ABSTRACT # 11519

Phase II Study of Atezolizumab in Advanced Alveolar Soft Part Sarcoma (ASPS)

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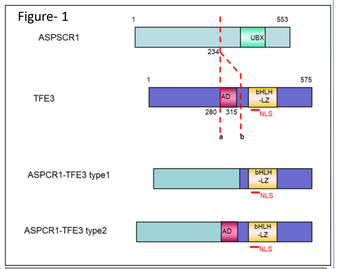
Background

- ASPS is a rare soft tissue sarcoma (STS), accounting for < 1% of all STS cases[1]. ASPS has an indolent growth pattern combined with unexpectedly high metastatic (particularly pulmonary) activity. It is characterized by the ASPSCR1-TFE3 fusion gene, which is encoded by the unbalanced translocation der(17)t(X;17)(p11;q25) (Figure1).
- High PD-L1 expression was reported in two ASPS xenograft models (Pediatric Preclinical Testing Consortium), suggesting that the PD-1/PD-L1 axis likely contributes to immunosuppression in ASPS.
- Responses in STS are modest (<20%) likely due to the immunologically "cold" tumor microenvironment[2]. However there have been case reports of immune checkpoint inhibitors showing efficacy in ASPS[3,4].
- In a recent phase 2 study of pembrolizumab + axitinib[5], 6 of 11 evaluable patients with ASPS achieved a partial response (54·5%).
- Atezolizumab is a human monoclonal antibody directed against programmed death-ligand 1 (PD-L1). It works by enhancing tumor-specific T-cell priming, expansion, and/or effector function.

Figure- 1



ASPS-TFE3 fusion variants: Breakpoints in the TFE-3 gene are marked as "a" and "b". The N-terminus of *ASPSCR-1* is fused in-frame with *TFE3* at exon 3 ("a") or exon 4 ("b"), resulting type-2 or type-1 fusions, respectively. At the molecular level, the first 234 amino-terminal amino acids from *ASPSCR-1* are fused to *TFE3* at amino acid positions 280 ("a") or 315 ("b"). Type 2 contains the activation domain of TFE3 while type 1 does not, but both form novel transcription factors and are functional.

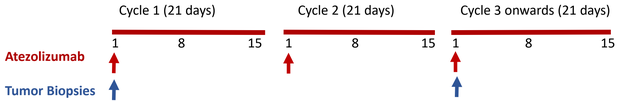
[1]Paoluzzi et al. *JAMA Oncology*; [2]Raj et al. *Sarcoma* 2018; [3]Conley et al. *JGO* 2017; [4]Groisberg et al. *JITC* 2017; [5]Wilky et al. *Lancet Oncol.* 2019

Objectives

- **Primary Objective**: Determine the objective response rate (ORR) of atezolizumab in adult (≥18 years) and pediatric/adolescent (≥ 2 years) patients with advanced ASPS.
- **Secondary Objectives:** Determine duration of response (DOR); measure progression-free survival (PFS) ;correlate response with expression of immunopharmacology biomarkers in paired tumor biopsies.

Key Eligibility Criteria and Study Design

- Histologically confirmed ASPS, age ≥ 2 years at the NCI Clinical Center (≥14 years at other participating sites) including patients with newly diagnosed, unresectable, metastatic, and measurable disease who show clinical evidence of disease progression.
- Exclusion criteria: prior anti-PD-1/PD-L1 therapy, history of grade 3/4 immune-related adverse events with anti-CTLA-4 therapy, RANK ligand use, history of autoimmune disease, and use of supraphysiologic steroid doses.



Multicenter, open-label, single-arm phase 2 study; atezolizumab is administered at a fixed dose of 1200 mg in adults or 15 mg/kg (1200 mg max) in pediatric patients aged ≥2 years once Q21 days. Tumor biopsies (mandatory) are collected from patients ≥18 years of age at baseline and prior to cycle 3 day 1 (±3 days). Data cutoff for analysis was set as April 20, 2021.

Results

Patient Characteristics

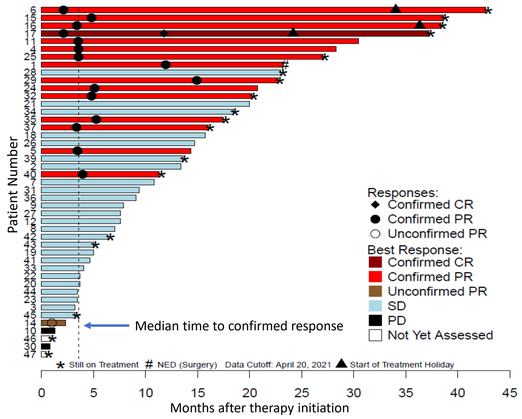
Characteristic	N= 45
Age in years, median (range)	31 (12-70)
Gender:	
Female	23
Male	22
Race:	
Black	13
Asian	05
Caucasian	25
Not reported	02
ECOG:	
0	23
1	21
2	01
Median prior lines of therapy (range)	1 (0-6)

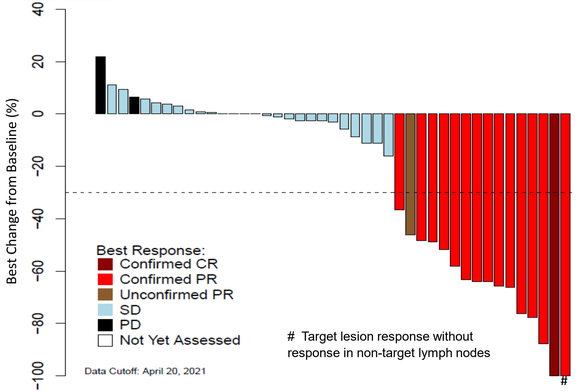
- As of April 20, 2021, **46 of 53** patients have been enrolled of which **45** were treated. Tumor RECIST 1.1 evaluations were available for **43** patients.

Patient Outcomes

Best Response	No. of Patients
CR	01
PR	
confirmed	14*
unconfirmed	01
SD	25
PD	02
Total evaluable	43

- Observed response rate: **37.2% (16/43)**
- Median time on study was **11.3 months** (range, 0.5–42.8)
- Median time to confirmed response: **3.5 months** (range, 2.1-14.9)
- Median duration of confirmed response: **16.6 months** (range, 7.4-40.6).
- **Three** patients have been on treatment holiday per protocol and have maintained PR after stopping therapy for a median of **8.6 months**





Safety Summary

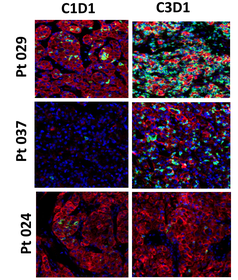
Adverse Events (AEs) Related to Atezolizumab	No. of Patients Evaluable for AEs (n=43)
	Grade 1-2 AEs; N (%) *(observed in ≥10% of patients)*
Anemia	9 (21.0)
Arthralgia	5 (11.6)
Alkaline Phosphatase Elevated	9 (21.0)
Fatigue	15 (34.8)
Fever	5 (11.6)
Thyroid Dysfunction	
Hypothyroidism	5 (11.6)
Hyperthyroidism	7 (16.3)
Hyponatremia	6 (14.0)
Lymphocyte count decreased	9 (21.0)
White blood count decreased	7 (16.3)
Nausea	7 (16.3)
Pruritis	6 (14.0)
Rash	
Maculopapular	6 (14.0)
Acneiform	8 (18.6)
Transaminitis	5 (11.6)

One or more **grade 3** adverse events potentially related to atezolizumab were reported in **13.9% (6/43)** of distinct patients. These included diarrhea, hypothyroidism, transaminitis, anemia, extremity pain, myalgia, pneumonitis, rash, and stroke (N=1 each). No grade 4 or 5 events have been reported.

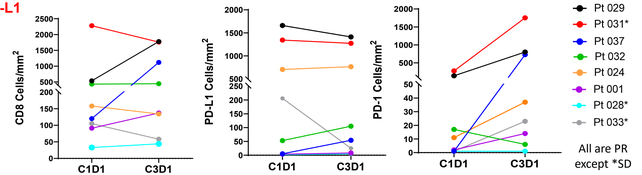
Tumor Pharmacodynamic Assessment

- Tumor specimens were analyzed with multiplex immunofluorescence immuno-oncology panels to quantify CD8+, PD-1+, and PD-L1+ cells/mm^2 in the tumor microenvironment. CD8+ density was calculated as the total number of CD8+ cells divided by the entire area (mm^2) of viable tumor plus its invasive margin in the biopsy section. Evaluated tumor areas ranged from 2.5 to 14 mm^{2}of the tumor and invasive margins of the biopsy.
- Among 8 cases with evaluable biopsy pairs, both baseline and C3D1 specimens in all cases demonstrated CD8+ T cell infiltration and PD-L1 expression.

Tumor IFA microscopy for CD8 ;PD-L1



CD8+, PD-1+, and PD-L1+ cells/mm^2 in tumor and invasive margins



- PD-1 expression was detected at baseline in 5 cases and at C3D1 in 7 cases.
- In 6 cases (3 SDs and 3 PRs), treatment did not change CD8+ cell density. In the other 2 cases (Pt 029 & 037; both PRs), CD8+ density increased > 3x baseline by C3D1.
- Analyses of T cell activation using pharmacodynamic response biomarkers, along with whole exome and RNA-seq to evaluate the genomic and transcriptomic landscape of ASPS, are ongoing.

Conclusions

- Atezolizumab is well tolerated and demonstrates promising single agent activity with durable responses in patients with advanced ASPS.
- Preliminary tumor biomarker analysis confirms the presence of multiple PD-1/PD-L1 immune checkpoint (IC) components, indicating that advanced ASPS is an ideal candidate for therapeutic IC inhibition.
- We are in the process of evaluating genomic/ transcriptomic landscape of ASPS type 1 vs. type 2 fusions and their relationship with clinical response to atezolizumab.

Acknowledgements

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