POST OSIMERTINIB TREATMENT OPTIONS

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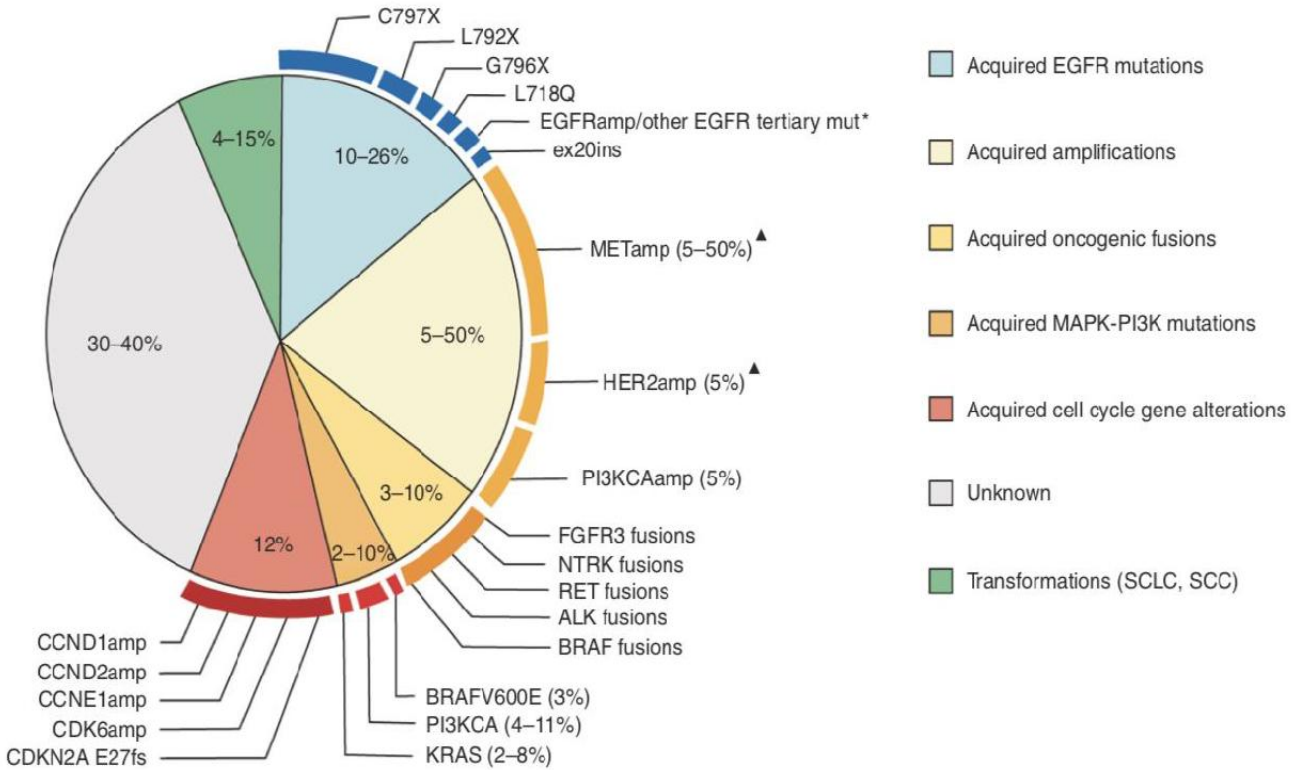
Introduction

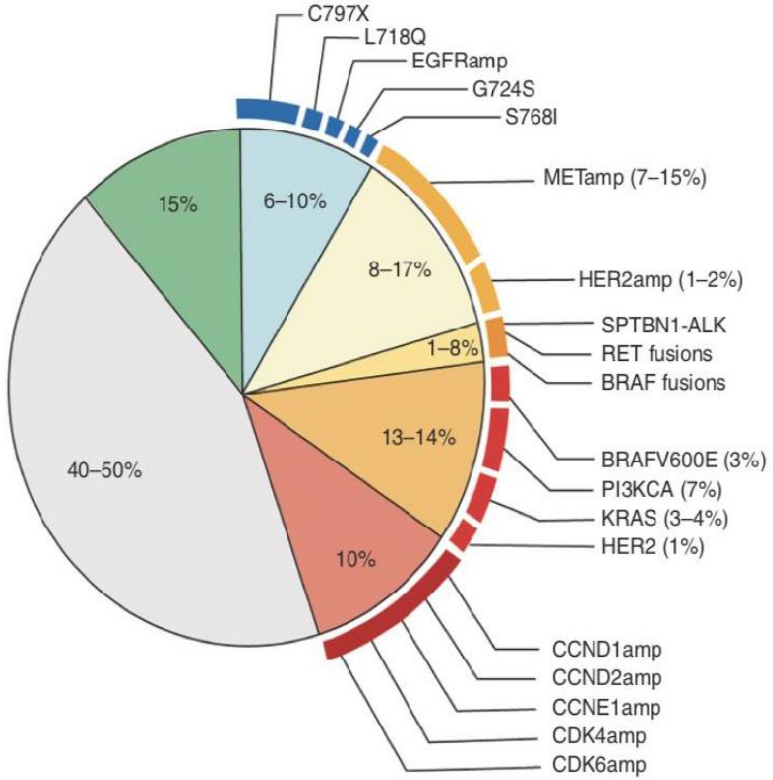
- First-line Osimertinib is now considered as preferred option in first line for patients with a tumor with sensitizing EGFR mutations.
- Osimertinib is the standard therapy for patients whose tumors are tested positive for T790M either in liquid biopsy or re-biopsy, if not received previously.
- After failure of EGFR TKI , platinum based chemotherapy has PFS of 4.4 -6.4 months
- Subsequent salvage therapies after failure of EGFR TKI and platinum based chemotherapy have PFS of 2.8- 3.2 months.

Resistance mechanisms to second-line osimertinib

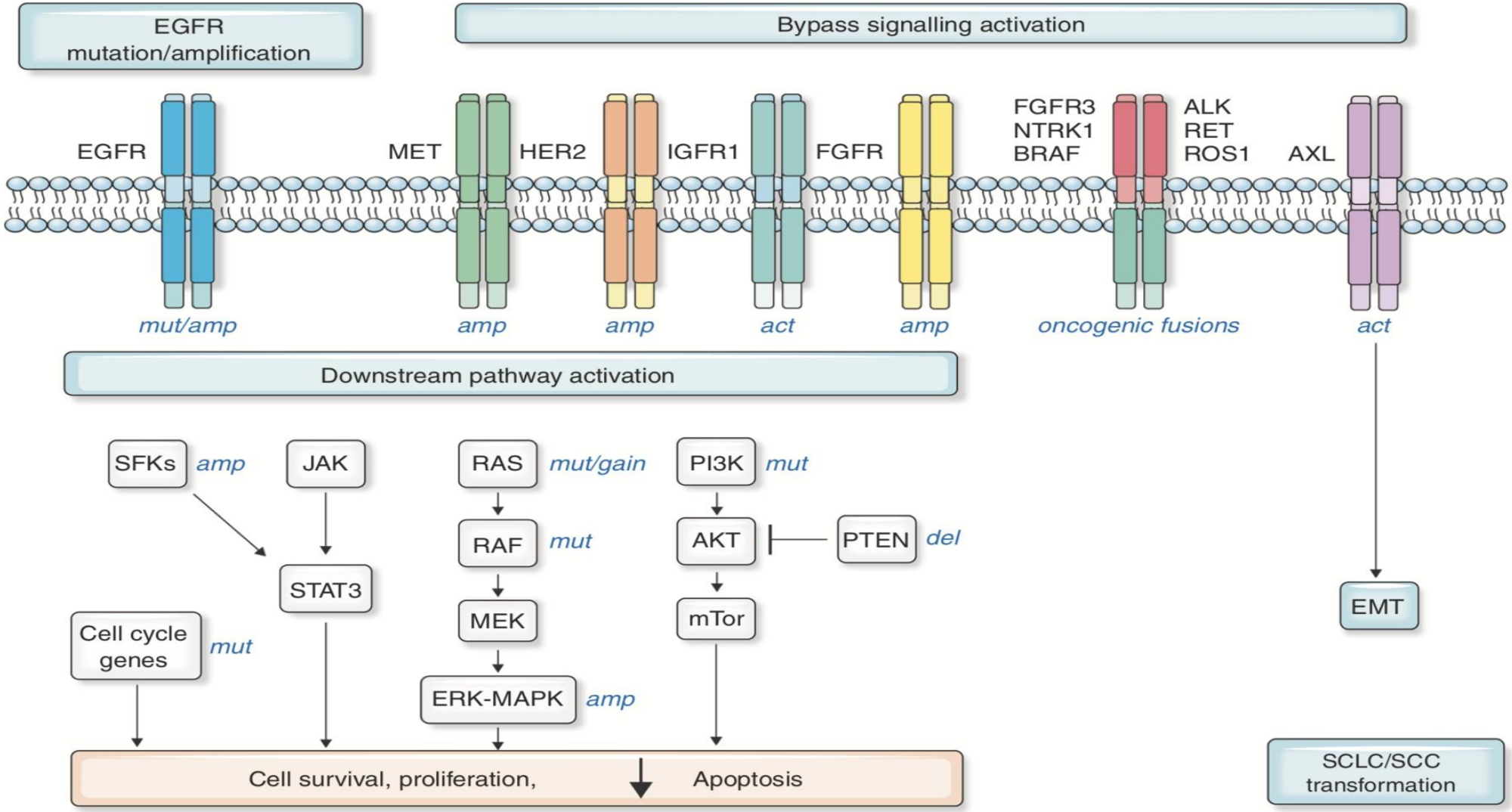


* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

Resistance mechanisms to first-line osimertinib



KNOWN RESISTANCE MECHANISMS OF OSIMERITINIB



Treatment regimens	Study patients	Study model and name	Mechanism
Amivantamab+ lazertinib	Advanced NSCLC with documented advanced or metastatic EGFR mutation. Includes an expansion cohort of participants with EGFR exon 19del or L858R mutated NSCLC progressed on or after osimertinib	**Phase I/Ib open-label study of Lazertinib as monotherapy or in combination with amivantamab (NCT04077463)**	Lazertinib is a third-generation EGFR TKI with efficacy against activating EGFR and T790M mutations. Amivantamab is an EGFR MET bispecific antibody that targets both activating EGFR and MET mutations
Patritumab deruxtecan	Patients with locally advanced or metastatic EGFR mutation-positive NSCLC with prior EGFR TKI therapy. About 86% of the study patients were treated with prior osimertinib	**Phase I dose-escalation/ expansion study (NCT03260491)**	HER-3-directed antibody-drug conjugate that consists of a fully human monoclonal antibody to HER3
BLU-945	Patients with EGFR-mutated NSCLC who have previously received at least one prior EGFR- targeted TKI. Expansion groups consist of EGFR T790M and C797S mutation (group 1); EGFR T790M but not C797S (group 2); or EGFR C797S but not T790M (group 3).	**Ongoing Phase I/II trial (NCT04862780) that include a dose-escalation portion**	Fourth-generation EGFR TKI that potentially inhibits triple-mutant EGFR
Osimertinib in combination with other targeted therapies	Patients with EGFR-mutant NSCLC and disease progression on a prior EGFR TKI treatment	**Multi-arm phase Ib TATTON study (NCT02143466)**	Selumetinib (MEK1/2 inhibitor), savolitinib (MET-TKI) or durvalumab (anti-PD-L1)

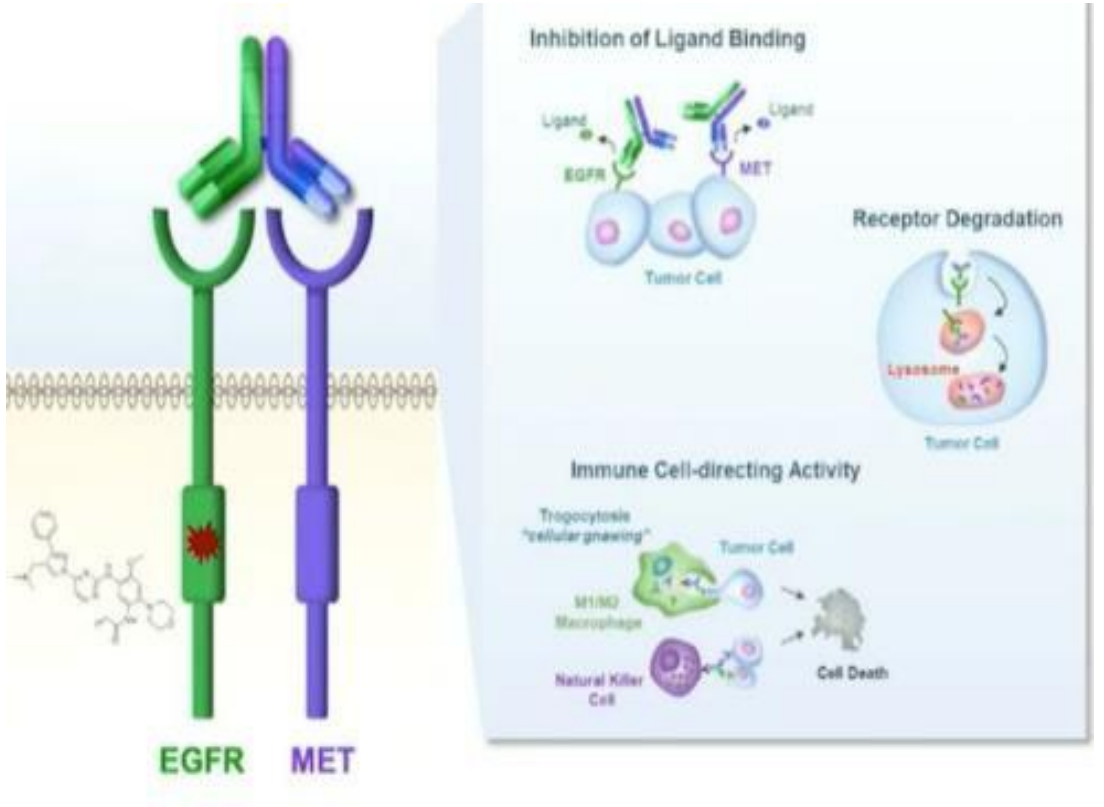
AMIVANTAMAB + LAZERTINIB

Amivantamab

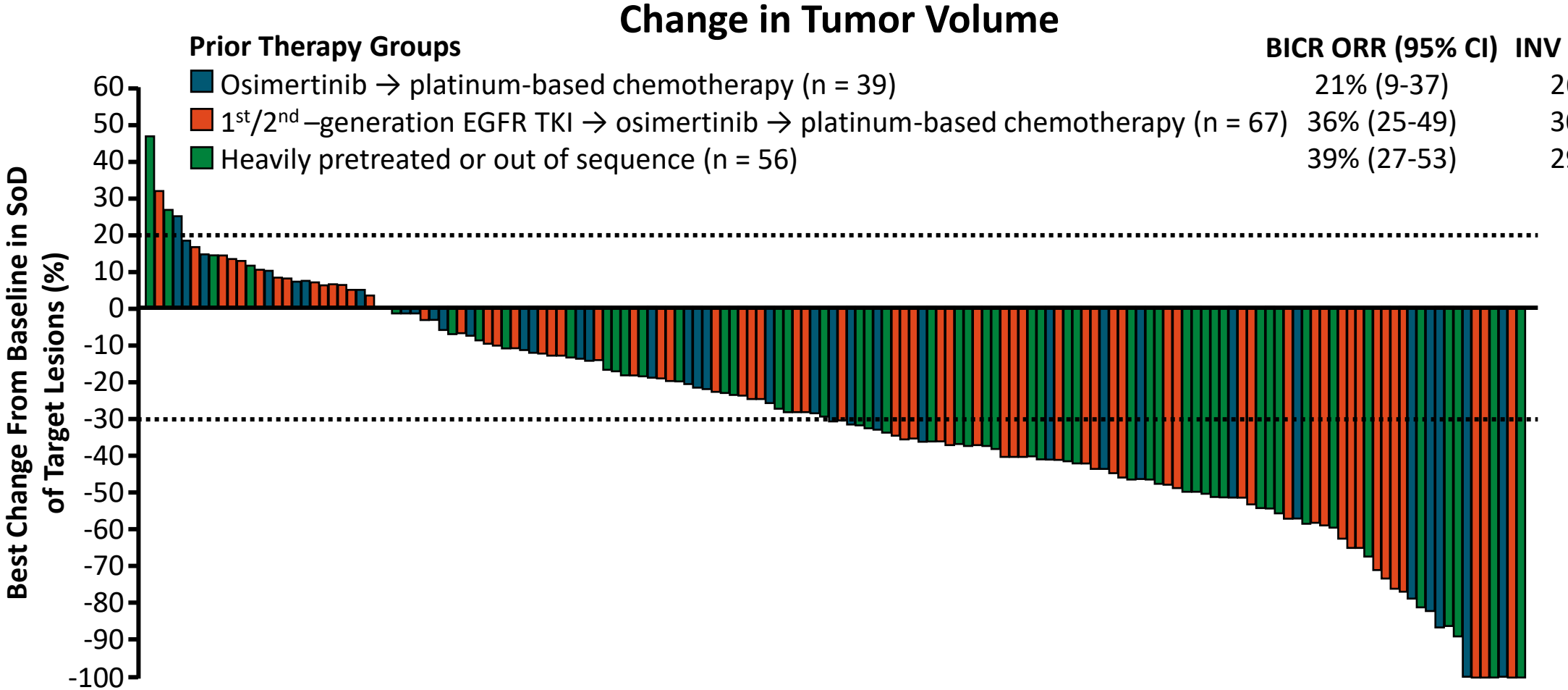
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

LAZERTINIB

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules



CHRYSALIS-2 Cohort A Update: BICR-Assessed ORR by Prior Therapy



- 10 patients were not evaluable for postbaseline target lesion measurements

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CHRYSALIS-2 Cohort A Update

- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%) Majority were grade 1–2

- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

- MARIPOSA-2 (NCT04988295) trial - assessing amivantamab + lazertinib as first-line therapy and amivantamab + lazertinib + carboplatin + pemetrexed following progression on osimertinib

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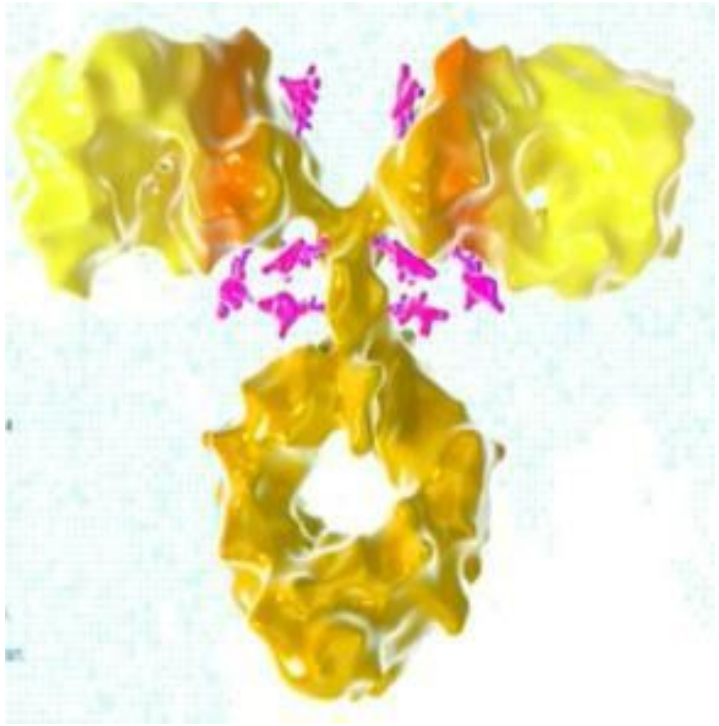
PATRITUMUMAB DERUXTECAN



- **A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to a topoisomerase I inhibitor payload, an exatecan derivative, via tetrapeptide-based cleavable linker**

PATRITUMUMAB DERUXTECAN

- HER 3 expressed in 80% of all EGFR activating mutated NSCLC
- In a phase 1 dose expansion study patritumab deruxtecan (5.6 mg/kg every 3 weeks) in cohort 1 showed improved ORR of 39% in 44 patients who progressed on Osimeritnib and Platinum based chemotherapy
- FDA has granted BTD approval for this drug in patients of NSLC with resistance to EGFR TKI
- TAE - 94% patients has any grade of toxicities; 54% has grade 3 or higher toxicities
- Hematological toxicities - Thrombocytopenia, Decreased ANC Counts, FN, fatigue, anemia, dyspnea, hypokalemia.

OTHER OPTIONS…

- A phase 1 trial from ETCTN California Consortium presented final results of Osimeritinib +Necitumumab shows partial response in dose expansion cohort and met its primary end point in >3/18 patients and had median PFS of 2.3 months

- Another phase Ib studyTelisotuzumab vedotin(teliso-v) an ADC targeting MET overexpression after failure on prior Osimeritinib

- The overall response rate was 58% in 19 patients with resistance to osimeritinib

- Major TAE were peripheral sensory neuropathy (36%), nausea(20%), fatigue(20%), cough 20%.

OTHER OPTIONS…

- In phase Ib TATTON trial –
- osimeritinib+ savlotinib 600mg daily in a cohort of 18 patients who progressed on prior osimeritinib yielded an ORR of 67% and median duration of response was 12.4 months.
- TAE- most common were grade 3 AST transaminitis, Pneumothorax, Anaphylaxis(4%),decreased ANC counts
- 2 deaths occurred due to Acute renal failure
- This combination is now being prospectively evaluated in SAVANNAH trial

OTHER OPTIONS…

- In phase Ib TATTON trial -
- osimertinib+ selumitinib 75 mg BD intermittent schedule were used(MEK Inhibhitor)
- In a cohort of 18 patients who progressed on prior osimertinib yielded an partial response rate of 23%.
- TAE- most common were Diarrhea (70%) Rash (58%) Nausea (47%)

OTHER OPTIONS…

- C797S mutations - we can combine first and third generation EGFR TKI

like Erlotinib+ Osimeritinib.

- Oligo progression- Continue osimeritinib+ LAT (local ablative therapy)

- Findings from exploratory analysis of Impower 150 trial suggests that Atezolizumab with chemotherapy and Bevacizumab improved median OS to 13.9 months.

- SCLC transformation- Platinum+ Etoposide Doublet is a valid option

- CNS Progression- 160 mg Osimertinib+ Local CNS directed Therapy

OTHER ONGOING TRIALS

- Osimertinib+TDM1- TRAMEOS STUDY- PHASE I/II
- Osimertinb+Bcl2 inhibitors
- Osimertinib+PARPi
- Nazaritinib+ Tremitinib

THANK YOU