TPS4212 **Poster Session**

Repurposing itraconazole for secondary prevention of metaplasia and primary prevention of cancer in patients with high-risk Barrett's esophagus in combination with ablation.

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Background: To prevent invasive esophageal adenocarcinoma (EAC), endoscopic eradication therapy (EET) is used to remove its precursor, Barrett's esophagus (BE) with dysplasia. EET combines endoscopic removal of visible lesions with radiofrequency ablation (RFA) of surrounding BE to achieve complete remission of intestinal metaplasia (CRIM) and complete eradication of dysplasia (CED) to halt progression to cancer. Unfortunately, EET has metaplasia recurrence rates of 12.4%/year; thus, adjunctive cancer interception agents are needed to maintain the gains of EET. Data from pre-clinical studies and patient tissues demonstrate that the Hedgehog (Hh) pathway regulates esophageal stem cell activity and cell fate determination (squamous versus intestinal). Post-RFA reactivation of Hh signaling is hypothesized to drive BE recurrence; however, current FDA-approved Hh inhibitors are expensive and toxic. The antifungal itraconazole inhibits Hh signaling and has demonstrated antitumor activity in multiple cancers. In addition, it inhibits VEGFR and PI3K-AKT pathways, which are critical to BE development and neoplastic progression. Given its safety and affordability, itraconazole represents a promising strategy to reduce BE recurrence and EAC risk. **Methods:** This randomized, phase 2b, double-blind, placebo-controlled trial will evaluate itraconazole's efficacy in accelerating BE eradication. Participants with high-risk BE, defined as BE $\geq$2 cm with low/high-grade dysplasia or intramucosal/T1 adenocarcinoma, undergoing ablation will be enrolled. Participants will be randomized 1:1 to receive 300 mg of oral itraconazole or placebo for two weeks before and four weeks after their first 2 sessions of EET. The primary endpoint is time to CRIM, a surrogate for long-term BE recurrence, measured in days. Secondary endpoints include time to CED, 12-month BE recurrence rates, safety, tolerability, and correlations between itraconazole levels and patient-reported outcomes. We will enroll 74 patients (37 per arm). We shall use a two-sided log rank test for right-censored time to event analysis to assess differences. The sample size calculation is based on anticipated surviving proportions at specific study times. We assume that the surviving non-CRIM proportions of patients at 3, 6, 9, and 12 months in the control arm to be 0.8, 0.5, 0.2, 0.1, respectively, and in the treatment arm to be 0.5, 0.2, 0.1, 0.05, respectively. To detect this effect size with 80% power at 5% level of significance, we need 30 evaluable participants in each group (with a plan to enroll 37 per arm to account for attrition). A Cox model will adjust for demographic and clinical variables. If successful, this trial could establish itraconazole as a novel adjunct to EET, reducing BE recurrence and lowering EAC risk. Clinical trial information: NCT06732388. Research Sponsor: National Cancer Institute; UG1-CA242632.