TPS8123 **Poster Session**

Trial in progress: Sacituzumab govitecan for the treatment of patients with diffuse pleural mesothelioma.

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Background: Diffuse pleural mesothelioma (DPM) is an aggressive malignancy with poor outcomes and only three FDA-approved treatments (all first-line). Even when first-line treatment is effective, most patients experience progression within a year, and there are no approved, nor accepted, second-line approaches. Analysis of our novel library of DPM patient derived xenografts (PDXs) nominated TROP-2 as a candidate target for therapy. The role of TROP-2 expression in proliferation, colony formation, migration, and invasion was determined along with the antitumor efficacy of a TROP-2 targeting antibody-drug conjugate (ADC). Exogenous TROP-2 expression increased tumorigenicity *in vitro* and *in vivo* across multiple DPM models and induced upregulation of pro-oncogenic pathways. Treatment of PDXs with the TROP-2 ADC sacituzumab govitecan-hziy (SG) inhibited tumor growth with higher efficacy than gemcitabine (a standard of care later-line treatment) or the cytotoxic payload alone (irinotecan; results previously presented at WCLC 2024). These data identified TROP-2 as a promising therapeutic target in DPM leading to the development of an investigator-initiated trial with Department of Defense support (HT9425-24-1-0754). **Methods:** A single arm phase 2 unblinded Simon two-stage single-institution study recently commenced at Memorial Sloan Kettering Cancer Center (MSK) assessing the primary endpoint of overall response rate to SG by modified (m)RECIST v1.1 in patients with recurrent and/or unresectable/metastatic pathologically confirmed DPM (NCT06477419). Secondary endpoints include overall survival, progression-free survival, and safety. Key eligibility criteria include receipt of at least one prior line of standard systemic therapy and agreement to undergo study biopsies at screening, prior to cycle 3, and end of treatment (optional) if safe and feasible. SG will be administered intravenously at the FDA-approved dose/schedule established in breast cancer (10 mg/kg on days 1 and 8 of a 21-day cycle). Patients will undergo imaging after the first 2 cycles and subsequently every 3 cycles until progression. In the first stage, 19 patients will be treated. If at least 4 responses are observed, then an additional 14 patients will be accrued. To date, 4 patients have been enrolled. Tumor material will undergo 1) routine histologic subtyping, TROP-2 immunohistochemistry, and next-generation sequencing (MSK-IMPACT), 2) flow cytometry, 3) proteomic analyses/mass-spectrometry, and 4) RNA sequencing/methylation analysis. These studies will characterize how SG alters tumoral expression of TROP-2 and signaling pathways supporting cancer growth and survival. Clinical trial information: NCT06477419. Research Sponsor: U.S. Department of Defense; HT9425-24-1-0754; Gilead Science.