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METASTATIC NON-SMALL CELL LUNG CANCER:

Resistance to EGFR TKIs

CLINICAL CASE DISCUSSION

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DISCLOSURE

Consultant: Astra Zeneca, Boehringer Ingelheim, Pfizer, Genentech/Roche, Chugai Pharmaceuticals, Merrimack Pharmaceuticals, Ariad, Ignyta, LOXO Oncology, Eli-Lilly, Araxes Pharmaceuticals, Mirati Therapeutics, SFJ Pharmaceuticals

Research Support: Astellas, AstraZeneca, Daiichi-Sankyo, PUMA, Eli-Lilly, Boehringer Ingelheim

Stockholder: Gatekeeper Pharmaceuticals, LOXO Oncology

Other: LabCorp – post-marketing royalties from DFCI owned intellectual property on *EGFR* mutations

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CLINICAL PRACTICE GUIDELINES

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

D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

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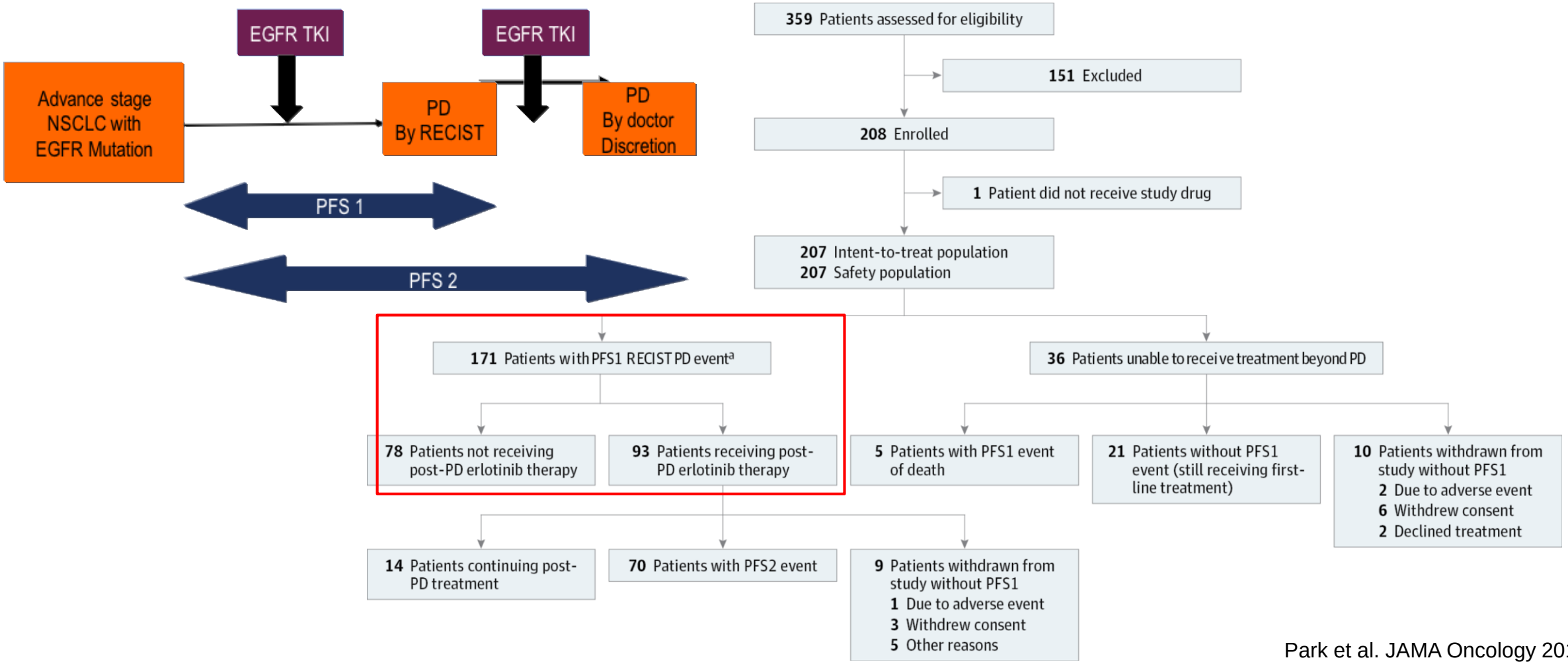
Q1. Treatment options?

1. Continue erlotinib until patient is symptomatic?
2. Switch to chemotherapy and stop erlotinib?
3. Add in chemotherapy and continue erlotinib?
4. Perform rebiopsy and treat according molecular profile?
5. Switch to chemotherapy plus immunothreapy?

ASPIRATION Study – continuation of first-line erlotinib post RECIST defined progression



Park et al. JAMA Oncology 2016

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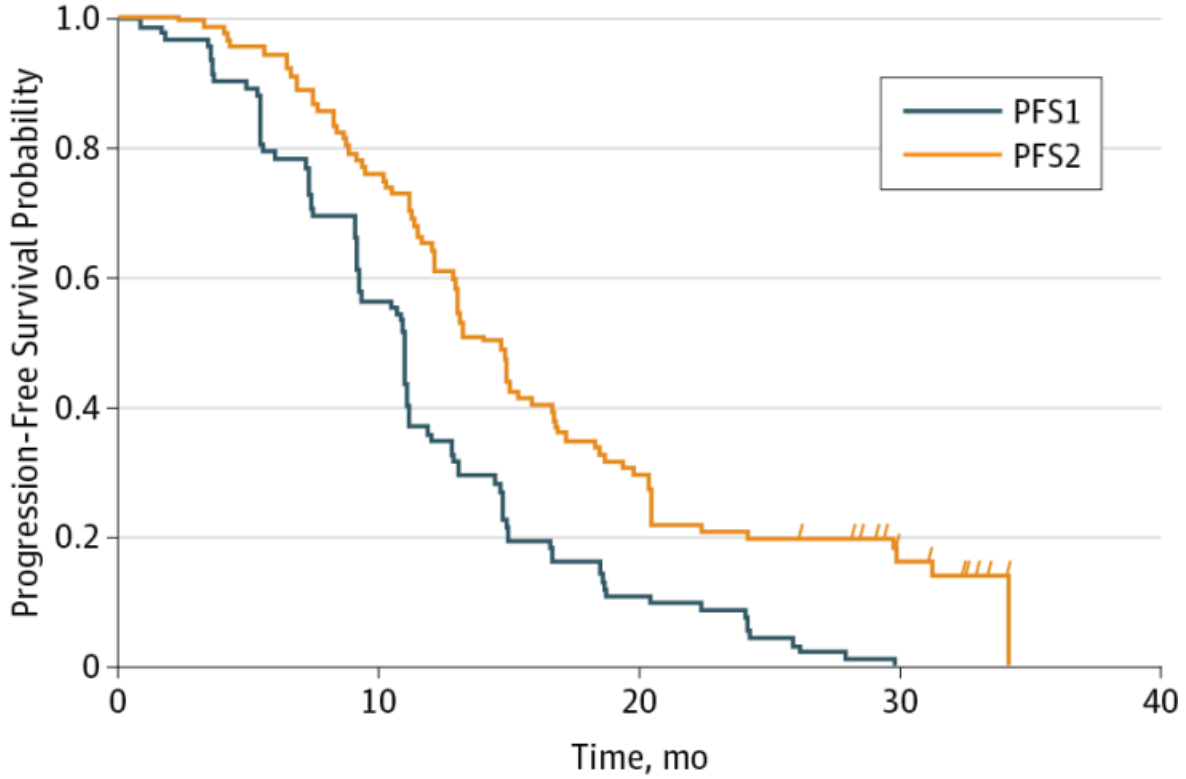
EGFR, epidermal growth factor receptor; NSCLC, non-small cell cancer; PD, PD-1, programmed cell death protein 1 and PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor;

ASPIRATION Study – continuation of first-line erlotinib post RECIST defined progression



No. at risk					
PFS1	93	52	10	0	0
PFS2	93	70	27	9	0

PFS 1 = 11.0 months; PFS 2 = 14.9 months

Patients who continued post PFS therapy had better PS, longer initial PFS and better depth of response

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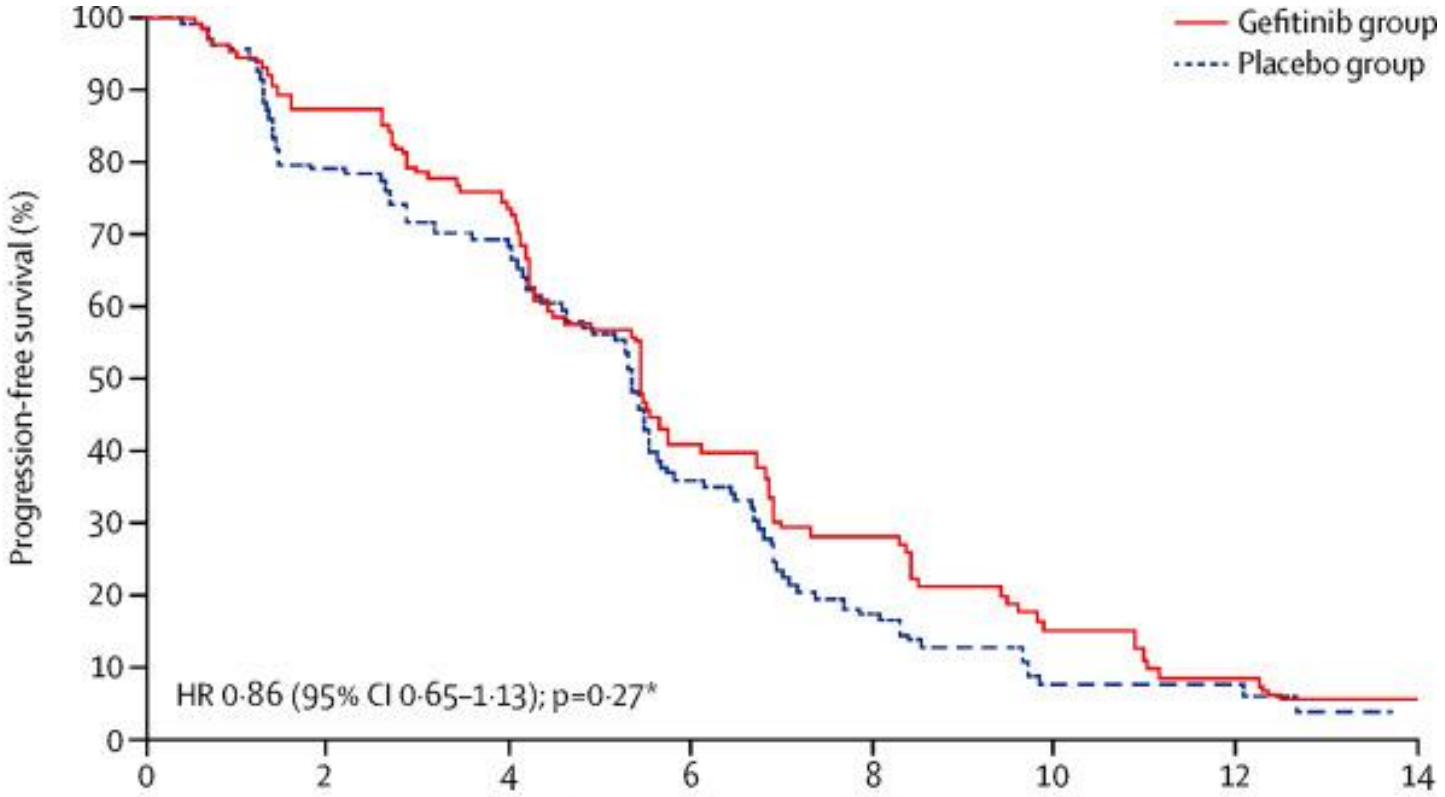
PFS, progression-free survival; PS, performance status

Park et al. JAMA Oncology 2016

IMPRESS – Evaluation of continuation versus stopping of gefitinib at the time of chemotherapy following disease progression to first-line gefitinib therapy



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

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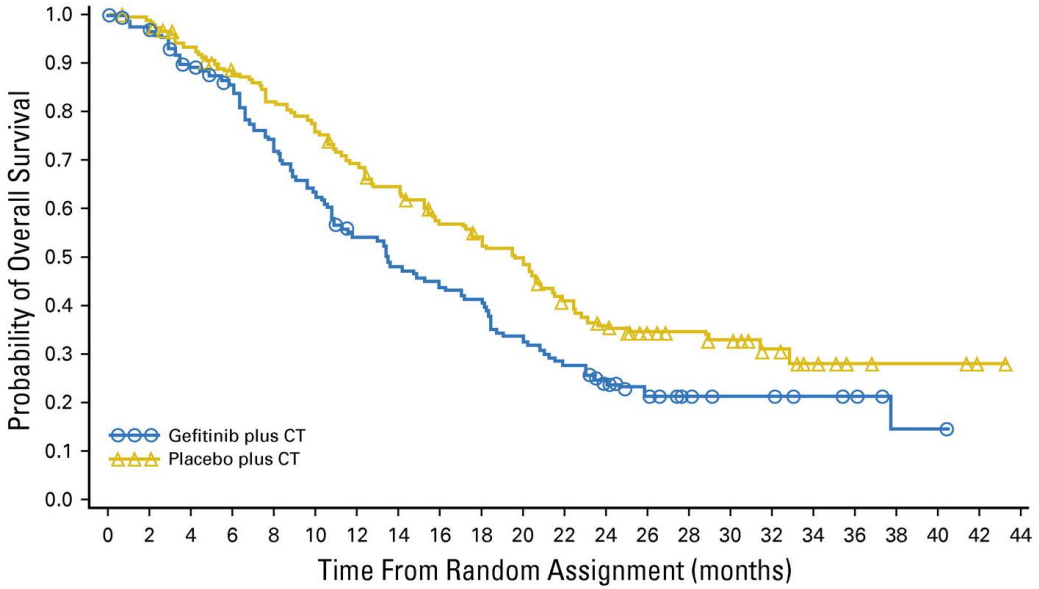
Soria JC et al. Lancet Oncol 2015

IMPRESS – Evaluation of continuation versus stopping of gefitinib at the time of chemotherapy following disease progression to first-line gefitinib therapy



No. at risk:

Gefitinib plus CT	133	125	111	103	87	76	63	56	51	48	38	32	23	16	11	9	9	6	5	2	2	0	0
Placebo plus CT	132	130	119	108	101	93	84	77	66	61	57	45	36	26	22	20	13	7	4	3	3	1	0

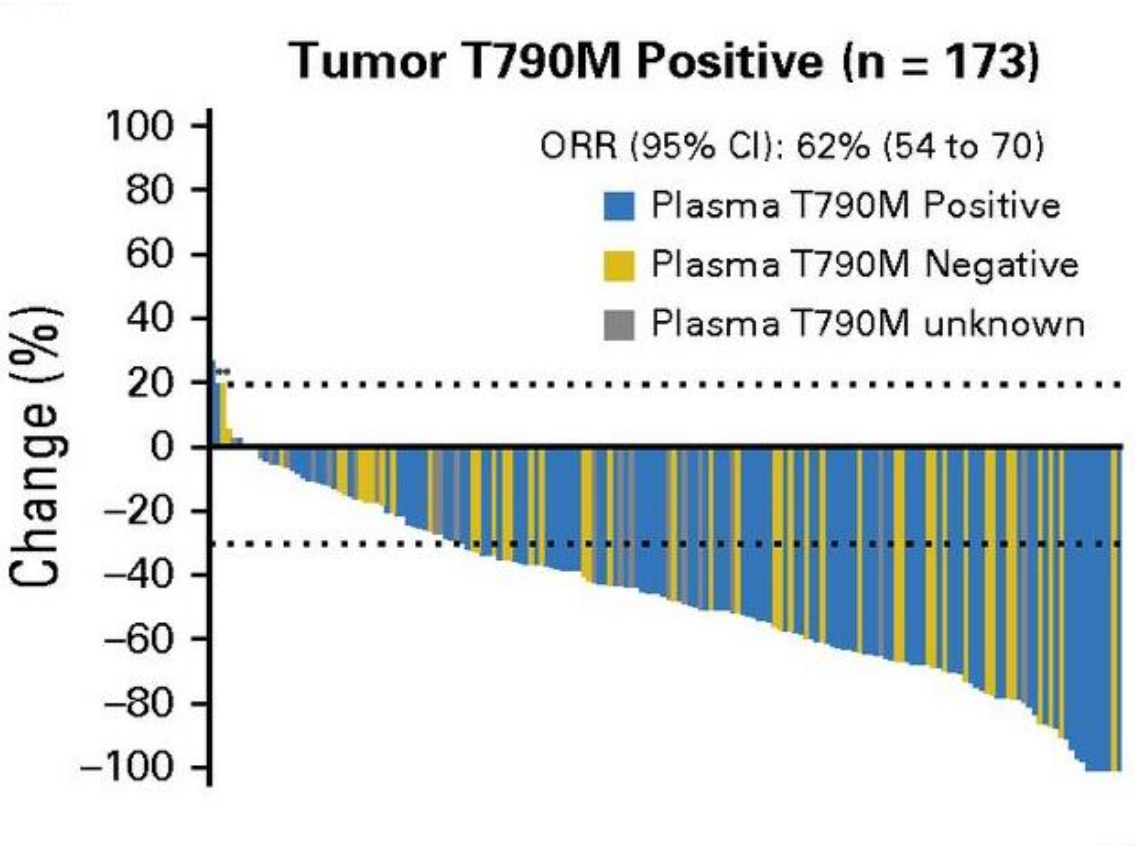
Final OS (66% maturity)	Gefitinib Plus CT (n = 133)	Placebo Plus CT (n = 132)
Median OS, months	13.4	19.5
No. of events, No. (%)	94 (70.7)	82 (62.1)
HR* (95% CI); *P* value	1.44 (1.07 to 1.94); *P* = .016	

2014 OS (33% maturity)	Gefitinib Plus CT (n = 133)	Placebo Plus CT (n = 132)
Median OS, months	14.8	17.2
No. of events, No. (%)	50 (37.6)	37 (28.0)
HR* (95% CI); *P* value	1.62 (1.05 to 2.52); *P* = .029	

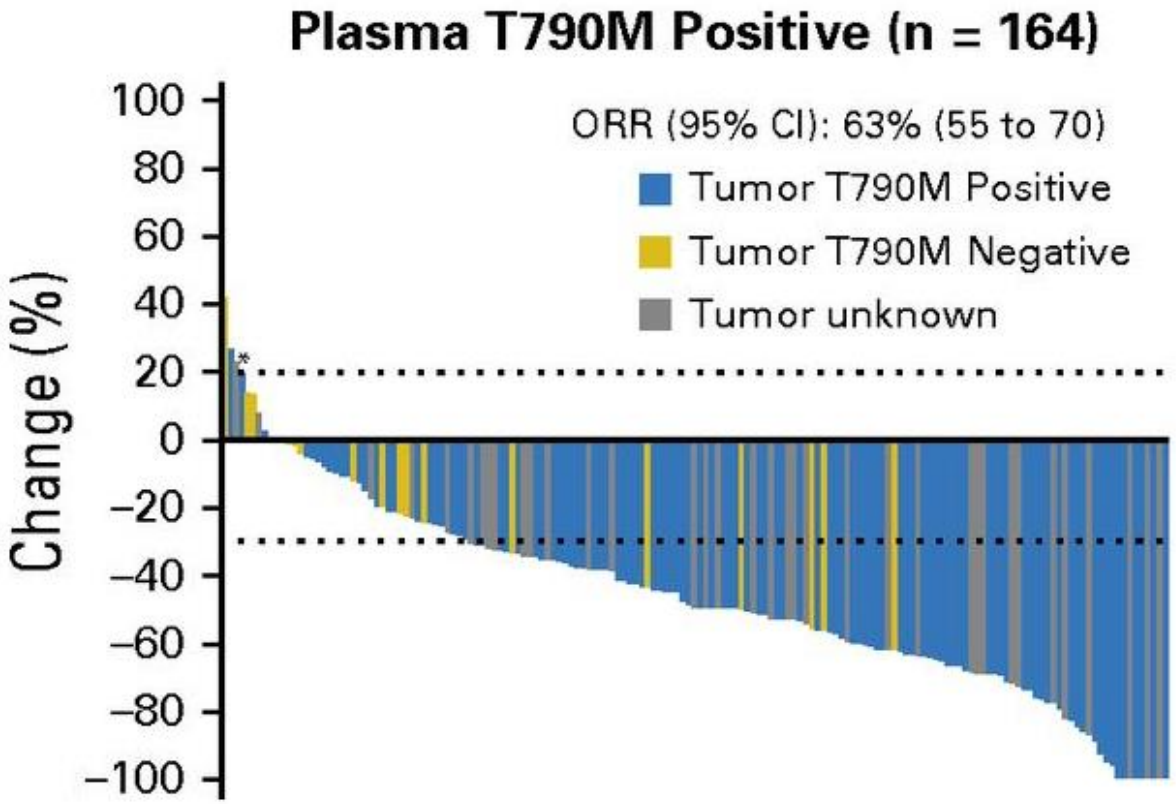
CT, chemotherapy; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Mok et al. JCO 2017

Use of tumour or plasma genotyping for *EGFR T790M* and the efficacy of osimertinib



PFS 9.7 months

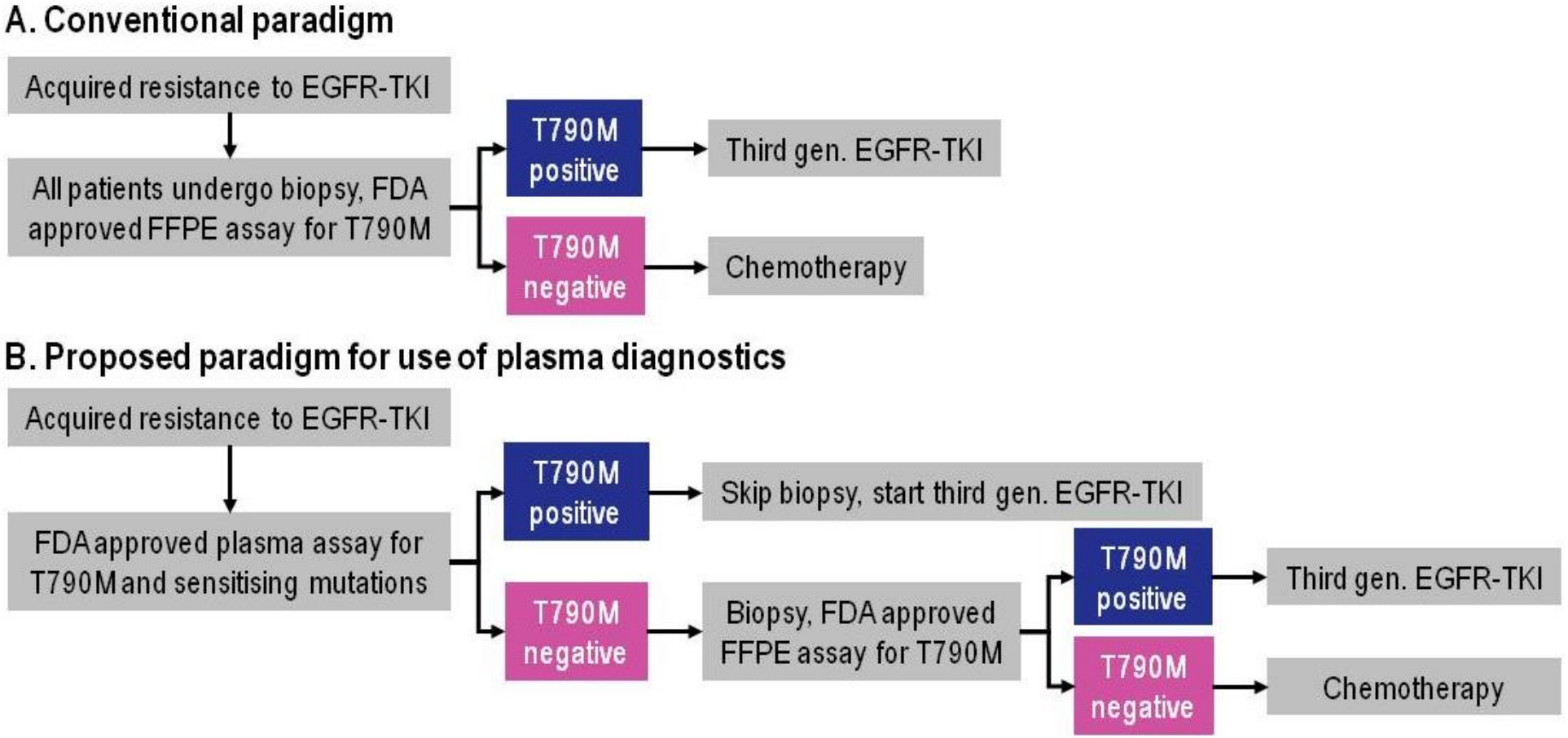


PFS 9.7 months

Oxnard et al. JCO 2016

EGFR, epidermal growth factor receptor; ORR, objective response rate; PFS, progression-free survival

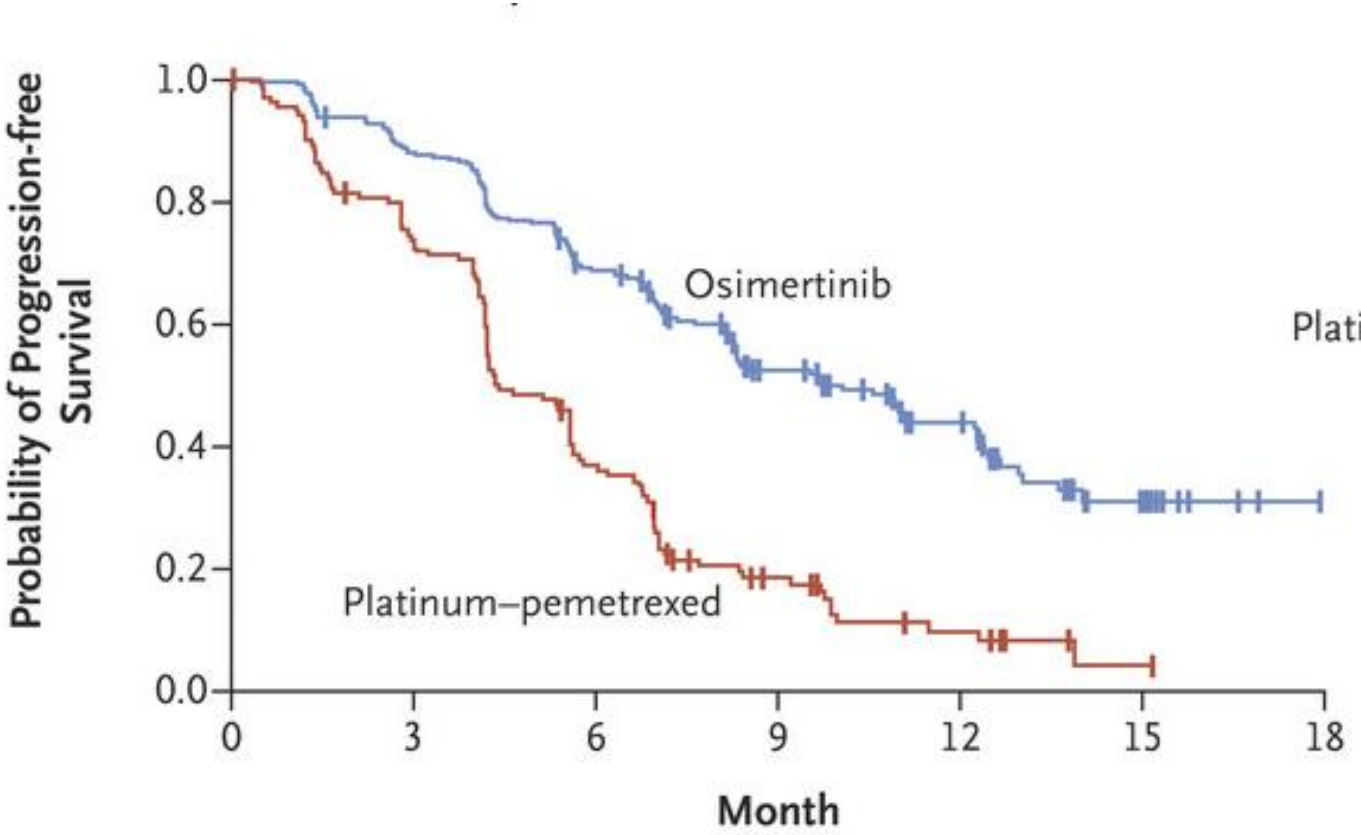
Use of tumour or plasma genotyping for *EGFR T790M* and the efficacy of osimertinib



Oxnard et al. JCO 2016

EGFR, epidermal growth factor receptor; FDA, United States Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; NSCLC, non-small cell cancer; RR, relative risk; TKI, tyrosine kinase inhibitor

Osimertinib versus chemotherapy in *EGFR T790M* NSCLC following progression on prior EGFR TKI treatment



	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

RR: 71% versus 31%; p < 0.001

Mok T. et al. NEJM 2017

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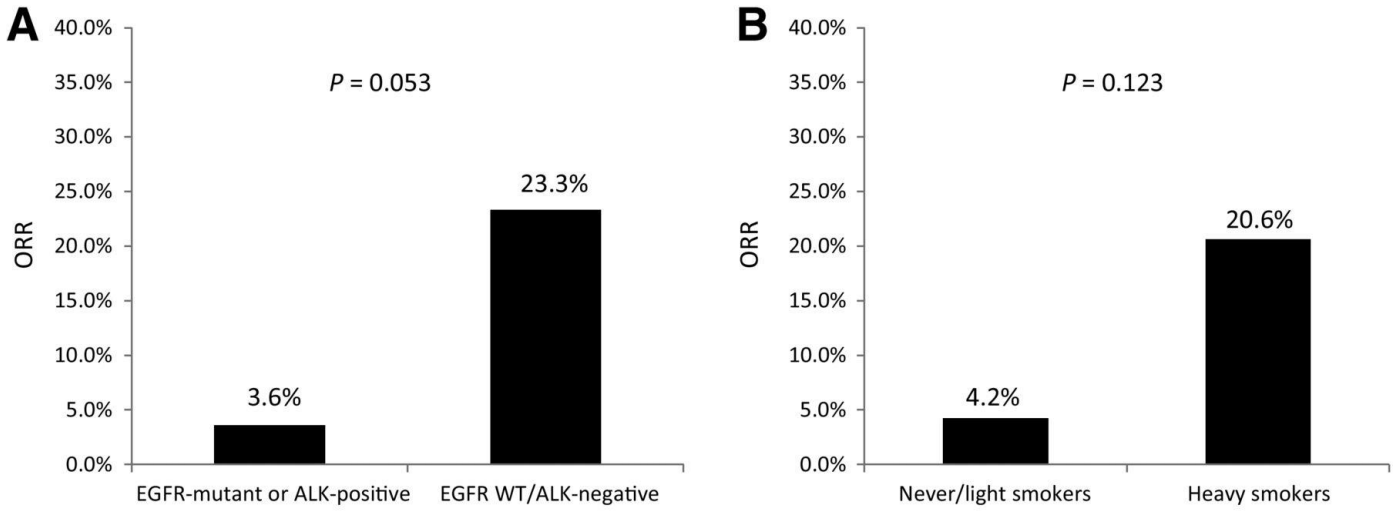
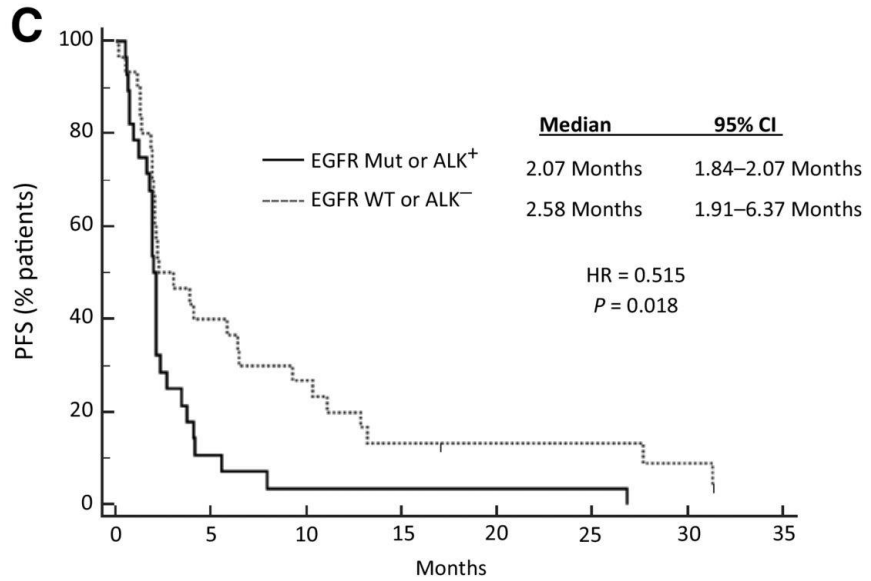
EGFR, epidermal growth factor receptor; NSCLC, non-small cell cancer; RR, relative risk; TKI, tyrosine kinase inhibitor

Efficacy of single agent anti-PD-1 or anti-PD-L1 therapies in *EGFR* mutant NSCLC patients



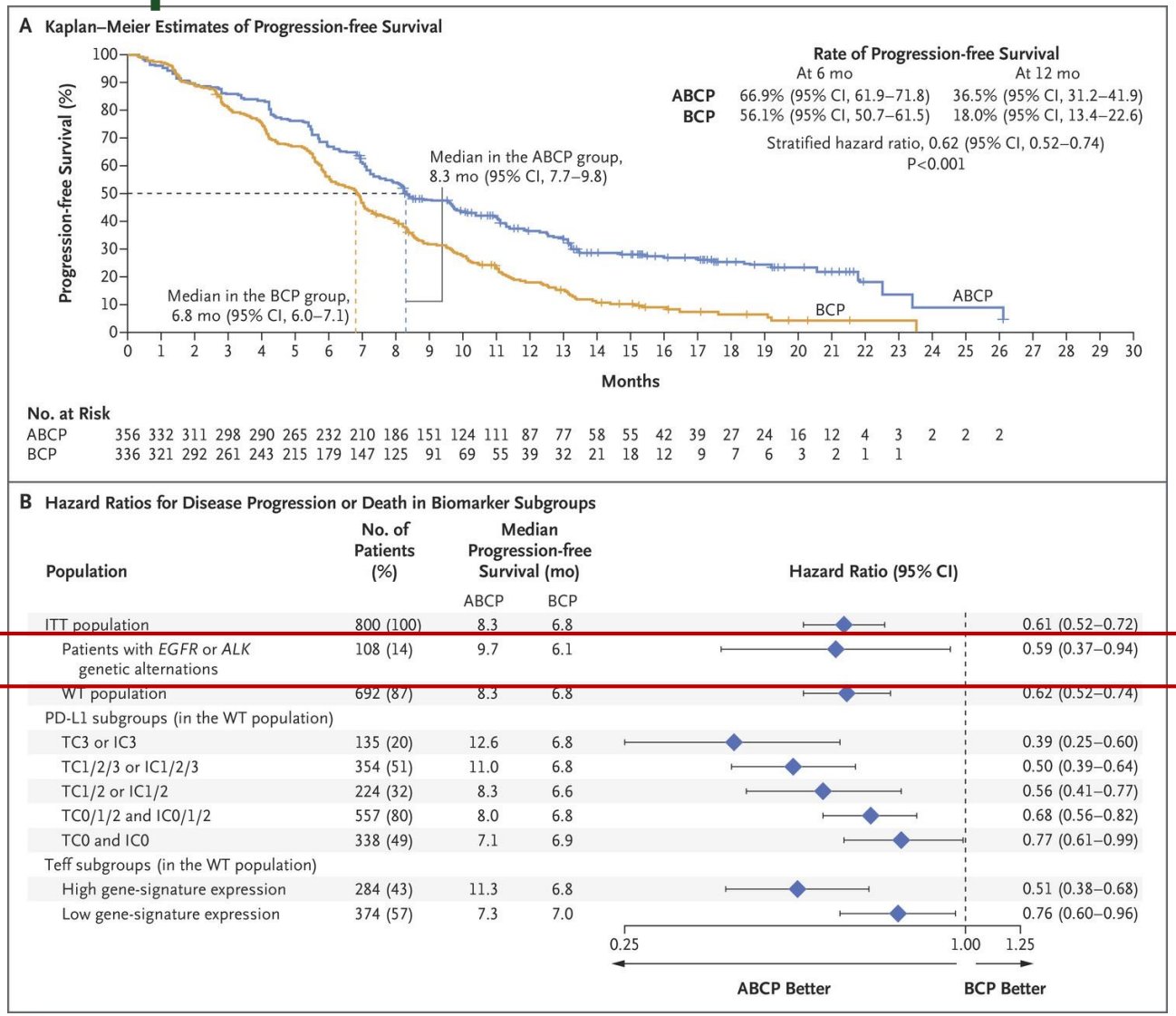


Chemotherapy/pembrolizumab trials (and label) excluded patients with *EGFR* mutations

Gainor et al. CCR 2016

EGFR, epidermal growth factor receptor; NSCLC, non-small cell cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1

Carboplatin/paclitaxel/bevacizumab/atezolizumab versus carboplatin/paclitaxel/bevacizumab in advanced NSCLC



ABCP, carboplatin/paclitaxel/bevacizumab/atezolizumab; BCP, carboplatin/paclitaxel/bevacizumab; NSCLC, non-small cell cancer

Socinski et al. NEJM 2018

Second-line treatment of *EGFR* mutant NSCLC – Summary

- EGFR TKI should be stopped when patient starts chemotherapy treatment for EGFR inhibitor resistance
- All tumours with clinical evidence of resistance, not previously treated with osimertinib, should be tested for *EGFR T790M*
- Testing for *EGFR T790M* can be from a liquid biopsy; if negative a tumour biopsy should be performed
- Osimertinib is the standard of care for patients with *EGFR T790M* detected either from a liquid or tissue biopsy
- Platinum based doublet chemotherapy is the standard of care for patients who are *EGFR T790M* negative from tissue biopsy (or liquid biopsy when tissue biopsy not feasible)
- Combination of carboplatin/paclitaxel/bevacizumab/atezolizumab is a potential treatment option once all targeted therapies have been exhausted

NSCLC, non-small cell cancer

ESMO Guidelines 2018, Planchard et al. Ann Oncol 2018

Progression after osimertinib

Chemotherapy alone or combination of carboplatin/paclitaxel/bevacizumab/atezolizumab are potential treatment options following progression of second-line osimertinib

Clinical trials underway to evaluate optimal strategy for osimertinib resistance including resistance based on a specific molecular alteration