Background The p38 mitogen-activated protein kinase (MAPK) pathway limits dendritic cell priming and we have discovered a novel tumor-intrinsic immune-exclusion role for p38 MAPK across multiple tumor types. ARRY-614 (pexmetinib) is a p38 MAPK inhibitor that enhances immune-checkpoint blockade (ICB) in murine models. Here we report on the safety and anti-tumor activity of ARRY-614 with nivolumab (N), ipilimumab (I), or N+I in human subjects with advanced solid tumors.

Methods Subjects received daily, oral ARRY-614 (de-escalated from 800 to 200mg) with N (480 mg), I (3 mg/kg), or N+I (1 mg/kg) on either 28- or 21-day cycles. The primary objective was safety and tolerability of ARRY-614 with N, I, or N+I and selection of the recommended phase II dose (RP2D) using a Bayesian dose-finding strategy. Preliminary anti-tumor activity per RECISTv1.1 or irRECIST were secondary objectives.

Results Twenty-eight subjects were recruited (n=15 with N; including NSCLC, GEJ, RCC and mesothelioma; n=13 with I or N+I; all melanoma). Most were male (71.4%) with median age 67, three prior therapy lines, and 93% previously exposed to PD(L)1 (all meeting SITC PD(L)1 resistance definition)[1]. Treatment-related adverse events (TRAEs) were documented in all 28 subjects with 17.2% TRAEs reported as clinically significant, 9.2% grade 3, and 7.0% deemed immune-related adverse events (irAE). Eight subjects experienced dose-limiting toxicities (DLT) including rash, colitis, atrial fibrillation, hypotension, dyspnea, anaphylaxis, and visual disturbances; all in patients receiving a starting dose ≥400mg ARRY-614 and equally distributed in N vs N+I cohorts. The RP2D is 200 mg ARRY-614 with ICB and preliminary ARRY-614 PK assessment suggesting a dose-exposure relationship with DLT via area under the curve. Response was evaluable in 20 subjects (eight were nonevaluable due to toxicity or early progression) with three confirmed PRs and nine SD/irSD (figure 1). Median duration of response is not reached with two PR ongoing more than 1.5 years (NSCLC: PD-L1 0%, TMB 5.4 muts/Mb, prior chemotherapy + anti-PD1 / RCC: prior TKI, IL2, multiple PD(L)1 combinations). Six-month progression-free survival was achieved in six subjects including two patients with SD/irSD reaching >12 months (and three with continued benefit despite early drug cessation due to irAE; figure 2). Length of prior treatment time on most recent anti-PD(L)1 therapy did not associate with outcome. Immune monitoring and pharmacodynamic assessments are in progress.

Conclusions Inhibition of the p38 MAPK pathway with ARRY-614 is well tolerated at 200mg in combination with ICB, eliciting durable responses and disease control in poor risk and PD(L)1-refractory subjects.

Trial Registration NCT04074967

REFERENCE