TPS2683 **Poster Session**

INVOKE: A phase 1 study of OKN4395, a first-in-class EP2/EP4/DP1 triple prostanoid receptor antagonist, in patients with advanced solid tumors.

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Background: Immunotherapy is an established cancer therapy, although mechanisms of non-response & resistance are emerging, leaving few options post-relapse. The immunosuppressive pathway of prostaglandin E_2 (PGE_2), part of the cyclooxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of CD8 T, NK, and dendritic immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDS) have shown some survival benefit in patients with colon, lung, prostate, and endometrial cancer (Cao et al., 2016; Lim et al., 2012; Huang et al., 2014; Takiuchi et al., 2018), however results are inconsistent, likely due to toxicity limiting complete blockade of the pathway, highlighting the need for more potent but selective COX pathway inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4 and DP1, downstream receptors for COX-derived PGE_2, and PGD_2, respectively. DP1 has described roles in immunosuppression and inhibition of apoptosis, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response as monotherapy, and to potentiate the effect of immunotherapies such as checkpoint inhibitors, both of which are evaluated in INVOKE. **Methods:** INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with pembrolizumab 200mg IV 3-weekly (combo), in patients with advanced solid tumors that have evidence of COX-associated immunosuppression. Ph1a is a Bayesian dose escalation in mono, followed by combo dose confirmation, primarily assessing safety, establishing the optimal dose for Ph1b. Using multimodal artificial intelligence (AI) drug-matching algorithms, Ph1b tumor types were selected, and response will be assessed (cohorts of n = 20 each): select sarcomas (mono), pancreatic carcinoma (mono), non-small cell lung cancer (combo), colorectal carcinoma (combo), head and neck squamous cell carcinoma (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Active CNS metastases, upper GI bleed risk factors, untreated H. pylori infection, and concomitant NSAIDs/COX inhibitors/prostaglandins are exclusionary. Ph1b mono cohorts will include exploratory analyses including evaluation of the effect of food & gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm. Ph1a of the study is currently recruiting in the US, UK, and Australia. Clinical trial information: 06789172. Research Sponsor: Epkin.