EUROPEAN LUNG CANCER CONFERENCE 2016

Plasma genotyping for predicting benefit from osimertinib in patients with advanced NSCLC

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Disclosures

Geoffrey R Oxnard – Honoraria: Chugai; consultancy/advisory board: ARIAD, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, Inivata, Sanofi, Sysmex

Kenneth S Thress, Mireille Cantarini, and J. Carl Barrett – Employees and shareholders: AstraZeneca

Rachael Lawrance – Shareholder and former employee: AstraZeneca

Cloud P Paweletz – Honoraria: Bioved, Clovis Oncology

James C-H Yang – Honoraria: AstraZeneca, Boehringer Ingelheim, Chugai, Merck, Roche; consultancy/advisory board: Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly, Merck, Novartis, ONO, Pfizer, Roche/Genentech

Pasi A Jänne – Consultancy/advisory board: Acea Biosciences, AstraZeneca, Boehringer Ingelheim, Chugai, Merrimack Pharmaceuticals, Pfizer, Roche; research funding: Astellas, AstraZeneca

Ryan S Alden – no conflicts of interest

Introduction

- Osimertinib (AZD9291) is an oral, potent, irreversible EGFR-TKI which has shown clinical efficacy and manageable tolerability in patients with EGFR T790M positive advanced NSCLC[1,2,3]
- Osimertinib was recently approved for treatment of EGFRm T790M mutation positive metastatic NSCLC in US[4], EU[5] and Japan[6]
- Currently, testing for T790M at disease progression requires an additional biopsy which can lead to treatment delays and may not be feasible for all patients
- We hypothesized that genotyping of plasma cell-free DNA (cfDNA) could identify patients who gain clinical benefit from osimertinib

1. Cross et al. Cancer Discov 2014;4:1–16; 2. Jänne et al. Ann Oncol 2015;26:i60(abstr LBA63A); 3. Jänne et al. N Engl J Med 2015;372:1689–1699;
4. TAGRISSO (osimertinib) prescribing information, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf;
5. TAGRISSO Summary of Product Characteristics; available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004124/WC500202022.pdf;
6. TAGRISSO (osimertinib) Japan prescribing information, March 2016 Version 1;
cfDNA, cell-free DNA; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer

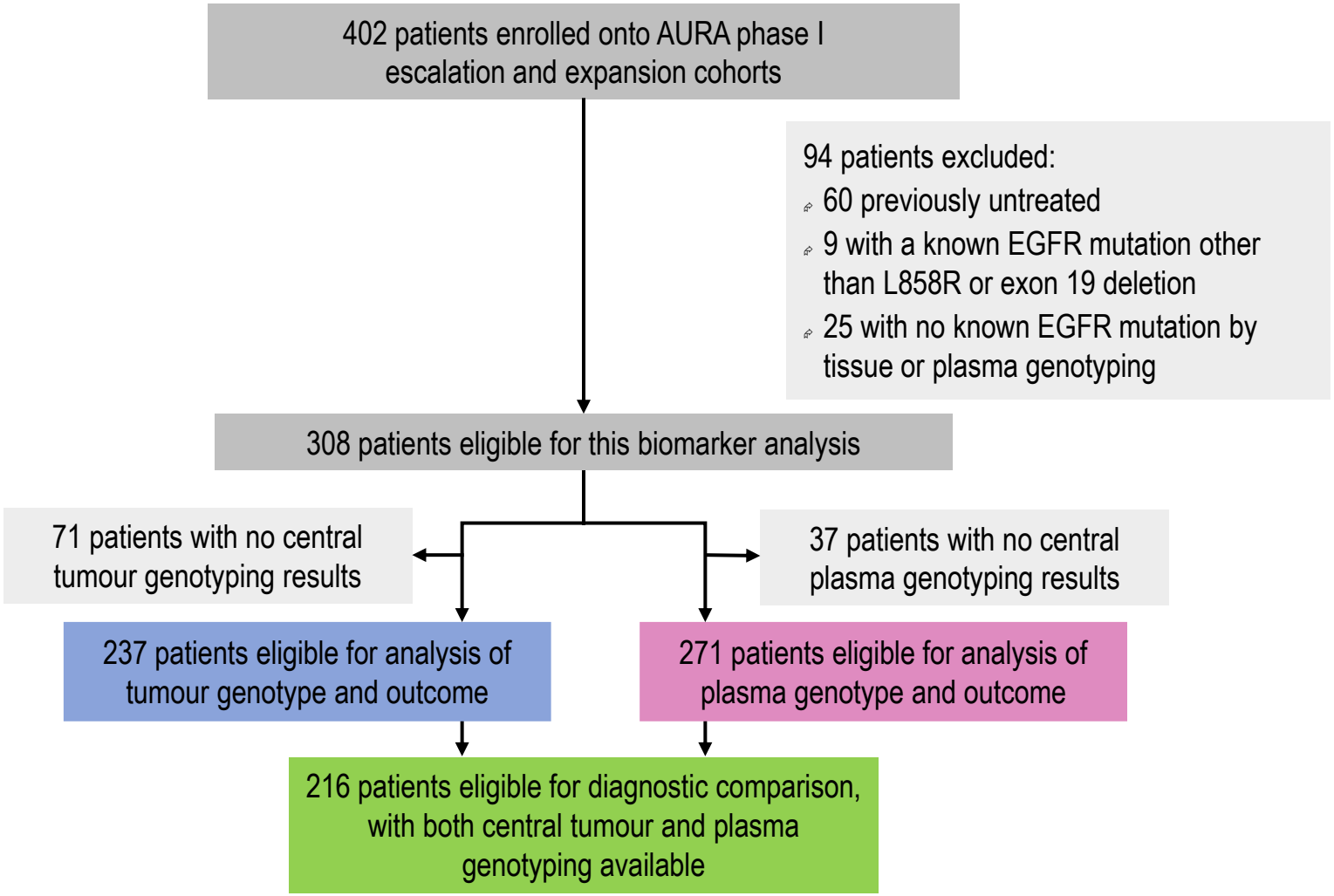
Plasma analyses in AURA trials

- Across the AURA trials (NCT01802632, NCT02094261), plasma was collected for analysis

	AURA Phase I	Phase II studies: AURA extension and AURA2
Treatment / dosing	Osimertinib dose escalation and dose expansion cohorts (20–240mg QD)	Osimertinib 80 mg QD
T790M status	T790M positive and negative	Only T790M positive
Analysis	Exploratory post-hoc analysis	Intention to treat for regulatory submission
Plasma assay	BEAMing	cobas
Method of comparison	ddPCR or cobas	NGS
ELCC presentation	Oxnard G. et al; 135O	Jenkins S. et al; 134O [Yang J. presenting]

The **cobas**® EGFR Mutation Test is not available for use with plasma samples in U.S
BEAMing, Beads, Emulsification, Amplification and Magnetics; ddPCR, droplet digital PCR; NGS, next generation sequencing; QD, once daily

Eligible study population



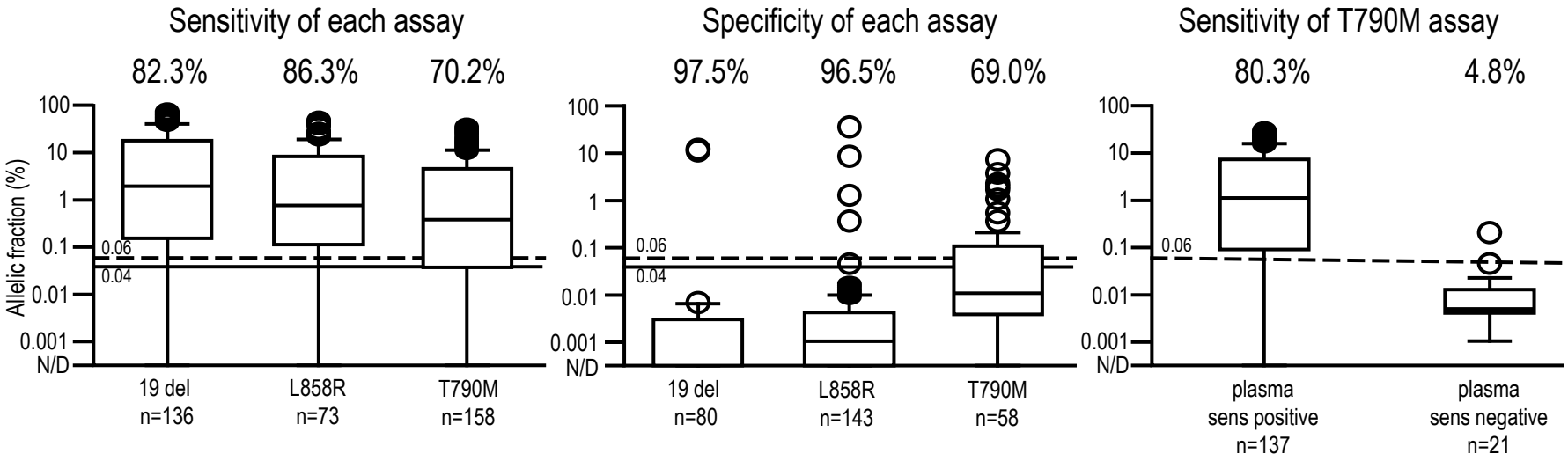
Data cut-off: 1 May 2015

Inclusion criteria and methodology

- Patients treated on the AURA trial (NCT01802632) were included if they had:
  - Previously treated advanced NSCLC
  - A common EGFR sensitising mutation
  - Central tumour genotyping or central plasma genotyping results
- Central plasma genotyping was performed using BEAMing
  - Positive for L858R or exon 19 del: Allelic fraction (AF) ≥ 0.04%*
  - Positive for T790M: Allelic fraction (AF) ≥ 0.06%*
- ORR and median PFS were assessed based on:
  - Presence or absence of a T790M mutation in tumour genotyping
  - Presence of absence of a T790M mutation in plasma genotyping
  - Data cutoff for this analysis: 1 May 2015

*Plasma was considered positive by BEAMing for a given mutation if the mutation was detected above the thresholds used for clinical application of the BEAMing assay
AF, allelic fraction; ORR, objective response rate; PFS, progression free survival

Sensitivity / specificity of plasma genotyping



- Sensitivity was 82–86% for sensitising mutations and 70% for T790M
- False positive rate was 3–4% for sensitising mutations but higher (31%) for T790M, perhaps due to heterogeneous presence of a resistance mutation missed in the reference tumour biopsy
- Sensitivity for T790M was highly associated with detection of a sensitising mutation in cfDNA

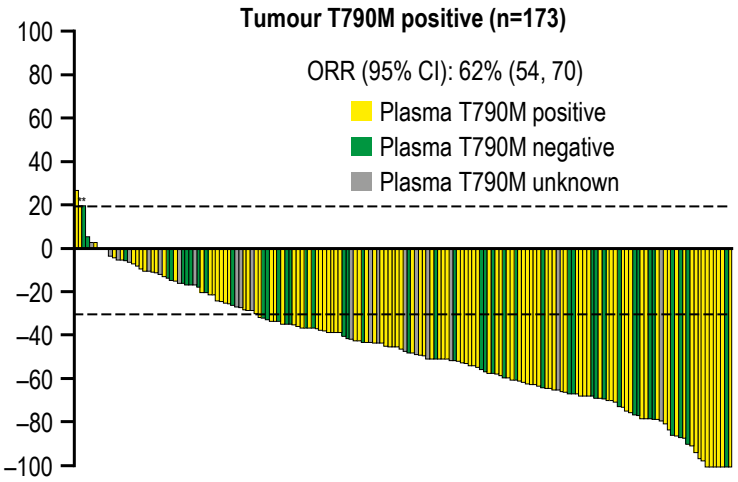
Data cut-off: 1 May 2015; 19 del, exon 19 deletion; sens positive, detectable TKI-sensitive EGFR mutation; sens negative, no detectable TKI-sensitive EGFR mutation

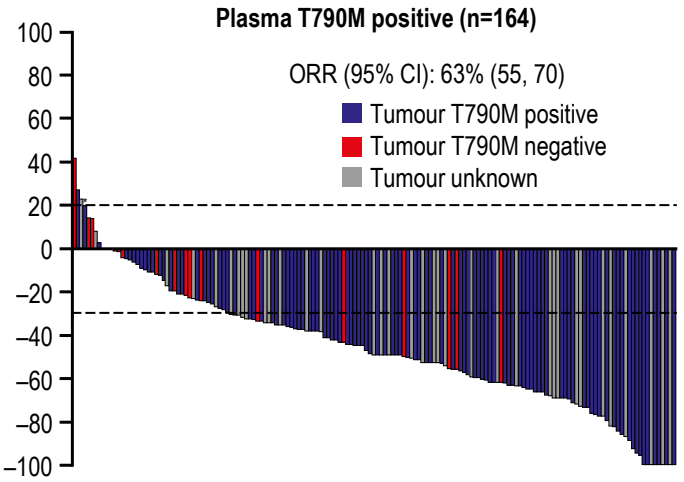
Understanding plasma T790M "false positives"

- Cases T790M negative in tumour and T790M positive in plasma were further studied using orthogonal plasma genotyping assays: ddPCR or cobas
- Of 18 "false positives", 14 could be confirmed using an orthogonal assay
- Note, no false positives for T790M were seen in 100 NSCLC cases with no known EGFR mutation

Pt	Central tumour genotyping for T790M	Central plasma BEAMing for T790M	T790M allelic fraction (BEAMing)	T790M detected with alternative assay	Alternative plasma assay used
1	Not detected	Detected	7.051%	Yes	ddPCR
2	Not detected	Detected	3.449%	Yes	ddPCR
3	Not detected	Detected	2.243%	Yes	ddPCR
4	Not detected	Detected	2.036%	Yes	cobas
5	Not detected	Detected	1.653%	Yes	ddPCR
6	Not detected	Detected	1.113%	Yes	cobas
7	Not detected	Detected	0.636%	Yes	ddPCR
8	Not detected	Detected	0.588%	Yes	ddPCR
9	Not detected	Detected	0.447%	Yes	cobas
10	Not detected	Detected	0.344%	Yes	cobas
11	Not detected	Detected	0.340%	Yes	cobas
12	Not detected	Detected	0.191%	No	ddPCR
13	Not detected	Detected	0.124%	Yes	cobas
14	Not detected	Detected	0.092%	Yes	ddPCR
15	Not detected	Detected	0.091%	No	ddPCR
16	Not detected	Detected	0.080%	No	cobas
17	Not detected	Detected	0.073%	No	cobas
18	Not detected	Detected	0.061%	Yes	ddPCR

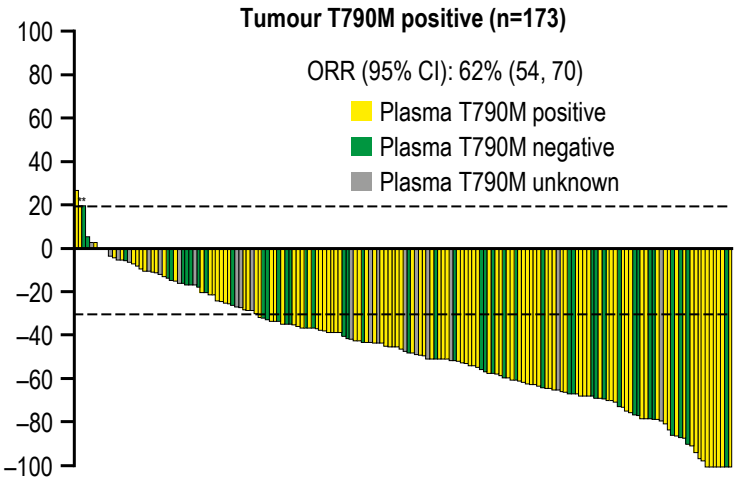
High ORR in patients with tumour or plasma positive T790M

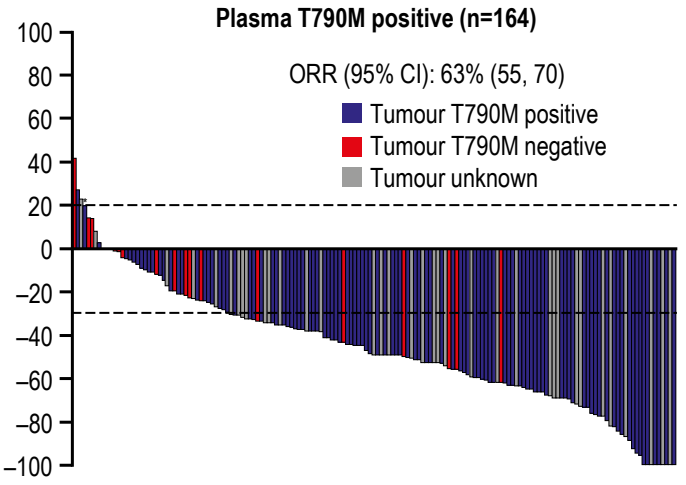


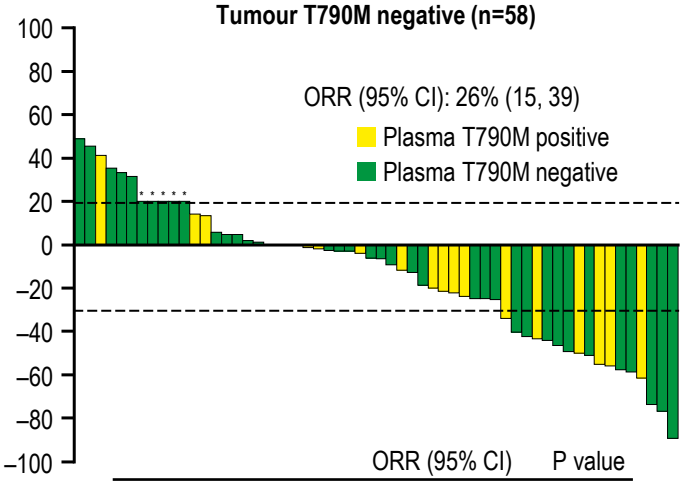


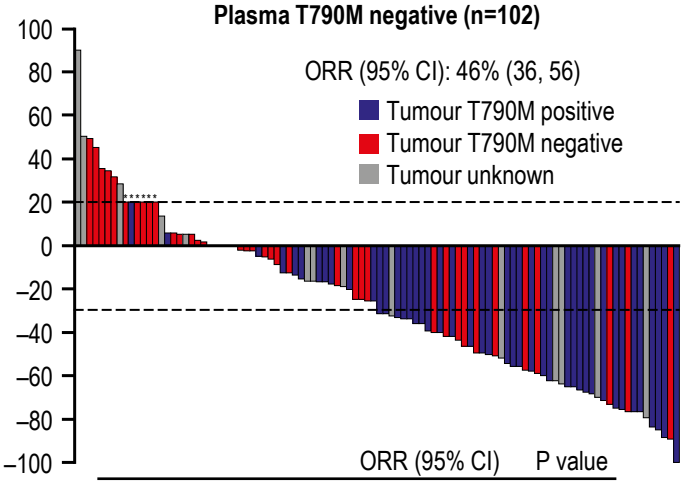
Data cut-off: 1 May 2015
CI, confidence interval

High ORR in patients with tumour or plasma positive T790M







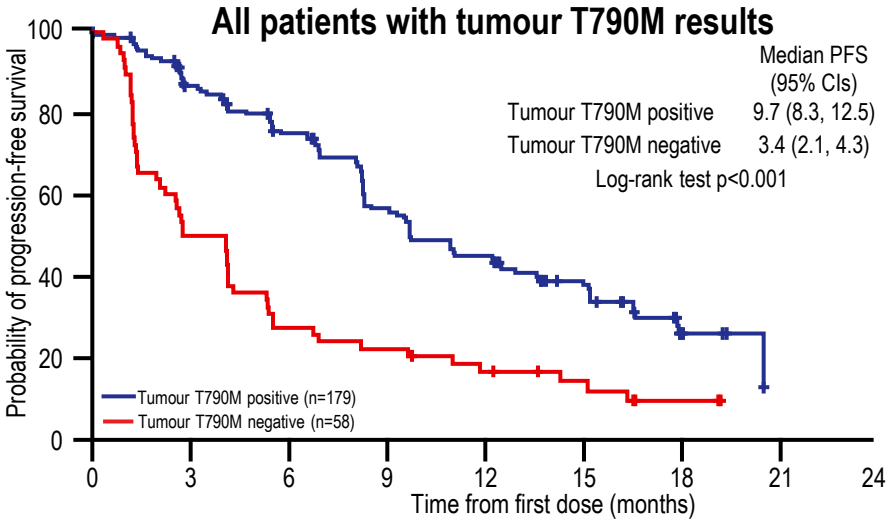


	ORR (95% CI)	P value
Tumour T790M positive	62% (54, 70)	< 0.0001
Tumour T790M negative	26% (15, 39)	

	ORR (95% CI)	P value
PlasmaT790M positive	63% (55, 70)	0.011
PlasmaT790M negative	46% (36, 56)	

Data cut-off: 1 May 2015
CI, confidence interval

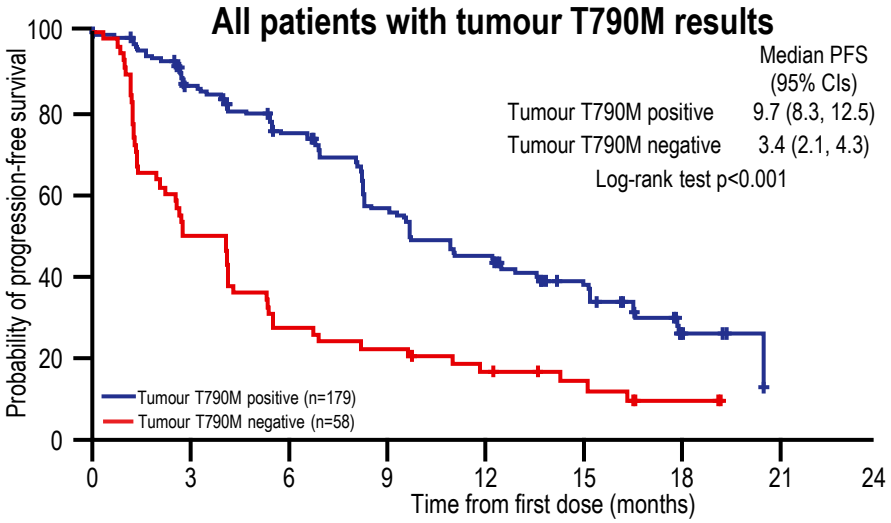
PFS by tumour and plasma T790M status

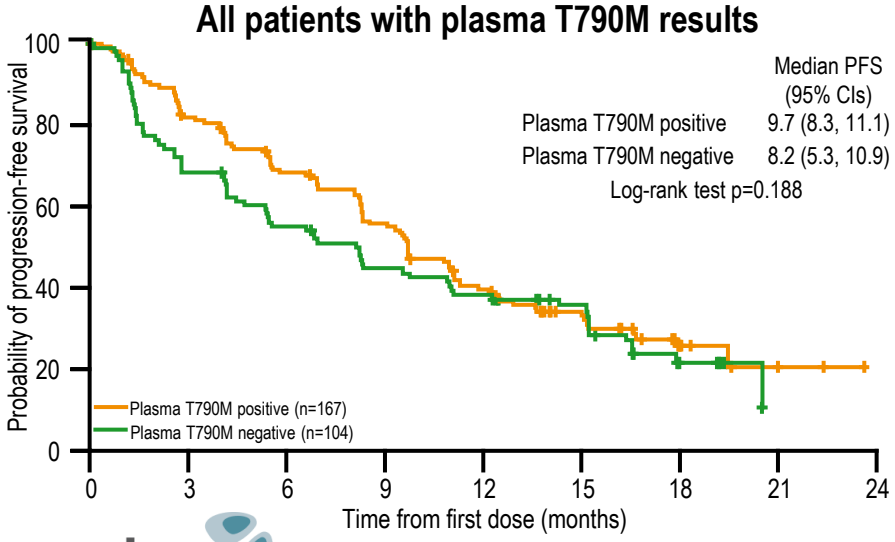


- Tumour T790M positive predicts for a prolonged median PFS of 9.7 months, longer than seen in tumour T790M negative cases ($p<0.001$)

Data cutoff: 1 May 2015. Multiple doses included

PFS by tumour and plasma T790M status



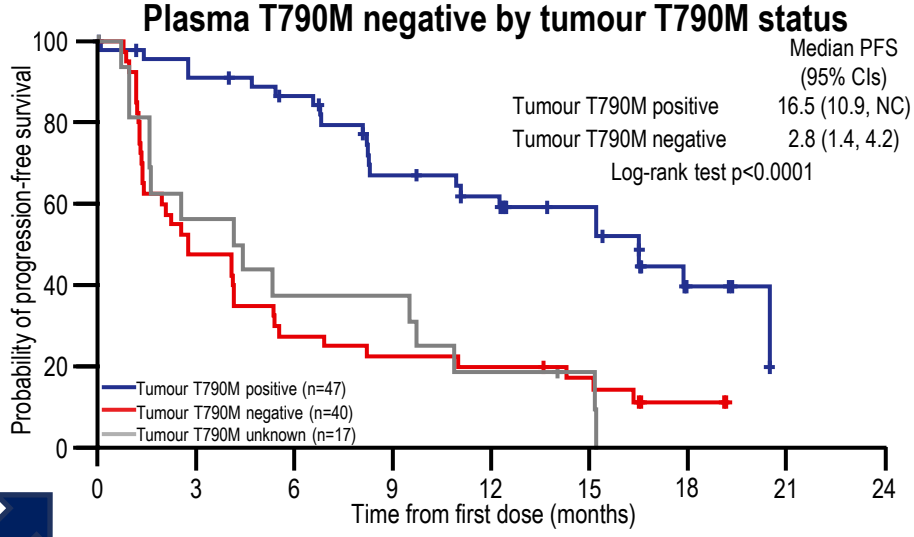


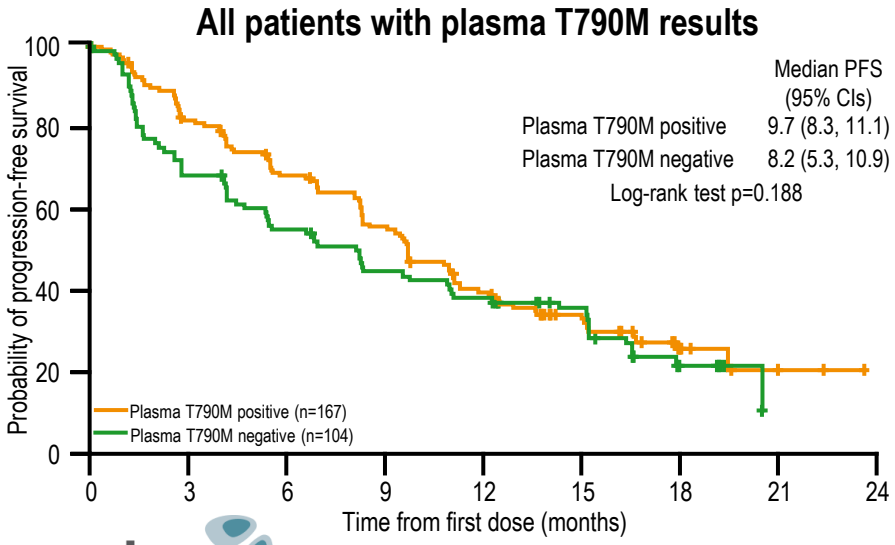
- Tumour T790M positive predicts for a prolonged median PFS of 9.7 months, longer than seen in tumour T790M negative cases (p<0.001)
- Plasma T790M positive status also predicts for a prolonged PFS of 9.7 months; however, this is not significantly longer than seen in plasma T790M negative cases (p=0.188)
- Plasma T790M negative outcomes may be better than expected due to the occurrence of T790M plasma false negatives

Data cutoff: 1 May 2015. Multiple doses included

PFS by tumour and plasma T790M status

- In plasma T790M negative patients, tumour genotyping can distinguish those patients with better and worse outcomes

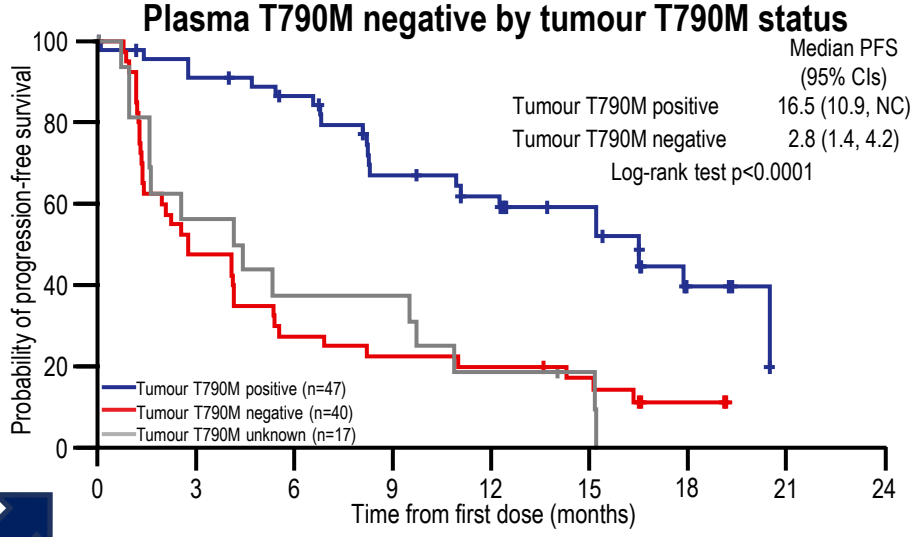


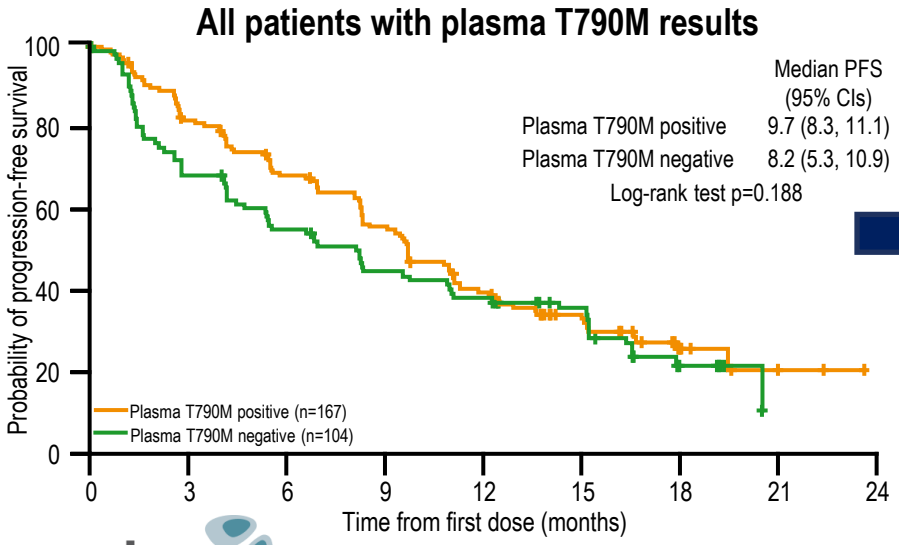


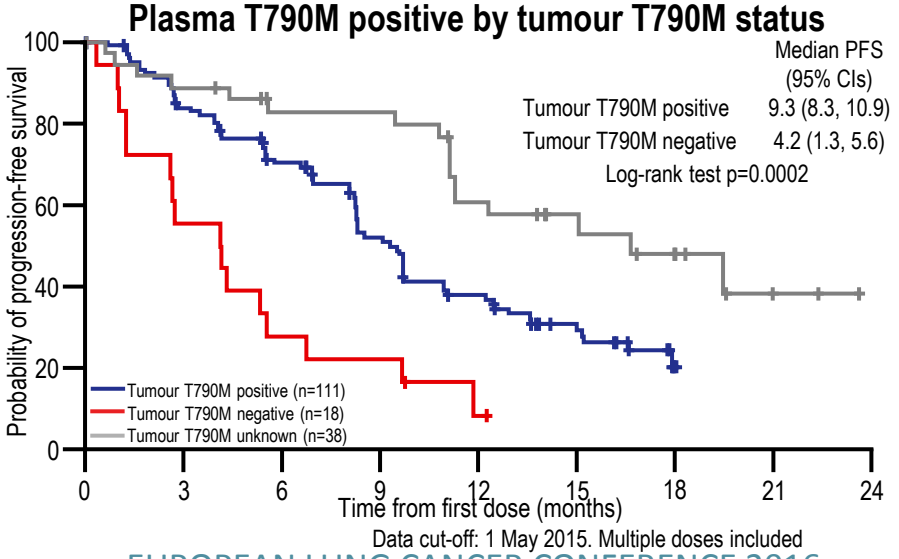
Data cut-off: 1 May 2015. Multiple doses included

PFS by tumour and plasma T790M status

- In plasma T790M negative patients, tumour genotyping can distinguish those patients with better and worse outcomes
- Interestingly, a difference based on tumour genotype is also seen in plasma T790M positive cases



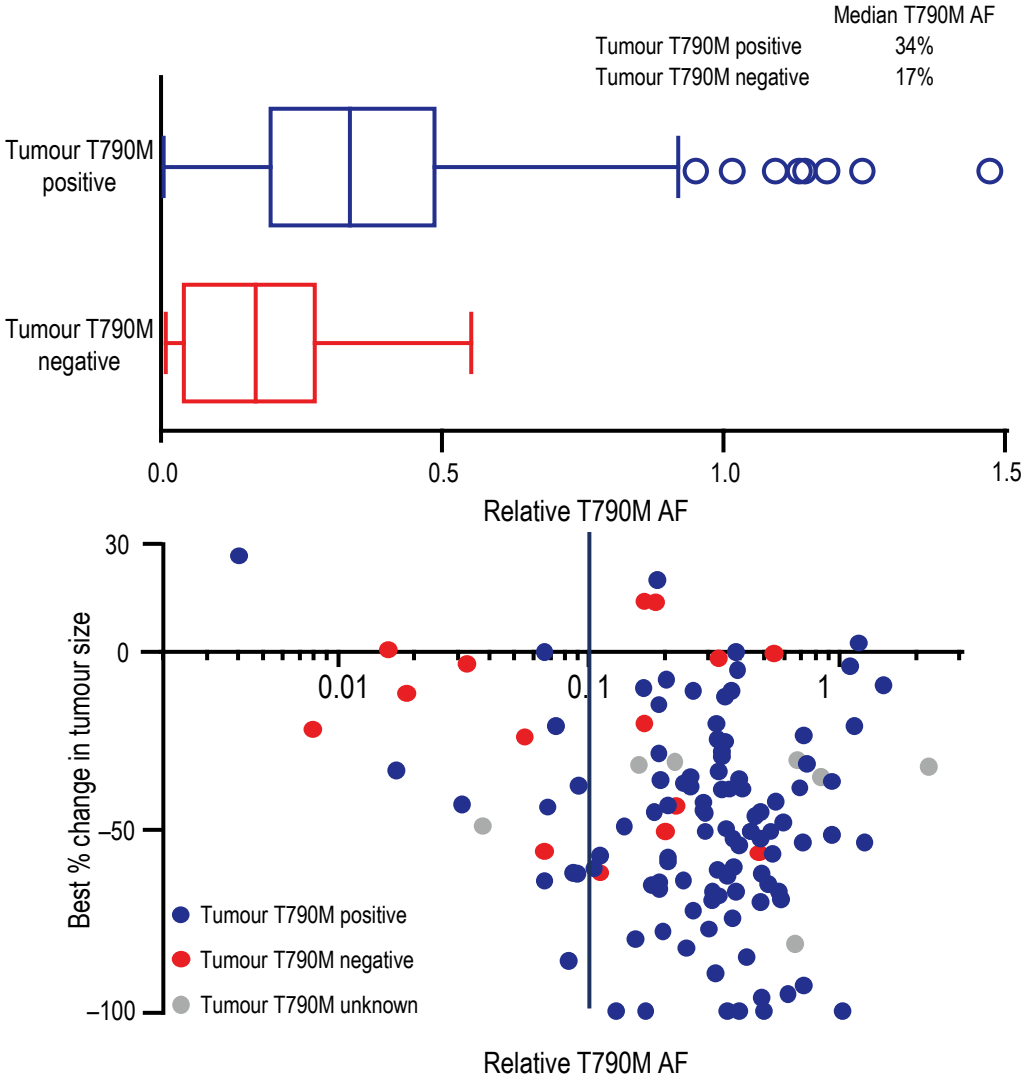




Data cut-off: 1 May 2015. Multiple doses included

T790M heterogeneity in plasma "false positives"

- We hypothesized that cases T790M negative in tumour and T790M positive in plasma might have heterogeneous presence of T790M
- Relative T790M AF was calculated as a proportion of EGFR sensitising AF:
  - T790M AF / sensitising AF
- Relative T790M AF was lower in cases with T790M negative in tumour, suggesting T790M may be present as a minor clone
- There was a trend toward lower response magnitude in the group with relative T790M AF <10% (p=0.08)

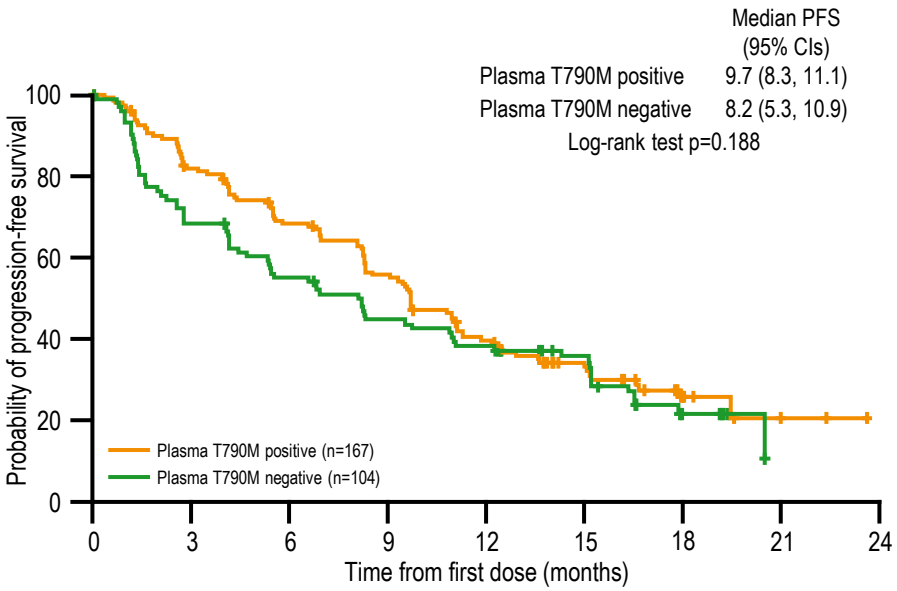


Data cut-off: 1 May 2015

Relative T790M AF was calculated as a proportion of EGFR sensitising AF

Detection of sensitising mutation as a control

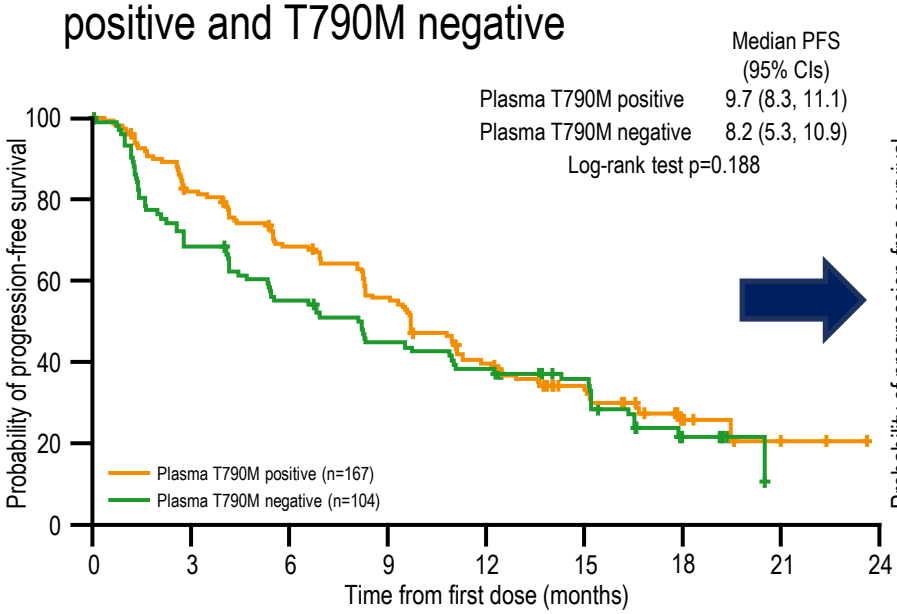
- In the 104 patients with T790M negative plasma genotyping, we studied whether detection of the sensitising mutation helped to understand true negative versus false negative

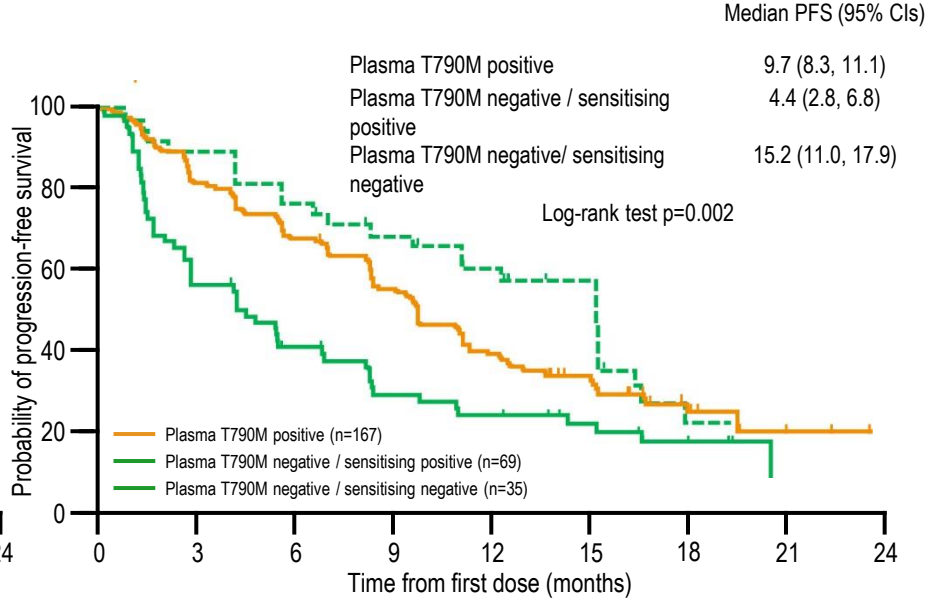


Data cut-off: 1 May 2015

Detection of sensitising mutation as a control

- In the 104 patients with T790M negative plasma genotyping, we studied whether detection of the sensitising mutation helped to understand true negative versus false negative
  - Plasma T790M negative / sensitising positive: 38% ORR, 4.4 month median PFS
  - Plasma T790M negative / sensitising negative: 64% ORR,15.2 months median PFS
- If plasma T790M negative / sensitising negative are excluded from PFS analysis reflecting their unknown plasma T790M mutation status, a significant difference is seen between T790M positive and T790M negative



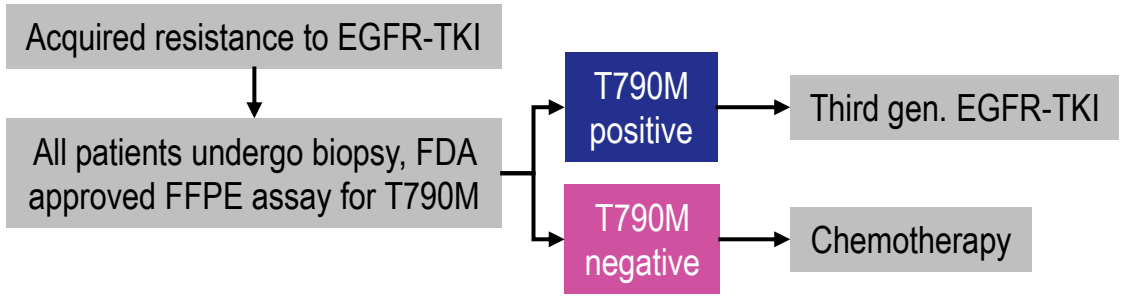


Data cut-off: 1 May 2015

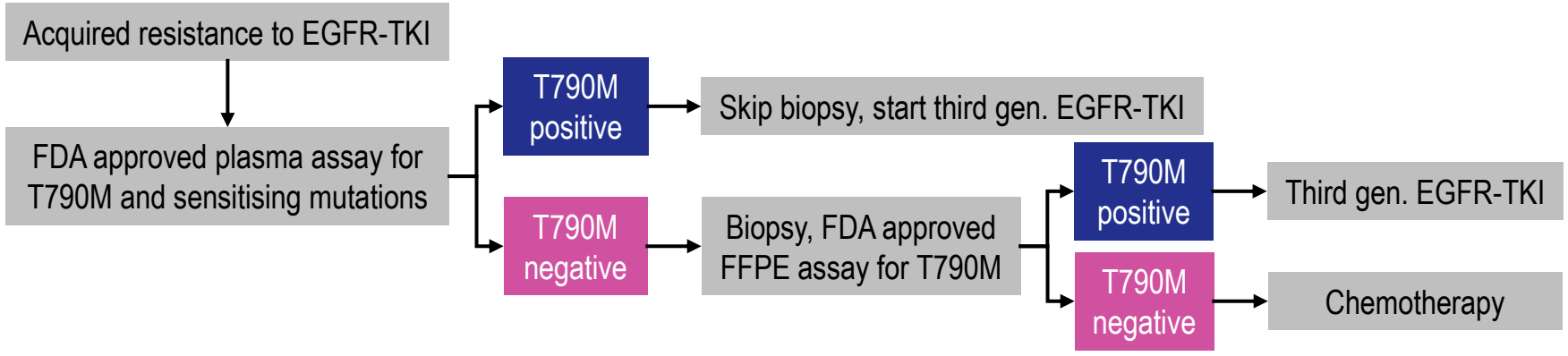
Tissue-based paradigm for use of plasma genotyping

- These data support consideration of a paradigm where plasma genotyping is used as a screening test for T790M, prior to performing an EGFR resistance biopsy

A. Conventional paradigm



B. Proposed paradigm for use of plasma diagnostics



FFPE, formalin-fixed paraffin-embedded

Conclusions

- For patients with acquired resistance to EGFR-TKI, plasma genotyping has high sensitivity for EGFR T790M mutations (70%)
  - Sensitivity is higher in cases with a sensitising mutation detected (80%)
- Apparent false positives for T790M in plasma (~30%) may be explained by heterogeneous or subclonal presence of the resistance mutation
- Plasma T790M positive status predicts for a high response rate and prolonged PFS on osimertinib, similar to what is seen when treating osimertinib based on central tumour genotyping
  - In contrast, plasma T790M negative status cannot fully replace a tumour biopsy because of a mixture of true and false negatives which have dramatically different outcomes on osimertinib

Acknowledgements

- Thanks to all the patients and their families
- Thanks to the staff and investigators at all sites

This study was sponsored by AstraZeneca, NCT01802632

We thank Laura Griffin, PhD, from iMed Comms, an Ashfield Company, who provided technical editing support funded by AstraZeneca