S1619 A trial of neoadjuvant cisplatin-pemetrexed with atezolizumab in combination and maintenance for resectable pleural mesothelioma

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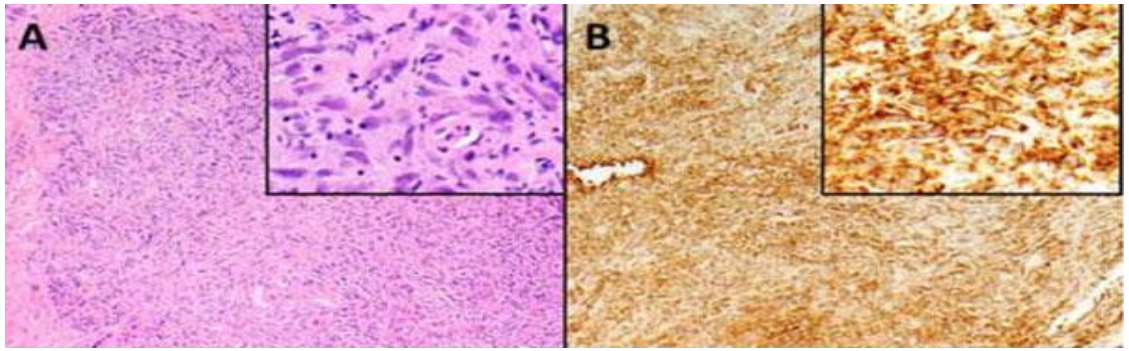
Funding: NIH/NCI grant awards U10CA180888, U10CA180819 and U10CA180820

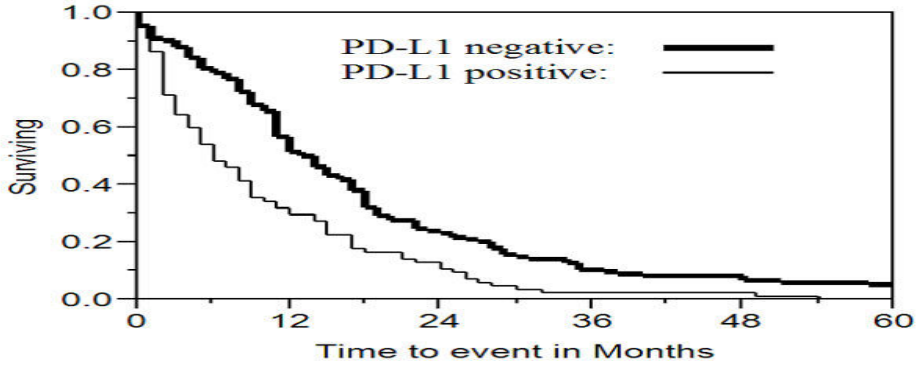
Anne Tsao DISCLOSURES

Ineligible Company (formerly: Commercial Interest)	**Relationship(s)**
BMS, Eli Lilly, Genentech, Roche, Novartis, Ariad, EMD Serono, Merck, Seattle Genetics, Astra-Zeneca, Boehringer-Ingelheim, Sellas Life Science, Daichi Sanyo, Takeda,	Advisory Boards
Eli Lilly, Millennium, Polaris, Genentech, Merck, Boehringer-Ingelheim, BMS, Ariad, Epizyme, Seattle Genetics , Novartis	Research Grants

Background

- Malignant pleural mesothelioma (MPM) is an orphan disease with limited treatment options. In the curable population, neoadjuvant chemotherapy, surgical resection, and adjuvant radiation yield median OS 17-25 months.
- MPM is an immunogenic disease and the PD-L1 is a negative prognostic biomarker.[1]
  - Mansfield et al. reports 40% PD-L1 expression in MPM (n=224) anti-human B7-H1 (clone 5H1-A3) antibody and associates IHC expression with more disease burden and worse survival (6 months vs 14 months, p<0.0001)

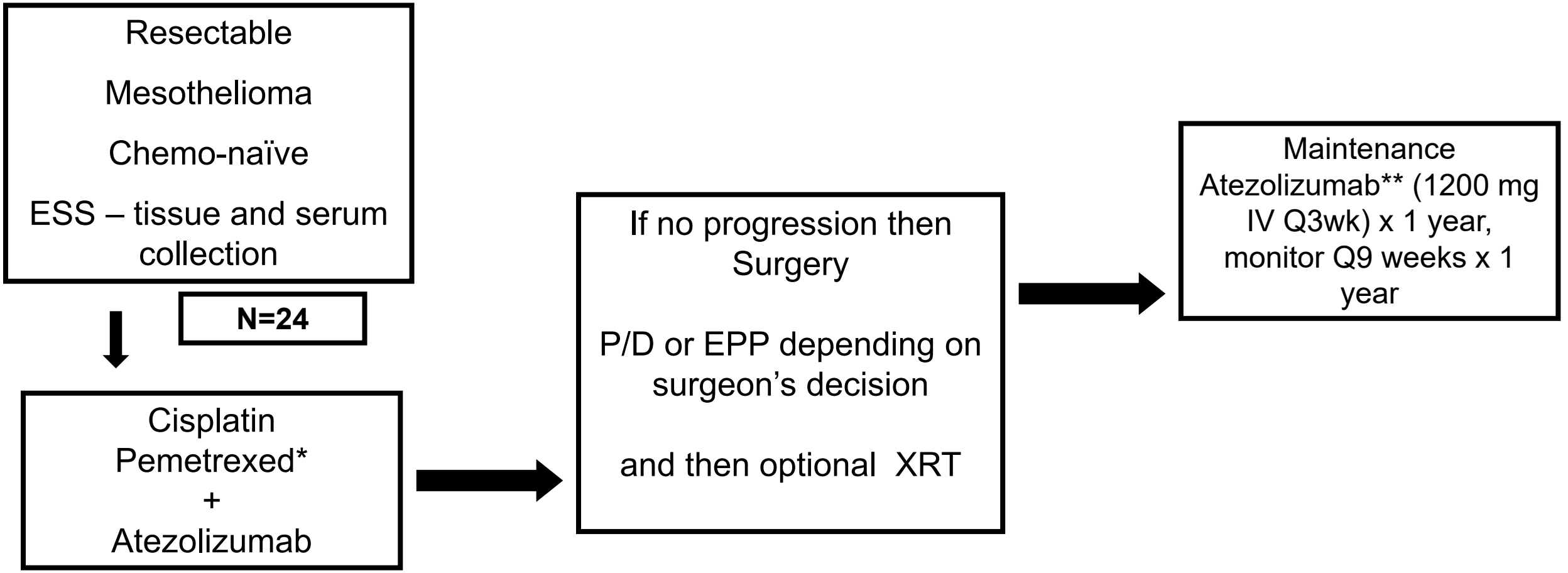




- **Study Rationale:** We propose that adding anti-PD-L1 inhibitor to neoadjuvant cisplatin-pemetrexed and then maintenance immunotherapy after surgical resection and adjuvant radiation will enhance T-cell activation against microscopic disease and potentially increase overall survival outcomes.

[1]Mansfield et al. Journal of Thoracic Oncology 9 S7-S52, 2014

S1619 Neoadjuvant Mesothelioma Trial Schema



*Cisplatin 75 mg/m^2 , Pemetrexed 500 mg/m^2 IV + Atezolizumab 1200 mg IV Q3wk

Serum blood for translational correlates obtained baseline, cycle 1-4, post-op, then prior to maintenance therapy, at time of PD

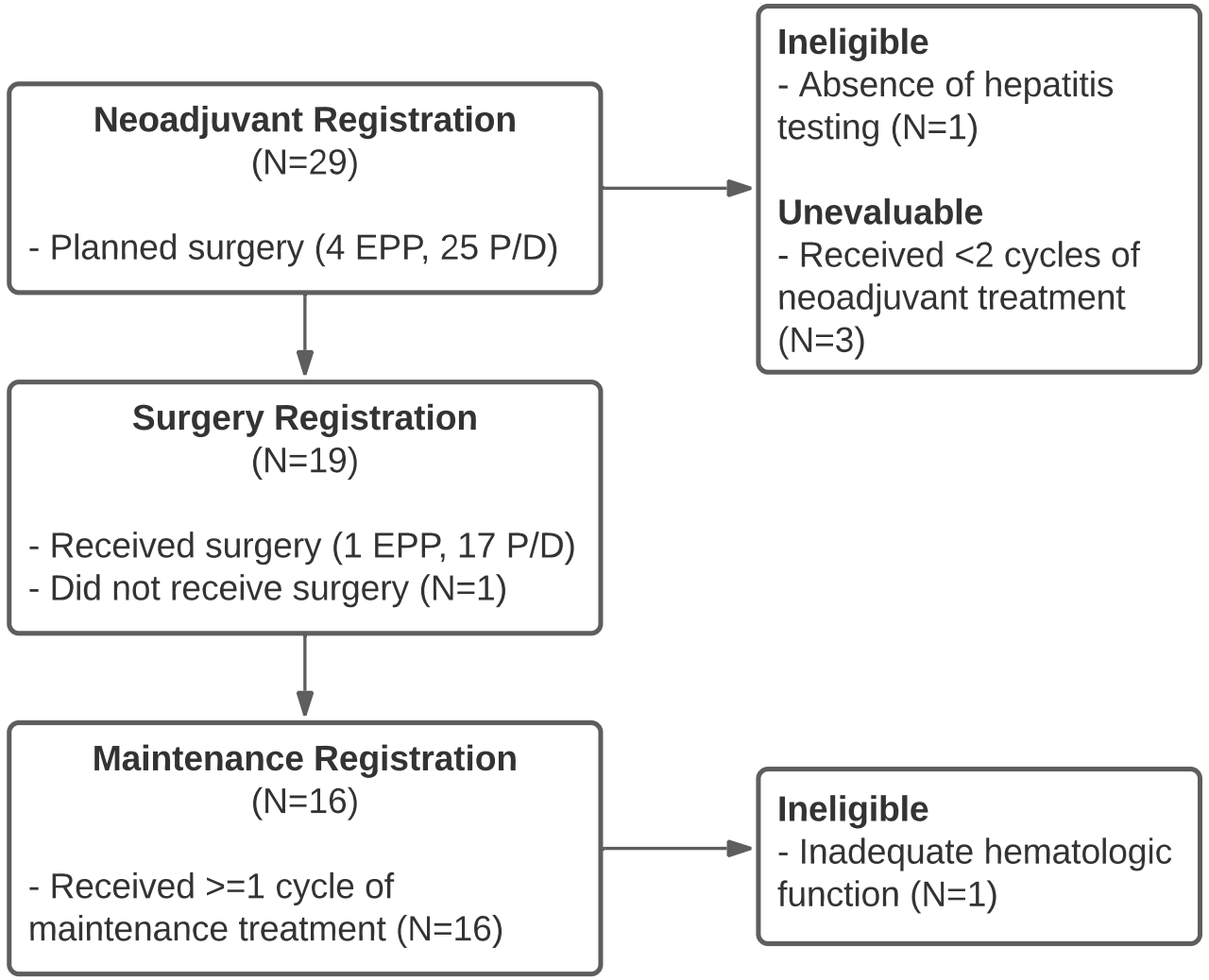
Primary endpoint: Evaluate the safety/tolerability and feasibility of neoadjuvant cisplatin-pemetrexed-atezolizumab, followed by surgery +/- radiation, followed by adjuvant maintenance atezolizumab.

- **Accrual goal**: 24 evaluable patients (12 EPP, 12 P/D)
  - Evaluable is defined as if they receive at least two cycles of the triplet neoadjuvant therapy (all three drugs). Patients who are not evaluable will be replaced. Both cohorts will be open in parallel.
  - Anticipated a total of 28 registered patients to accrue 24 eligible and evaluable patients.

- Safety/tolerability was defined as no Grade 4-5 immune-related adverse event
- Feasibility was defined as having 18/24 (75%) receive at least one dose of maintenance therapy.
- Analyses will separately evaluate patients who receive P/D and those who receive an EPP for their surgical procedure.

Consort Diagram Enrollment

28 eligible patients (Nov 2017 - May 2020)
25 received at least 2 cycles of CPA
18 underwent surgery
15 received maintenance atezolizumab



Patient Demographics

Characteristics	Patients (n=28)
Median age (range)	68.1 (31.4 – 77.3)
Gender (M:F)	20: 8
Ethnicity Caucasian Asian Unknown	 24 3 1
Planned Surgery EPP P/D	 4 24

Preliminary Outcomes

- 21 patients completed neoadjuvant therapy but seven patients did not proceed to resection.
  - 2 toxicity, 4 disease progression, 1 death (sepsis associated with non-immune related renal and respiratory failure)
- 18 patients with SD or PR proceeded to surgical resection
  - 17 received a P/D and 1 EPP.
  - 1 patient did not receive protocol-specified surgery due to PD.
  - Post-operatively, 1 patient had a fatal CVA.
- 16 patients registered to receive maintenance atezolizumab for 1 year
  - 1 patient was ineligible due to inadequate hematologic function.
- One patient remains ongoing with maintenance atezolizumab therapy.

Neoadjuvant therapy common TRAE and AE of interest

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute Renal Injury*				1	
Anemia	5	5	2		
Anorexia	7	4			
Constipation	5	2			
Creatinine increase	5	1			
Diarrhea			1		
Dysgeusia	3	2			
Fatigue	10	5			
Febrile Neutropenia			1		
Hyponatremia	4		1		
Infusion related reaction		3			
Nausea	9	10	1		
Neutropenia	4	4	3		
Pneumonitis*				1	
Respiratory failure*				1	
Sepsis*					1
Vomiting	4	2	1		

*same patient

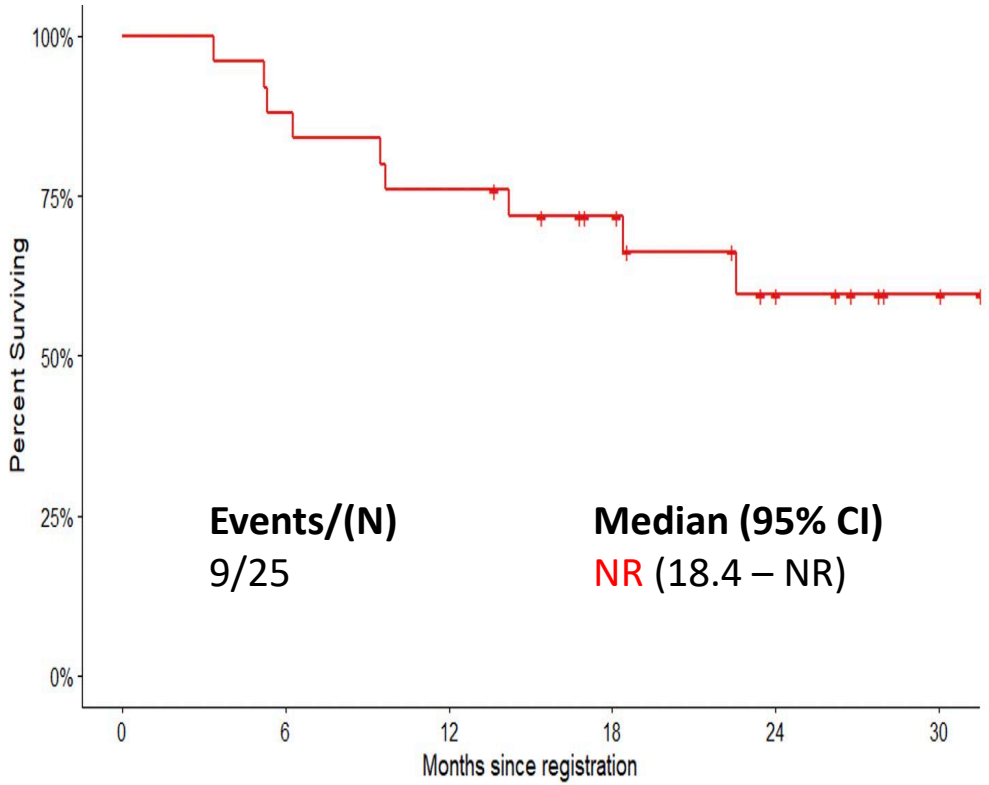
Maintenance therapy common TRAE and AE of interest

AE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Adrenal insufficiency		1			
Anemia	1				
Anorexia	2	1			
Constipation	2				
Creatinine increase	1	1			
Diarrhea	1				
Fatigue	5	1			
Hypotension			1		
Hypothyroidism	1	1			
Infusion related reaction		1			
Nausea	2	1			
Rash	2				
Vomiting	1				

Preliminary Survival

Median follow up time 10.3 (4.1-24.2) months for 15 patients that are currently alive

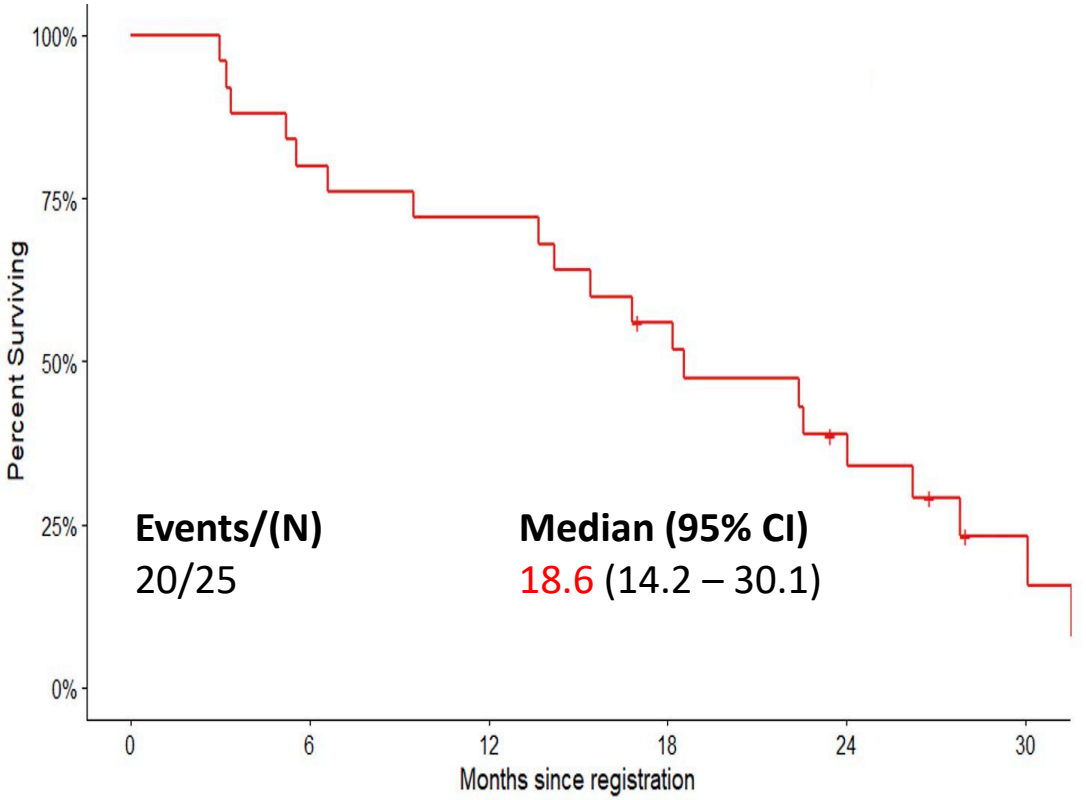
Overall Survival



Events/(N)
9/25

Median (95% CI)
NR (18.4 – NR)

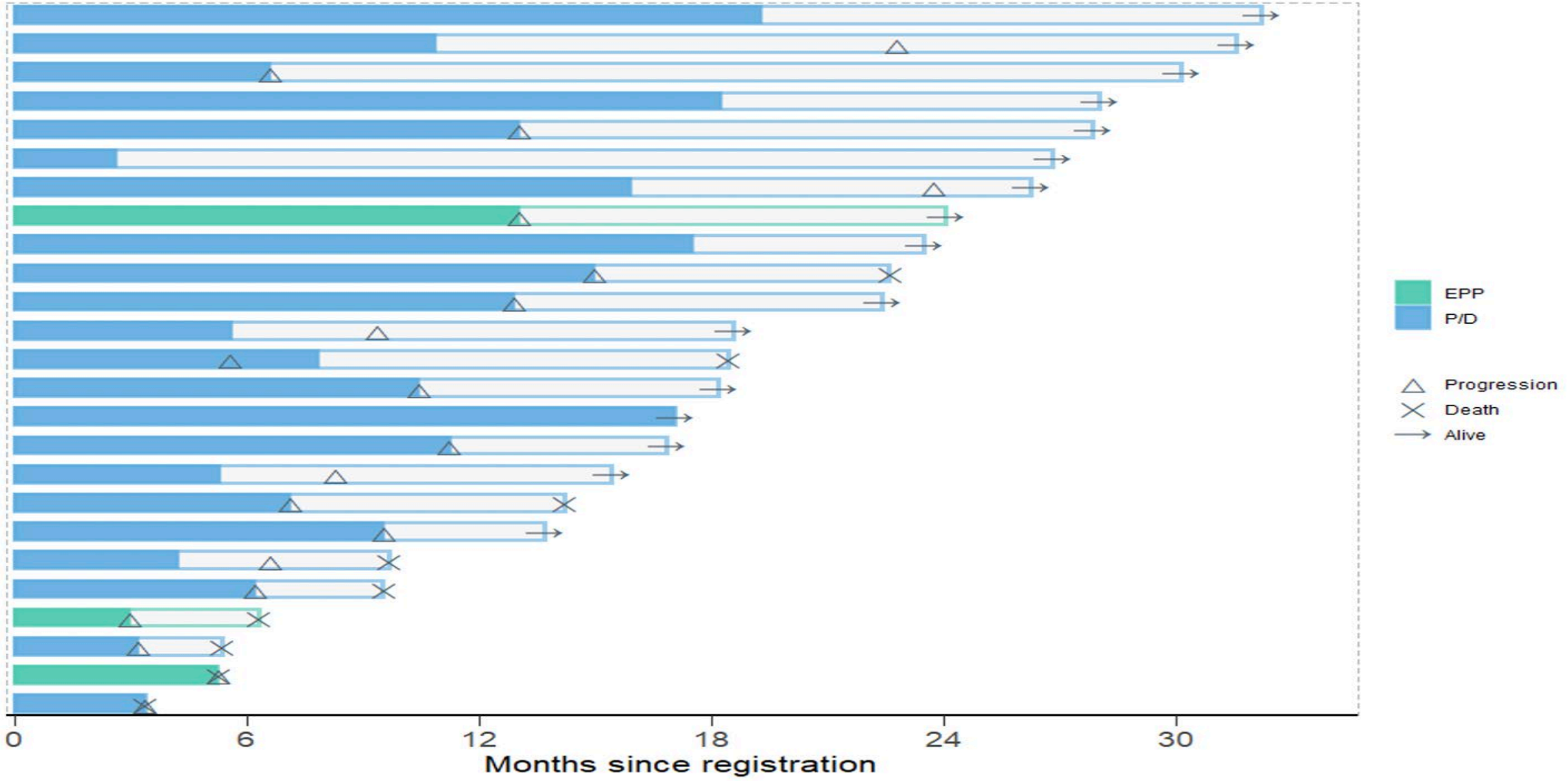
Progression-free Survival



Events/(N)
20/25

Median (95% CI)
18.6 (14.2 – 30.1)

Swimmer's Plot



S1619 Preliminary Take Home Message

- 4 cycles of neoadjuvant cisplatin-pemetrexed-atezolizumab successfully delivered in 21 eligible and evaluable patients.
  - 18 patients with radiographic SD or PR proceeded to surgical resection
  - 16 patients were able to proceed to maintenance atezolizumab
  - One patient ongoing with maintenance atezolizumab therapy.
  - Median f/u time 10.3 months, median PFS 18.6 months and median OS has not been reached.
- To date, no delayed treatment related adverse events > grade 3 reported.
- No new safety signals from the CPA regimen nor atezolizumab maintenance therapy.
- This trial highlights the challenging nature of neoadjuvant therapy trials in this patient population.
- Translational studies are pending.