PHASE 1 DOSE ESCALATION TRIAL OF THE SELECTIVE A2B ADENOSINE RECEPTOR ANTAGONIST PBF-1129 IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER (MNSCLC)

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Background Adenosinergic signaling has recently emerged as a powerful regulator within the tumor microenvironment (TME). Preclinical studies on interference with adenosine generation or signaling through A2A and A2B adenosine receptors (A2BAR) have been shown to relieve immunosuppression by reducing stress in the TME by decreasing expression of key adenosine-generating enzymes. A2BAR blockade enhances anti-tumor immunity through a reduction in myeloid-derived suppressor cell differentiation and an enhancement of the capacity of dendritic cells to evoke anti-tumor T cell responses. We conducted a phase 1 dose escalation trial of PBF-1129, a first in class selective A2BAR inhibitor in patients with mNSCLC who progressed on chemotherapy and immune checkpoint inhibitors (ICI).

Methods NCT03274479 was a single site dose escalation phase 1 trial. Patients received escalating doses of PBF-1129 orally daily (80 mg, 160 mg, 240 mg, 360 mg) until disease progression or intolerability. Primary objective was safety and tolerability as define by occurrence of dose limiting toxicities (DLT) and to determine maximum tolerated dose (MTD). PK, ORR, PFS, OS were secondary endpoints.

Results 21 patients (9 female), median age 61 years (range 49-75) were enrolled. 12 patients with adenocarcinoma, 7 with squamous, 1 with adenosquamous and 1 NOS. Median line of therapy was 4th (range 3-6). All patients received prior PD-1/L1 therapy and chemotherapy; 4 pts received prior anti-CTLA-4. PD-L1 expression negative in 6 pts, positive in 12 and unknown in 3 pts. No DLTs were observed at any dose level. No MTD was identified. Grade 3/4 treatment-related adverse events (TRAEs) occurred in 3 patients including lymphocytopenia (n=2), hyponatremia (n=1), hypertension (n=1), and encephalopathy (n=1). Most frequent TRAEs of any grade were lymphocytopenia (n=8, 38%), vomiting (n=8, 38%), anorexia (n=6, 29%), and fatigue (n=6, 29%). 18 patients were evaluable for response, best response of stable disease was observed in 3 pts; median PFS 1.5 months (95% CI 1.0, 1.9), median OS 4.6 months (95% CI: 2.1, 5.2). PK analysis revealed a dose-dependent exposure increase, with median C(max) ranging from 150 ng/ml at the 40 mg dose to 800 ng/ml at the 320 mg dose, together with a moderate half-life above 10h (figure 1). The 320 mg is able to maintain PBF-1129 free concentrations above the IC(50) against the adenosine A2b receptor for 24h.

Conclusions PBF-1129 was safe and tolerable in patients with heavily pretreated mNSCLC although limited single agent activity was observed. RP2D was identified as 360 mg orally daily. A trial of PBF-1129 given in combination with ICI is planned (NCT05234307).

Trial Registration NCT03274479
Ethics Approval The study was approved by the OSU institution’s Ethics Board (#2018C0019)
Consent All study participants granted a written informed consent prior to treatment initiation.