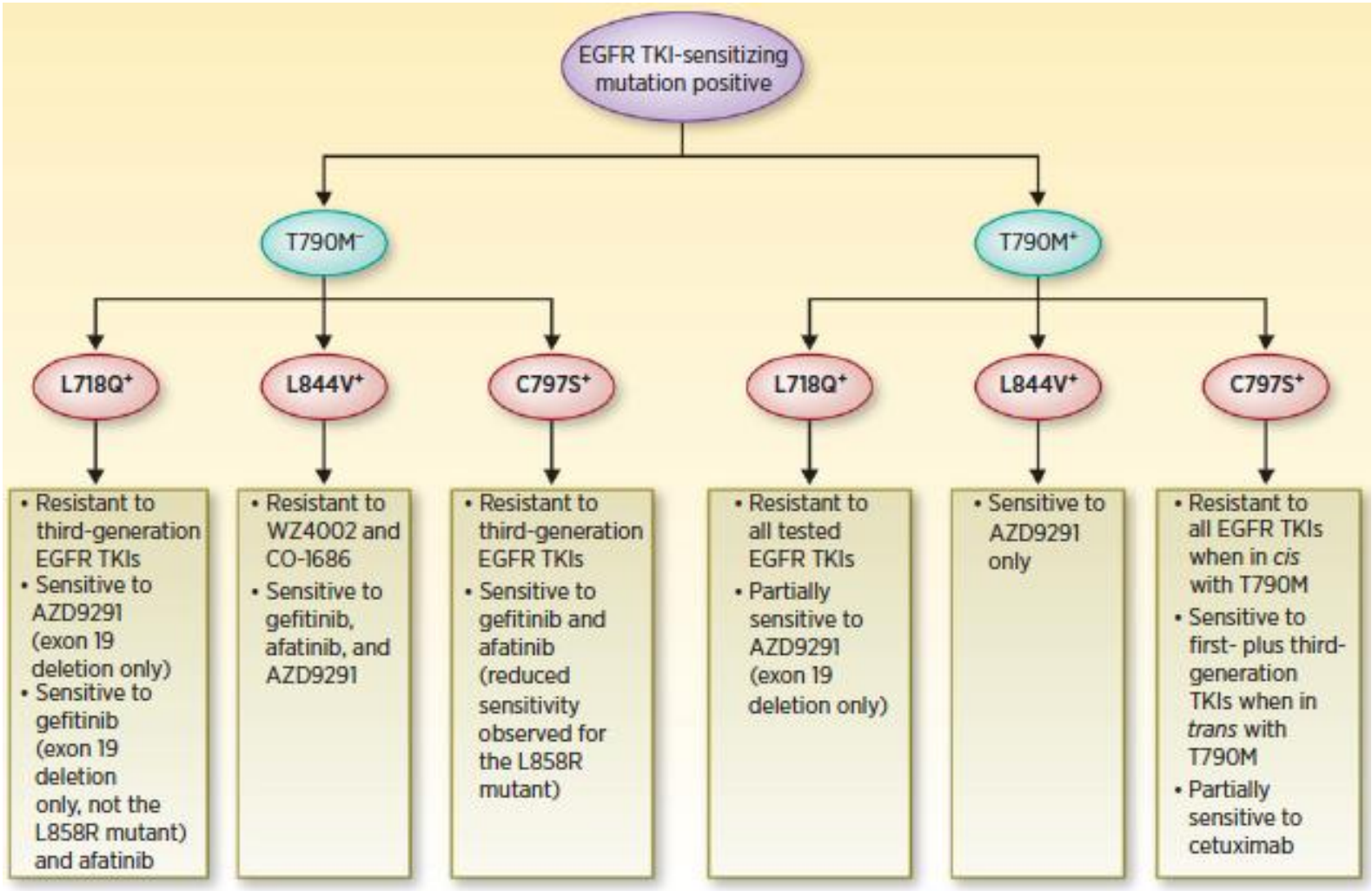
- Study of cell free plasma DNA (cfDNA) from 15 patients with acquired resistance to AZD9291 (all had T790M at the start of AZD9291).
- 6/15 cases: acquired C797S mutation
  - genotype: *EGFR* exon19 del, T790M, C797S
- 5/15 cases: maintained T790M; no C797S
  - genotype: *EGFR* exon19 del, T790M
- 4/15 cases: lost T790M mutation
  - genotype: *EGFR* exon19 del





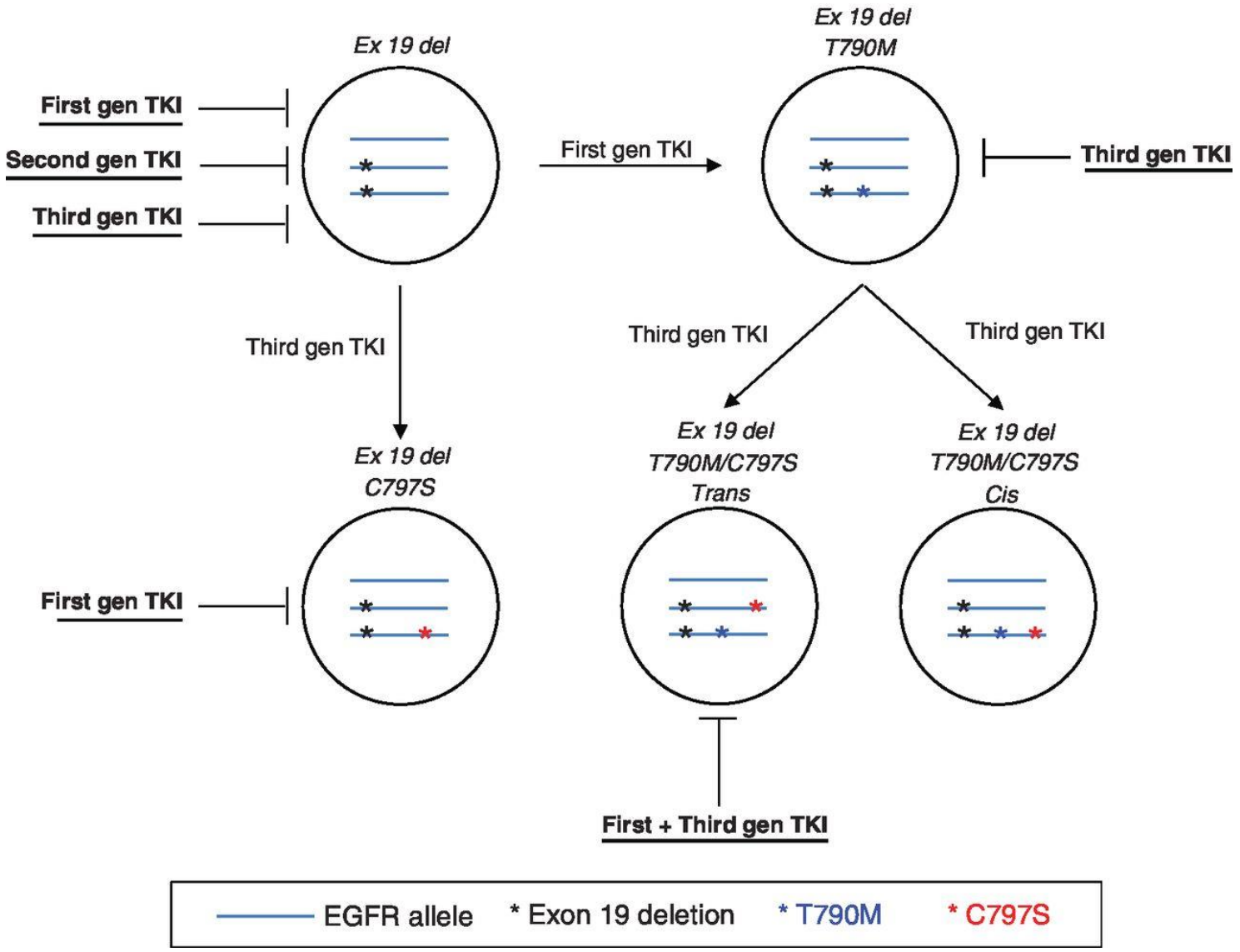
Thress et al Nature Medicine 2015

Sensitivity of different combinations of primary, secondary and tertiary combinations of EGFR mutations



Ayeni D. et al. Clin. Cancer Res. 2015; 21:3818-22

Acquired resistance to *EGFR T790M* specific TKIs
The next issue…New treatment algorythms?



Niederst MJ et al. Clin. Cancer Res. 2015; 21:3924-33

Future Directions & Ongoing Questions

1) Multiple third-generation EGFR inhibitors being developed.
   - ✓ High response rates across the board in first/second generation resistant tumors with T790m.

2) Optimal sequence of these EGFR inhibitors is currently unknown.
   - ✓ The presence of specific EGFR resistance mutations to 3rd generation EGFR TKIs will also matter in selecting therapy.
   - ✓ AEs may dictate use of specific agents in specific clinical contexts.

3) Will first generation EGFR TKIs be replaced as the first-line treatment in EGFR mutated tumors?

4) Will these agents be effective in the adjuvant setting?

5) How will immune therapy play a role in combination with these agents?

6) What is the prognostic role of these tertiary mutations ?

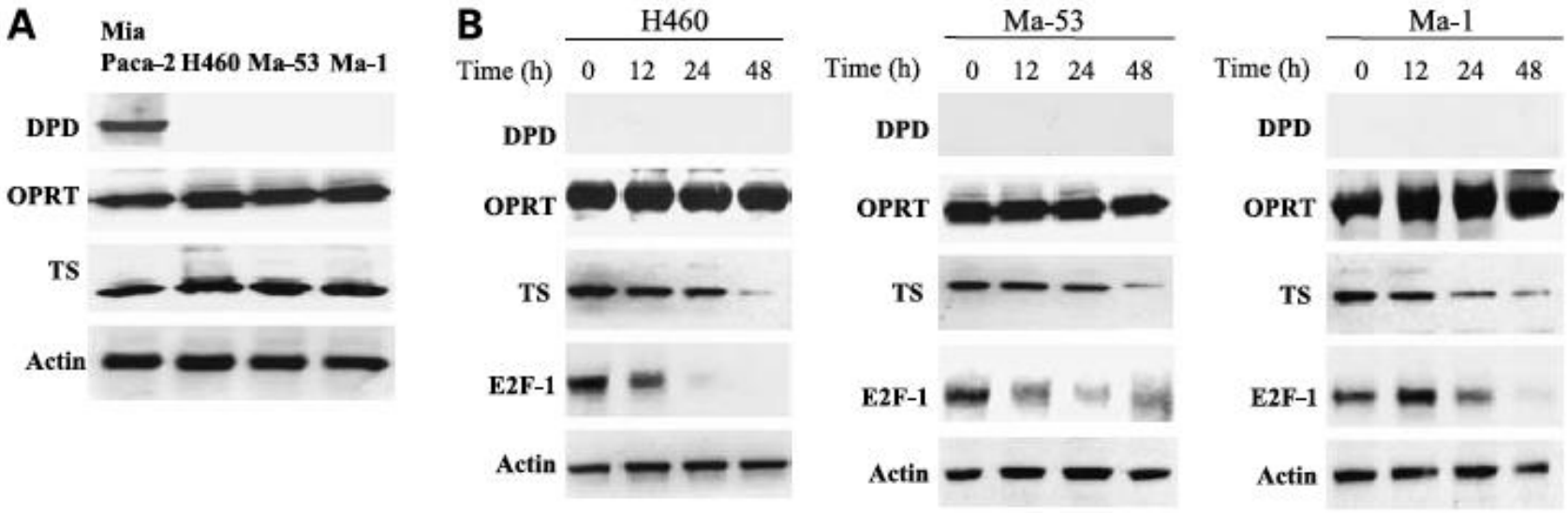
Discussion

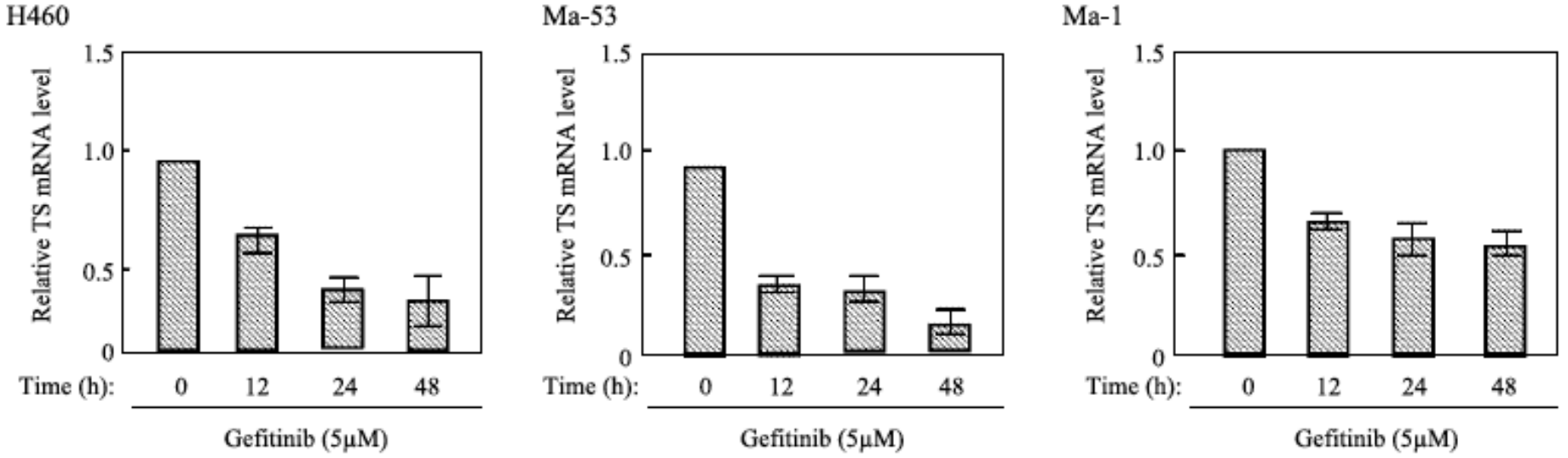
- *Abstract 130O – Efficacy and safety of BI 1482694 (HM61713), an EGFR mutant-specific inhibitor, in T790M-positive NSCLC at the recommended phase II dose – Keunchil Park et al*
- *131O - Combination of chemotherapy and gefitinib as first-line treatment of patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomised controlled trial - Baohui Han et al*

Key features of the study

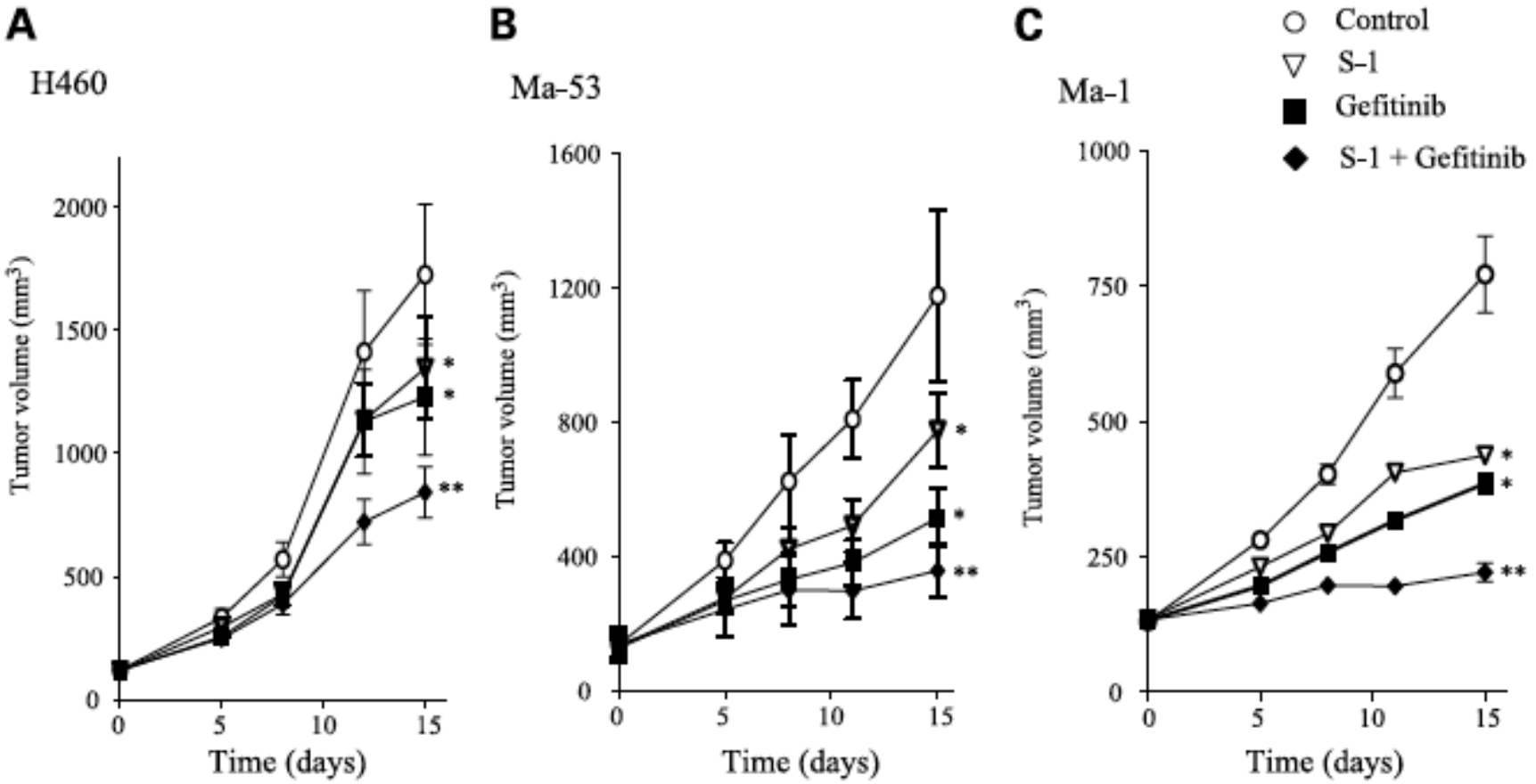
- **Hypothesis** : Lower TS expression in EGFR mutants and gefitinib down-regulate TS. **Activity of AC in front line when combined with Gefitinib**
- Small phase II randomized East-Asian study (≈ 40 per arm) with some (expected unbalances in demographics)
- DCR inferior for AC
- Data indicate a PFS benefit for AC+G versus G versus AC . OS data not available
- PFS data for del19 indicate a not significant difference between G and G+AC
- Toxicity profile of G versus G+AC pretty similar. No ILD

Down-regulation of TS by Gefitinib in NSCLC





Synergystic activity of gefitinib with S-1 through TS down-regulation

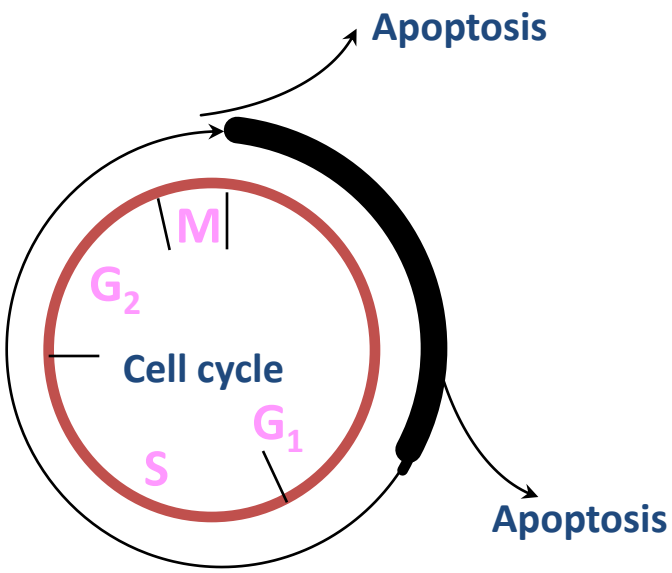


How to investigate Pem plus Gefitinib in the clinical setting

- Concurrent Gefitinib and Pemetrexed
  (as previously done in INTACT and TRIBUTE)
- Intercalating Gefitinib and Pemetrexed
- (as in the FASTACT trial)
- Pemetrexed followed by Gefitinib (similarly to INFORM trial)
- Adding Pemetrexed at progression
- Confounding Factors : EGFR mutation vs. clinically enriched vs. general population and line of therapy

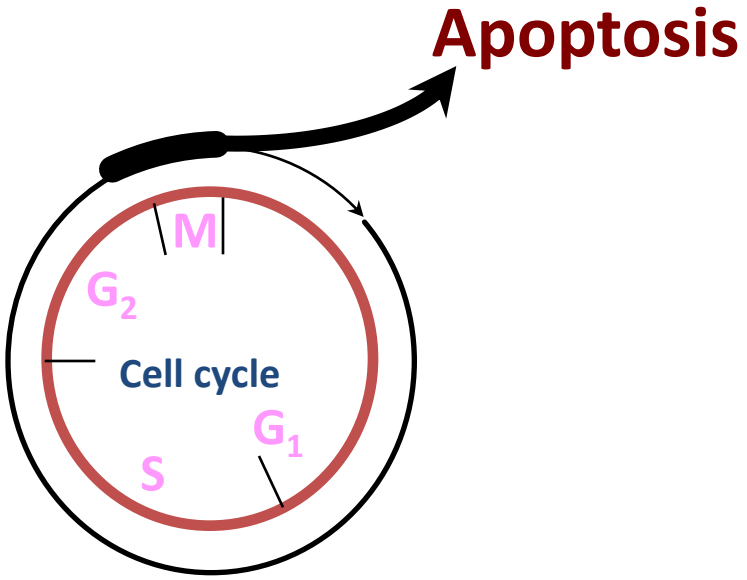
Intercalating EGFR-TKIs and Chemotherapy

Erlotinib → docetaxel



Erlotinib induces G_1 arrest, which can block the M-phase activity of docetaxel

Docetaxel → Erlotinib



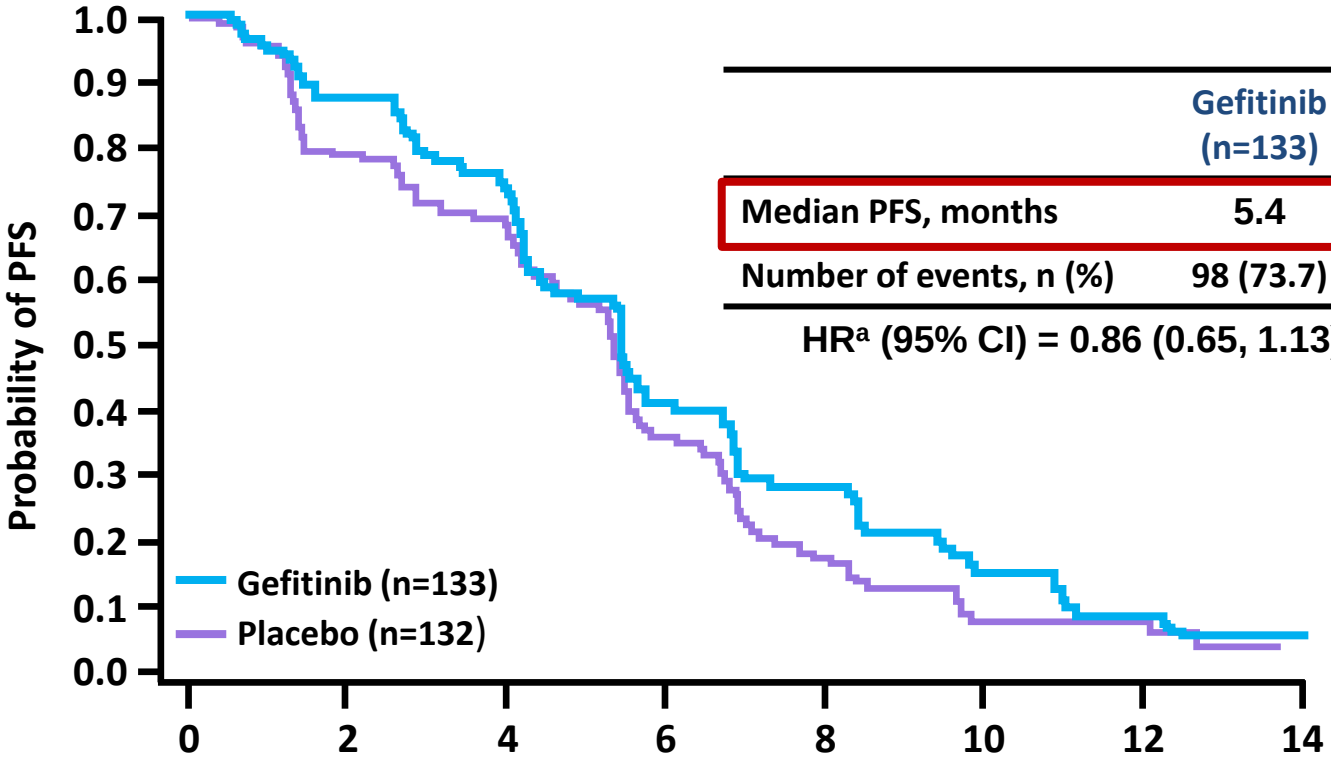
Docetaxel induces M-phase arrest and apoptosis,enhanced by the anti-cell survival effect of erlotinib

Gandara D, et al. Clin Cancer Res 2005;11(Suppl. 13):5057s–62s

Chemotherapy added to EGFR-TKI

Study	Phase	N	Primary Endpoint	Patients	Treatment arm
STEP (UMIN000006433)	II	60	PFS	Acquired resistance to Gefitinib →	Gefitinib + S-1
LOGiK1102 (UMIN000006976)	II	80	PFS	Acquired resistance to 2nd line~ EGFR-TKI →	EGFR-TKI + Singlet chemo Singlet chemo
JMTO LC12-01 (UMIN000007765)	II	60	PFS	≥75 years, Acquired resistance to 1st line Gefitinib →	Gefitinib + DTX DTX
LOGiK1105 (UMIN000008027)	II	70	PFS	≥70 years, Acquired resistance to 1st line Gefitinib →	Gefitinib + Singlet chemo Singlet chemo
NEJ017 (UMIN000008364)	II	100	PFS	≥75 years or PS2, Acquired resistance to 1st line EGFR-TKI →	EGFR-TKI + DTX or PEM DTX or PEM
IMPRESS (NCT01544179)	III	250	PFS	Acquired resistance to 1st line Gefitinib →	Gefitinib + CDDP/PEM CDDP/ PEM

IMPRESS - PFS (primary endpoint; ITT)



	Gefitinib (n=133)	Placebo (n=132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

HR[a] (95% CI) = 0.86 (0.65, 1.13); p=0.273

Patients at risk:

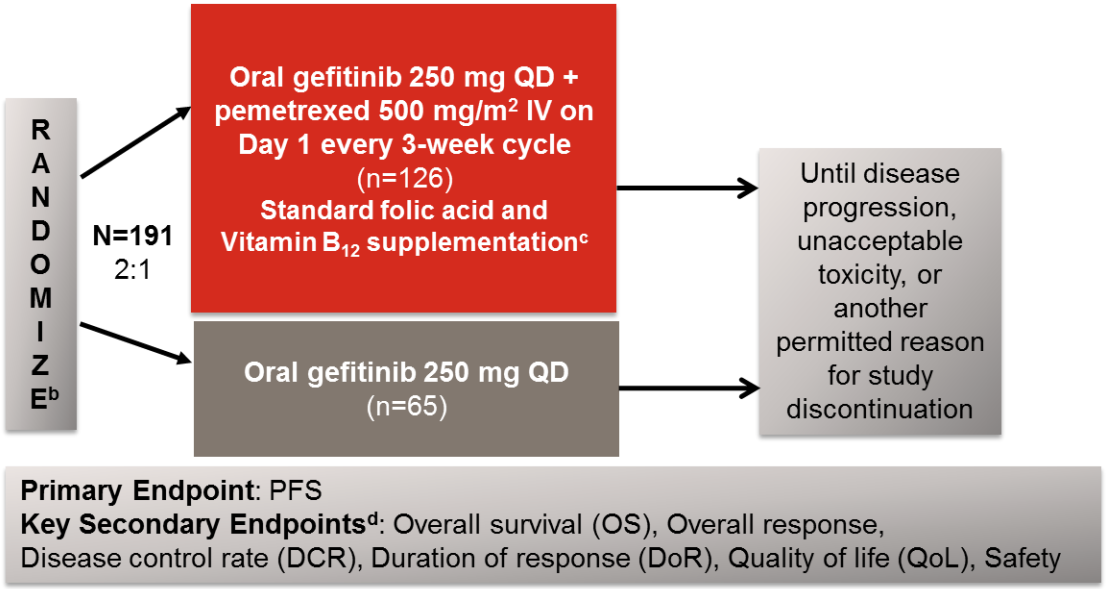
Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

Soria JC et al. Lancet Oncol. 2015; 16: 990-98

Phase II study of gefitinib ± pemetrexed as first line therapy in EGFR mutants

Inclusion Criteria:

- Adult patients ≥18 years (≥20 years in Japan and Taiwan)
- Confirmed advanced (Stage IV) or recurrent NS NSCLC[a]
- Activating EGFR mutations
- ECOG PS ≤1
- No prior systemic chemotherapy, immunotherapy, or biological therapy

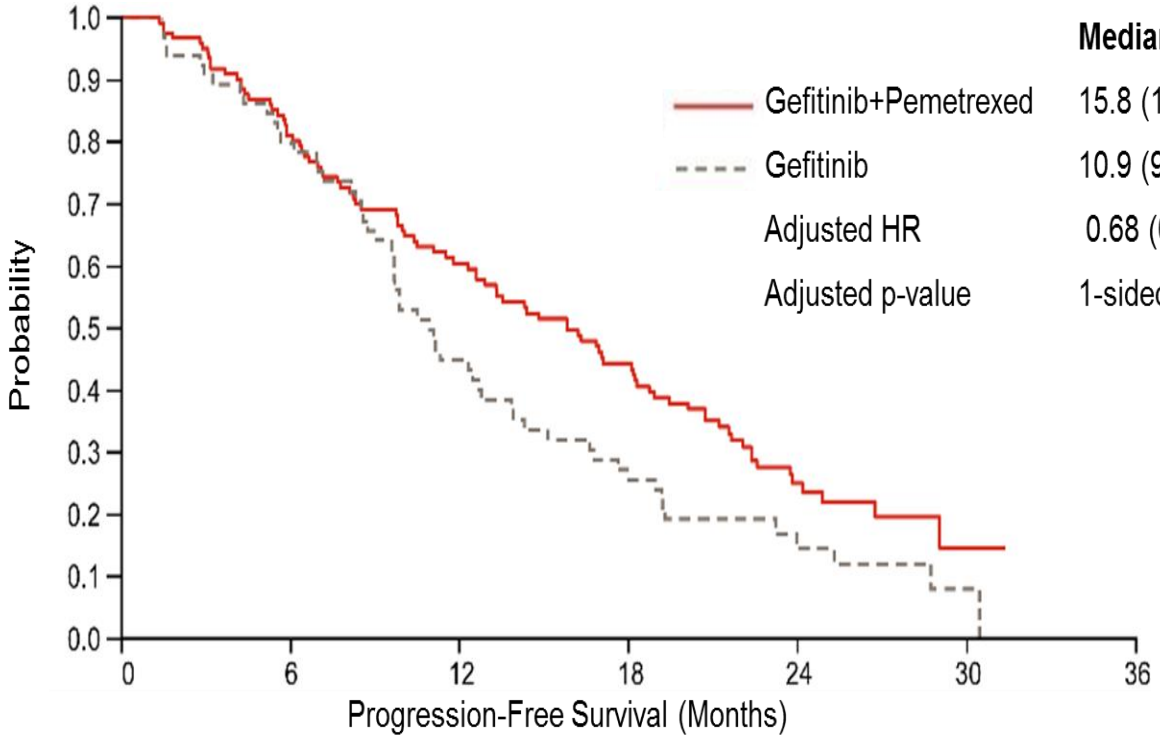


- **Enrollment period:** February 2012 – August 2013
- **Data cut-off date:** 22 April 2015

- Planned enrollment of 188 patients for 145 PFS events with 70% power to detect an HR=0.79 with a one-sided α level of 0.2
- Tumor samples were collected for biomarker analyses
- Patients were followed up approximately every 90 days (±14 days) after study treatment discontinuation for survival

Cheng Y. et al. Proc. IASLC 2015 –oral 17.2

Primary Endpoint: PFS – ITT Population



Median PFS, months (95% CI)	
Gefitinib+Pemetrexed	15.8 (12.6, 18.3)
Gefitinib	10.9 (9.7, 13.9)
Adjusted HR	0.68 (0.48, 0.96)
Adjusted p-value	1-sided=.014; 2-sided=.029

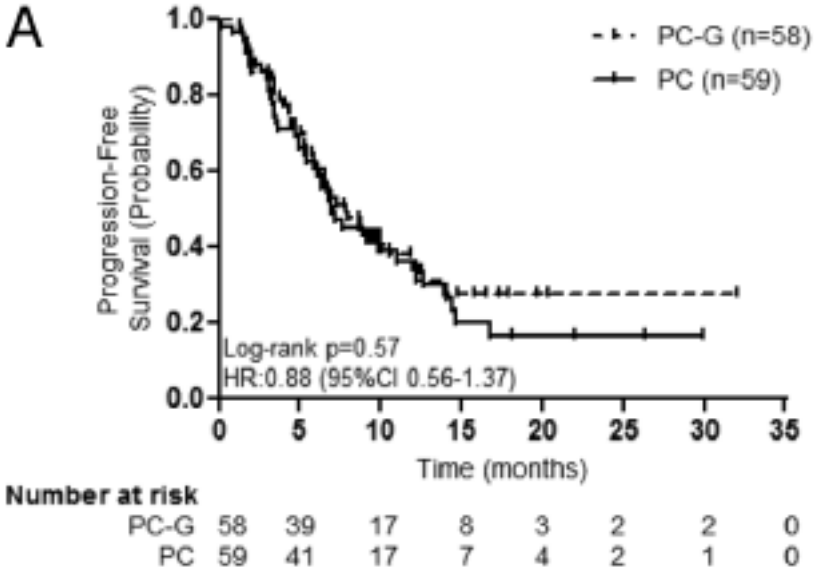
Patients at Risk							
Gefitinib+Pemetrexed	126	97	69	49	18	1	0
Gefitinib	65	51	28	17	6	1	0

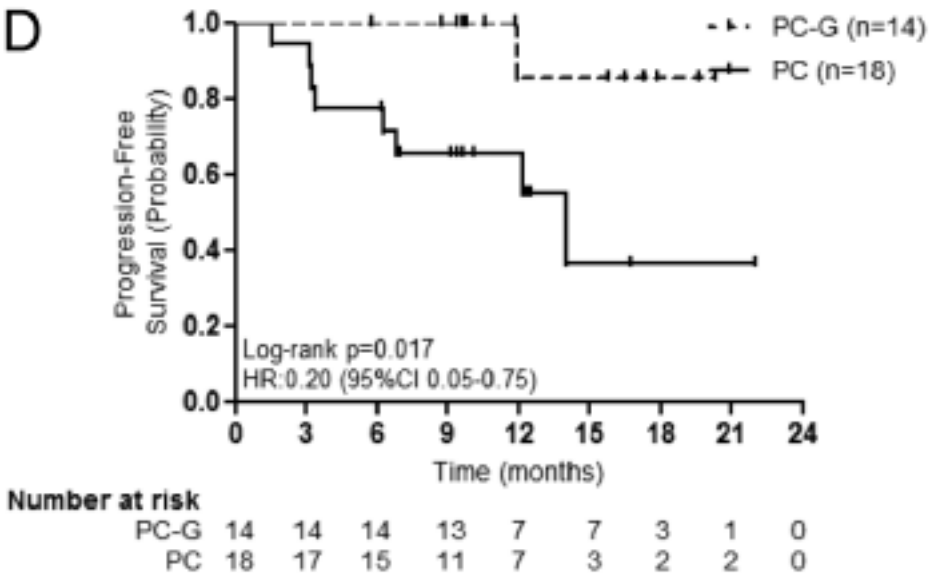
Subgroup analysis : G+P more active in female, never smokers and Korean vs. others patients

Cheng Y. et al. Proc. IASLC 2015 –oral 17.2

Randomised phase II study of gefitinib + pem/platinum vs. pem/platinum in NS- NSCLC

Gefitinib intercalated on days to 16 of a 3 week cycle
Enrolled and randomized n=117 – PC-G n=58 – PC n=59
Primary end point : non progression rate at 12-weeks (84.5% versus 83.1%, p=0.87)
ORR 50% versus 47.4%
Toxicity : Higher incidence of skin rush in PC-Gefitinib





Yu H. et al. Cancer Biol. Ther. 2014; 15:832-9

Phase III study of Pemetrexed /Cisplatin followed by Gefitinib versus Gefitinib Alone in Never Smoker Asians with advanced NS-NSCLC

- NSCLC: Non-squamous histology
- Stage IIIb/IV
- Chemo-naïve (1st line)
- PS: 0-1
- Never smoker or light ex-smoker**
- Unknown, untested, inconclusive EGFR mutation status

R

N=226

Pemetrexed 500mg/m² + Cisplatin 75mg/m², IV x 6 cycles, Q3W

Gefitinib 250mg/day PO

PD

CR/PR/SD

Gefitinib 250mg/day PO

PD

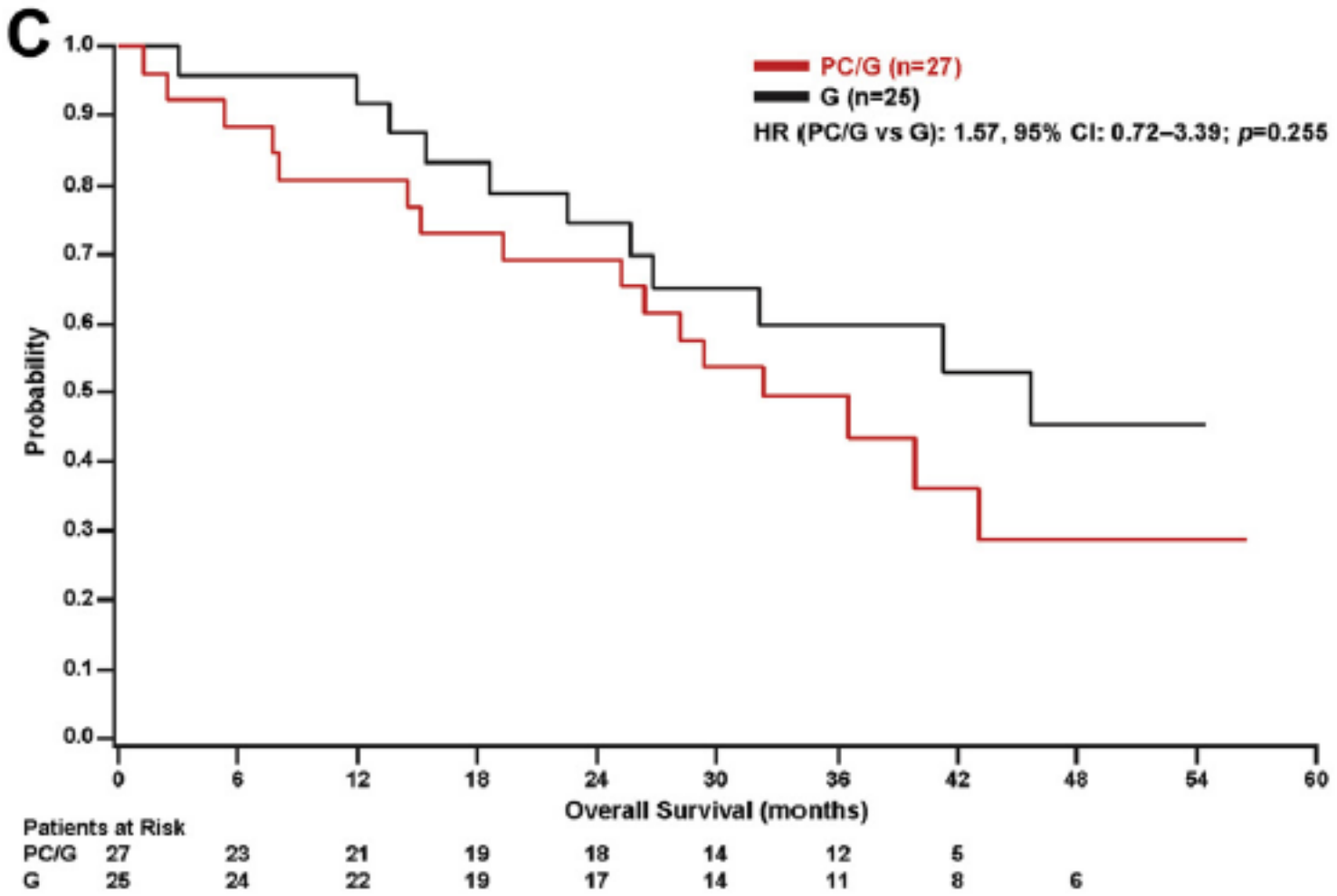
Primary Endpoint:

Superiority in PFS

Assuming HR: 0.68

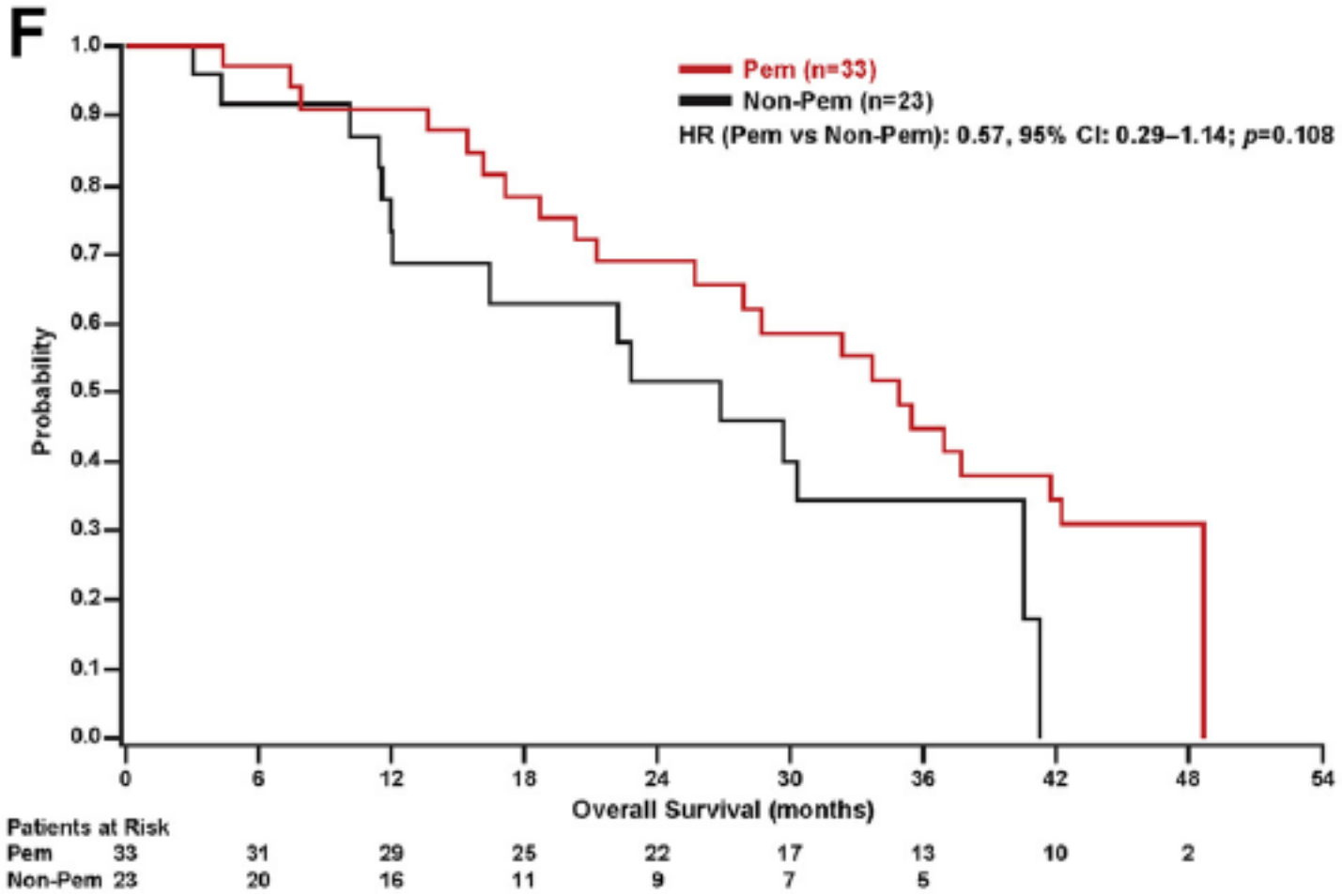
Yang J et al JTO 2016 ; 11:370-79

Phase III study of Pemetrexed /Cisplatin followed by Gefitinib versus Gefitinib Alone in Never Smoker Asians with advanced NS-NSCLC



Yang J et al JTO 2016 ; 11:370-79

Second line post-discontinuation therapy in the Gefitinib arm



Yang J et al JTO 2016 ; 11:370-79

Future Directions & Ongoing Questions

- Although chemo is more effective in EGFR mutants the level of activity is definitively inferior to dedicated targeted therapies
- Is the combination of pemetrexed and gefitinib (or any EGFR TKI) a research priority? No
- A role for chemo (concurrent od intercalated to EGFR TKI) may theoretically exist for Exon21 mutations
- Are the data today presented worth of a phase III study? Not sure