TPS3648 **Poster Session**

Phase II study of epacadostat (INCB024360) added to preoperative chemoradiation in patients with locally advanced rectal cancer.

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Background: Indoleamine 2,3-dioxygenase 1 (IDO1) metabolizes tryptophan along the kynurenine pathway and is recognized as a potent suppressor of tumor reactive immunity. Epacadostat is an orally active, potent and selective inhibitor of IDO1. In preclinical studies, IDO1 was found to promote resistance to radiation in rectal cancer, irrespective of microsatellite instability (MSI) status. IDO1 inhibition with epacadostat improved tumor radiosensitivity by relieving immune suppression and augmenting radiation-induced apoptosis while protecting the normal intestine from radiation damage. In a phase 1 trial, 17 patients were enrolled from 4/2019 to 8/2023. Epacadostat in combination with short-course radiation therapy (SCRT) and CAPOX was well-tolerated and the recommended phase 2 dose (RP2D) of epacadostat was determined to be 400 mg BID. An NCI supported Phase 2 trial is ongoing to further evaluate the promising disease responses reported in the dose escalation phase. **Methods:** This phase 2 multicenter, open-label trial includes treatment and biomarker cohorts. In the treatment cohort, epacadostat at 400 mg BID will be administered concurrently with SCRT followed by epacadostat monotherapy until 1 day prior to neoadjuvant chemotherapy, followed by standard-of-care (SOC) neoadjuvant chemotherapy and, ultimately, surgical resection or non-operative management (NOM). Biomarker cohort enrollment will commence at completion of treatment cohort accrual. Enrolled patients will be treated with SOC SCRT followed by SOC neoadjuvant chemotherapy and surgical resection or NOM. Eligible patients must be a treatment-naïve, newly diagnosed, pathologically confirmed, locally advanced rectal cancer (defined by 8th edition AJCC stage 2 or 3, or stage 1 not eligible for sphincter-sparing surgery) with plans to proceed with neoadjuvant SCRT and chemotherapy. The primary endpoint is the neoadjuvant rectal (NAR) score. Secondary endpoints are pathologic complete response (pCR) rate, complete clinical response (cCR) rate and progression-free survival (PFS). Exploratory endpoints are pharmacodynamics, PDX and organoid generation, identification of molecular predictors of response and resistance, correlation of radiographic and pathologic response and effect of treatment on patient quality of life. We aim to enroll 27 patients in the treatment cohort and 10 in the biomarker cohort. Clinical Trial Registration: NCT03516708. Research Sponsor: NIH (grant number 1R01CA278197-01A1); Incyte (drug only).