TPS2695 Poster Session

Phase 1/2 study of tiragolumab and atezolizumab in patients with relapsed or refractory SMARCB1- or SMARCA4-deficient tumors: PEPN2121.

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Background: The SMARCB1/A4 gene products are core subunits of the SWItch/Sucrose Non Fermentable (SWI/SNF) chromatin remodeling complex. Tumors with defects in SWI/SNF are histologically distinct aggressive cancers occurring in children and young adults. SMARCB1/A4 deficient tumors, particularly malignant rhabdoid tumor (MRT), atypical teratoid rhabdoid tumor (ATRT), poorly differentiated chordoma (PDC), epithelioid sarcoma (ES), and renal medullary carcinoma (RMC), have immune cell infiltrates and programmed death ligand 1 (PD-L1) expression. Responses to immune checkpoint inhibition (CI) have been observed in SMARCB1/A4 deficient tumors; however, responses are not durable. T cell immunoreceptor with Ig and ITIM domains (TIGIT) is a novel inhibitory receptor expressed on multiple immune cells. TIGIT inhibits T and NK cells by binding to its ligand poliovirus receptor (PVR) and Nectin2 on both tumor and antigen-presenting cells. Utilizing RNAseq data, SMARCB1/A4 deficient tumors demonstrate high expression of PVR and Nectin2. Tiragolumab is an antibody to the TIGIT receptor. The combination of tiragolumab and atezolizumab has shown promising activity in early phase studies, and phase 3 studies are ongoing in multiple adult indications. Thus, there is rationale that the addition of tiragolumab to CI may also enhance response rates in patients with SMARCB1/A4 deficient tumors. **Methods:** This is a phase 1/2 trial of tiragolumab monotherapy (300 mg if $\leq$ 15 kg; 420 mg if $>$ 15 kg to $\leq$ 40 kg; 600 mg if $>$ 40 kg or $\geq$ 18 years) and in combination with atezolizumab (15 mg/kg [max 1200 mg]) if $<$ 18 yrs or 1200 mg if $\geq$ 18 years) administered IV on Day 1 of 21-day cycles in patients $>$ 12 months of age with SMARCB1/A4 deficient tumors. Part A evaluating the safety of tiragolumab monotherapy in patients $<$ 18 years based on cycle 1 dose limiting toxicities is complete. Part B estimates the antitumor activity of tiragolumab in combination with atezolizumab in 6 histology-specific cohorts (RMC, MRT, ATRT, PDC, ES, and other SMARCB1/A4 deficient tumors) and is now open to all eligible age groups. Each cohort is conducted using a 6+4 Simon's two stage design. Enrollment for each cohort is as follows: Part A 6/6, Part B RMC 1/6, MRT 1/6, ATRT 4/6, PDC 2/6, ES 3/6, other 6/6. Radiographic imaging central response assessment for the first stage of the "other" cohort is ongoing. Cycle 1 toxicities of the combination therapy are monitored in Part B patients $<$ 12 yrs using a Bayesian Optimal INterval (BOIN) design with a target toxicity of 17%. Secondary objectives are to characterize the pharmacokinetics/anti-drug antibody development and to estimate progression free survival, overall survival, and duration of response. Enrollment is open at all Pediatric Early Phase Clinical Trial Network sites. Data cutoff: Jan 10, 2025. Clinical trial information: NCT05286801.
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