AIG HOSPITALS INSTITUTE OF ONCOLOGY
A unit of Asian Institute of Gastroenterology

EGFR TKI RESISTANCE

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- Oligoprogression?
- Progression in 1st gen TKI/1st gen + AntiVEGF/ 1st gen + Chemo
- Progression on 3rd generation?
- Progression after sequential 1st gen f/b 3rd gen

OLIGOPROGRESSION

- Is this an accepted term now? To treat with Local therapy and continue systemic
- Would you do testing for resistance at progression?

PROGRESSION AFTER 1ST /2ND GEN TKI

- T790M alone or Mutation panel ?

- Liquid biopsy followed by Tissue biopsy?
- Concurrent liquid and tissue?
- Tissue alone (where feasible) ?

NTU CANCER CENTER 台大癌醫中心

Simultaneous Tissue and Liquid Next-generation Sequencing after First-line EGFR Tyrosine Kinase Inhibitors Resistance in Advanced Non-small Cell Lung Cancer

Yen-Ting Lin;[1,2,3,*] Chao-Chi Ho;[2] Wei-Hsun Hsu;[4] Wei-Yu Liao;[2] Ching-Yao Yang;[2] Kien Thiam Tan;[5] Wen Hsiao;[5] Jin-Yuan Shih[1,2]

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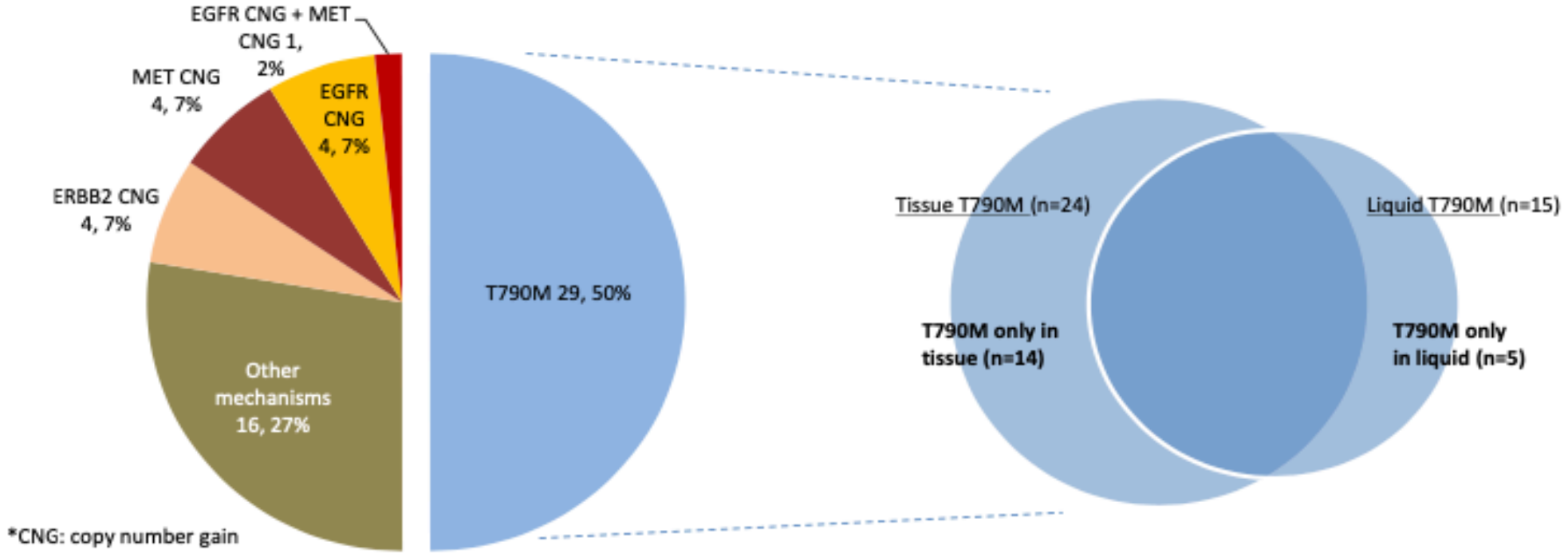
Poster #365

No variant detected in ctDNA

First-line 1st or 2nd generation EGFR TKI resistant mechanisms (n=58)



24 of 29 patients with T790M received second-line osimertinib (n=24)

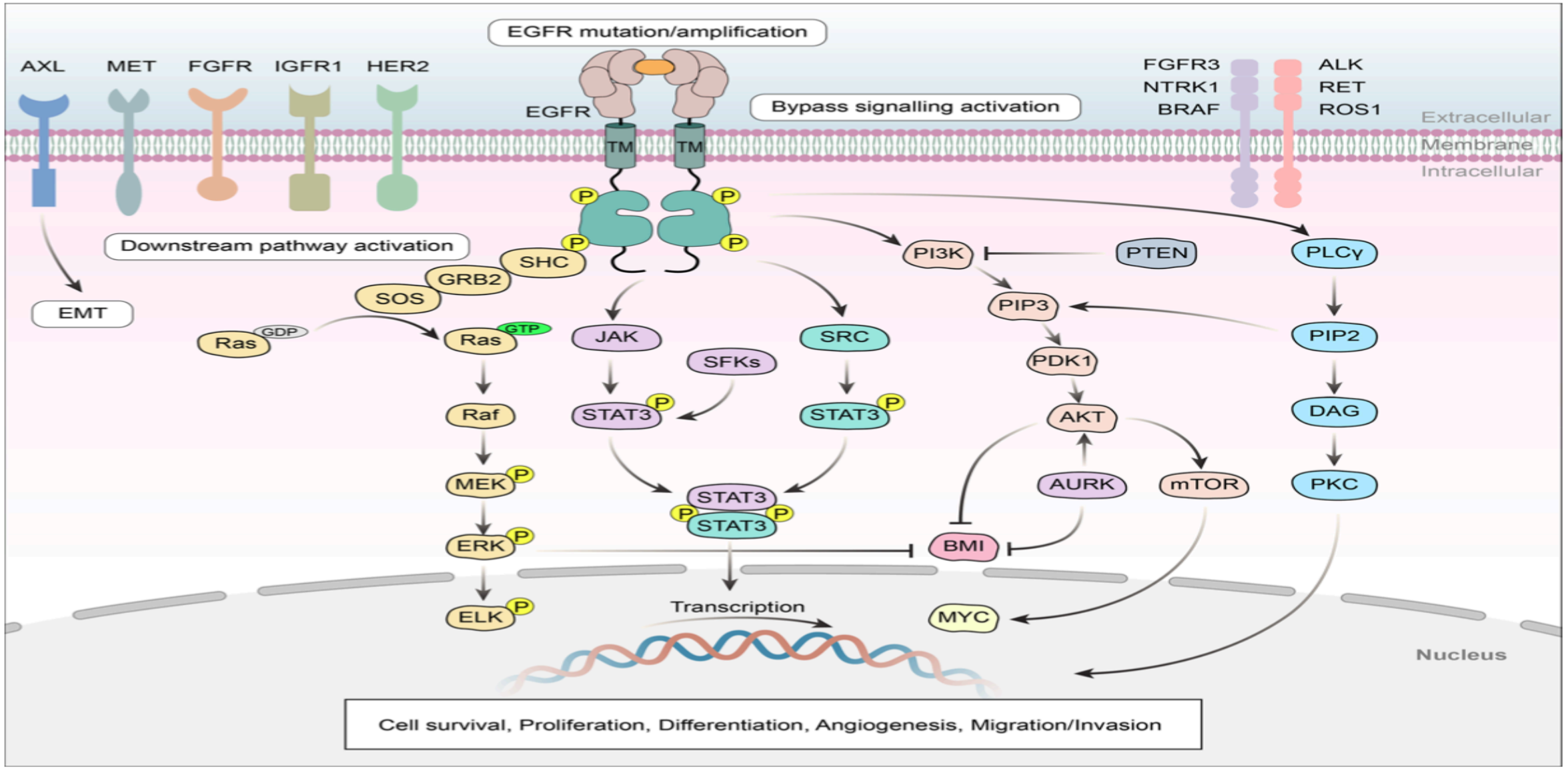


Fig. 3 Molecular mechanisms of acquired resistance. The mechanisms include target gene modification, parallel alternative pathway activation, downstream pathway activation, and histological/phenotypic transformation. Both amplification and mutation of receptor tyrosine kinases (RTKs) can induce downstream survival signaling pathways. Moreover, direct overexpression and/or mutation of components of downstream pathways can contribute to acquired resistance by promoting cancer cell survival

TREATMENT OPTIONS

- If T790M positive – only Osimertinib vs Osimertinib/ anti VEGF?

Why are only the erlotinib studies positive?

What are the results?

Study	ORR, %	DoR (m)	PFS (m)	PFS (HR)	OS (HR)	AE leading to discontinuation, %
FLAURA	80 v 76	17.2 v 8.5	18.9 v 10.2	**0.46 (0.37-0.57)**	**0.79 (0.64-0.99)**	13 v 18
JO25567	69 v 64	13.3 v 9.3	16.0 v 9.7	**0.54 (0.36-0.79)**	0.81 (0.53-1.23)	17 v 18
NEJ026	72 v 66	NR	16.9 v 13.3	**0.63 (0.43-0.91)**	1.00 (0.68-1.48)	19 v 15
CTONG1509	87 v 85	16.6 v 11.1	17.9 v 11.2	**0.55 (0.41-0.73)**	0.92 (0.69-1.23)	24 v 3
RELAY	76 v 75	18.0 v 11.1	19.4 v 12.4	**0.59 (0.46-0.76)**	0.83 (0.53-1.30	13 v 11
ALLIANCE	81 v 83	NR	17.9 v 13.5	0.81 (0.50-1.31)	1.41 (0.71-2.81)	26 v 0
BOOSTER	55 v 55	14.5 v 16.6	15.4 v 12.3	0.96 (0.68-1.37)	1.03 (0.67-1.56)	25 v 4
WJOG8715	72 v 55	NR	9.4 v 13.5	1.44 (1.00-2.08)	1.02 (0.43-2.44)	28 v 12

VP3-2021: A randomized phase II study of second-line osimertinib (Osi) and bevacizumab (Bev) versus Osi in advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) and T790M mutations (mt): Results from the ETOP BOOSTER trial

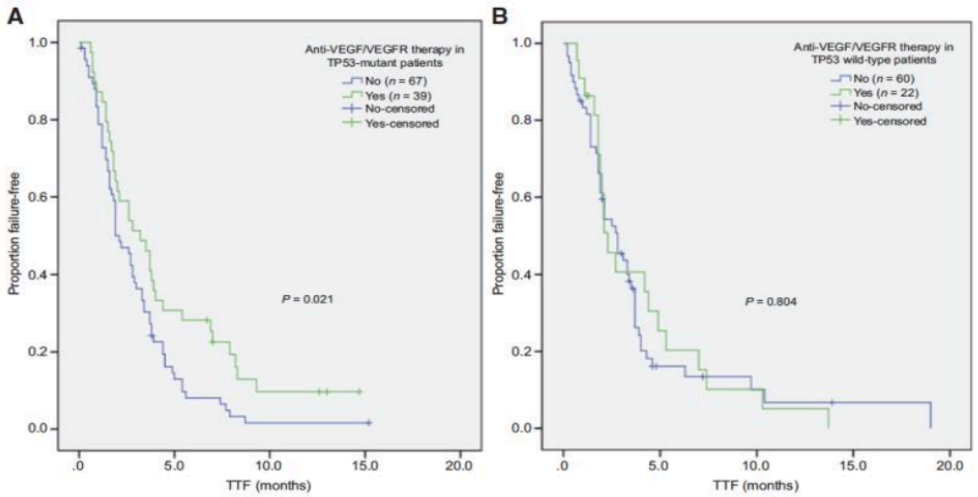
R. Soo • J-Y. Han • G. Dimopoulou • ... H. Roschitzki-Voser • R. Stahel • S. Peters • Show all authors

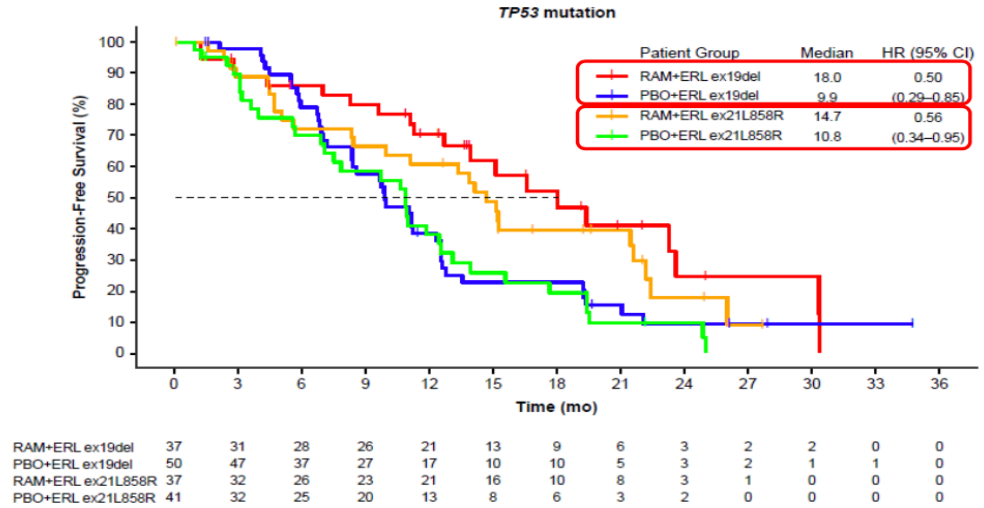
IIIb-c/IVa/IVb: 1%/70%/28%, 59% non-Asians. At a median follow-up of 34m, the median PFS was 15.4m (95% CI 9.2-18.0) and 12.3m (6.2-17.2) (PFS events: 64 & 65) in the Osi/Bev and Osi arm respectively (HR 0.96; 0.68-1.37; p=0.83). Median OS was 24.0m (17.8-32.1) in Osi/Bev and 24.3m (16.9-37.0) in Osi arm (deaths: 46 & 43) (HR 1.03; 0.67-1.56; p=0.91). ORR was 55% in both arms. Smoking history exhibits significant TX interaction for both PFS and OS

What is the basis of the enhanced signal observed in current/ former smokers in the BOOSTER trial?

Potential explanation

- Tobacco exposure produces genomic mutations in lung cancer, including *TP53* mutations.[1]
- *TP53* mutations are associated with improved outcomes with VEGF or VEGFR-inhibitors.[2-5]
- Translational studies are planned





Ross Soo, MB, BS; PhD; FRACP

Gibbons Mol Cancer Res 2013; 2. Schwaederle Cancer Res 2015; 3. Said Oncotarget 2013; 4. Wheler Mol Cancer Ther 2016; 5. Nakagawa Clin Cancer Res 2021

- If T790M negative –

- Chemotherapy?
- Immunotherapy?
- Combination?

PROGRESSION AFTER OSIMERTINIB

- How often are you doing mutational analysis– liquid or tissue or both??

- Options if no targets found …

- Chemotherapy alone
- Chemotherapy + Immunotherapy
- MET-TKIs – Savolitinib / Tepotinib

PROGRESSION AFTER TKI/antiVEGF

Poster Number 13P

Durvalumab plus chemotherapy in patients with advanced EGFR mutation-positive NSCLC whose disease progressed on first-line osimertinib: an ORCHARD study interim analysis

Objective

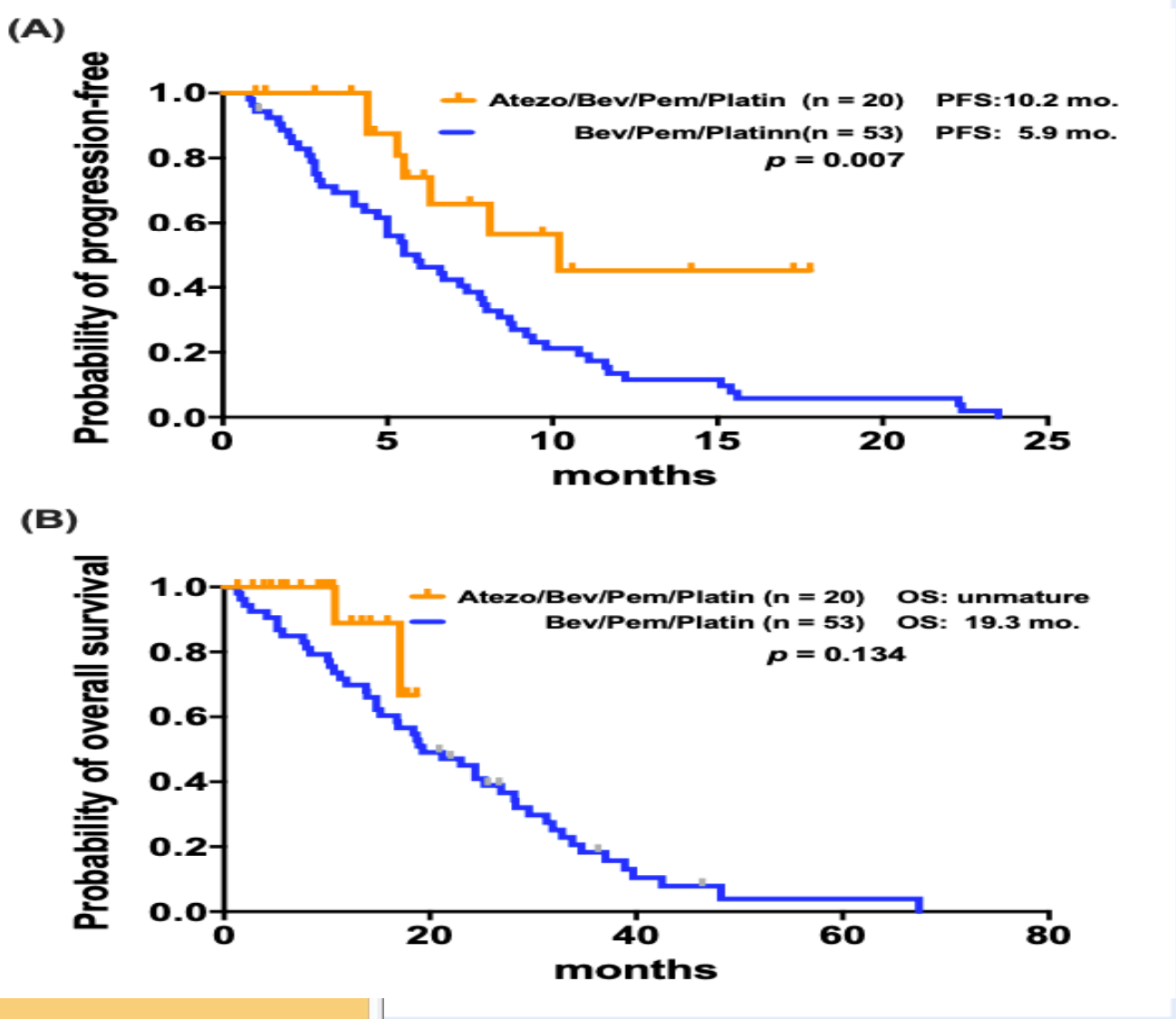
- To report data from an ORCHARD interim analysis concerning treatment with the anti-PD-L1 antibody durvalumab in combination with chemotherapy in patients with advanced epidermal growth factor receptor mutation-positive (EGFRm) non-small cell lung cancer (NSCLC) that had progressed on first-line (1L) osimertinib without detectable resistance mechanisms, or those patients for whom biomarker-directed study treatments were not available

Conclusions

- In this population, which comprised patients with advanced EGFRm NSCLC that progressed on 1L osimertinib with no biomarker-detected resistance mechanisms, or for whom biomarker-directed study treatments were not available, study stop criteria (≤10% chance that objective response rate [ORR] is ≥45%) were met following treatment with durvalumab and chemotherapy. On account of this, recruitment was closed for this specific ORCHARD study arm
- Durvalumab plus chemotherapy was well tolerated with no new or unexpected safety signals
- Further biomarker analyses are ongoing to better understand the efficacy data concerning use of immune checkpoint inhibitors (ICIs) plus chemotherapy in this particular patient population
- The ORCHARD study continues to evaluate other novel therapy combinations in biomarker-matched and non-biomarker matched patients with advanced EGFRm NSCLC that progressed on 1L osimertinib

Abstract #632
Poster #307

A phase II study of atezolizumab in combination with bevacizumab, carboplatin or cisplatin, and pemetrexed for *EGFR*-mutant metastatic NSCLC patients after failure of EGFR TKIs (ML41701).



CONCLUSIONS

- The combination treatment of atezolizumab, bevacizumab, pemetrexed and cisplatin/carboplatin provided favorable efficacy in *EGFR* mutation-positive NSCLC after TKI failure, and higher PD-L1 expression (≧ 1%) was associated with a higher ORR.
- The DCR and PFS of pemetrexed/platinum-based chemotherapy and bevacizumab could be improved by the addition of atezolizumab.

C797S mutations

- How often do you encounter this??
- What is your preferred therapy?

groups. **Conclusions:** These preclinical studies demonstrated that JIN-A02 is a potential best-in-class fourth-generation EGFR TKI with high potency and selectivity. JIN-A02 showed robust activities against EGFR C797S mutation including single and double EGFR mutations. It was also effective against L718Q, for which there are currently no treatment alternatives. JIN-A02 is expected to provide a therapeutic opportunity for patients who progressed upon previous EGFR TKI, and a future first-in-human trial is planned for testing clinical efficacy and safety. **Keywords:** 4th Generation EGFR-TKI, non-small cell lung cancer (NSCLC), C797S

DEFINED MUTATIONS

- MET Ex14 skipping mutation

- How common is this ?
- How do you usually manage this?

LUNG CANCER - NON-SMALL CELL METASTATIC

TPS9153 **Poster Session**

Capmatinib plus osimertinib versus platinum-pemetrexed doublet chemotherapy as second-line therapy in patients with stage IIIb/IIIc or IV *EGFR*-mutant, T790M-negative NSCLC harboring *MET* amplification.

- BRAF mutations

- How common
- Management

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THANK YOU