Phase I/II dose escalation and expansion study of FLX475 alone and in combination with pembrolizumab in advanced cancer.

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ABSTRACT

Background: Regulatory T cells (Tregs) can dampen anti-tumor immune responses in the tumor microenvironment (TME). The predominant chemokine receptor on human Tregs is CCR4, the receptor for the chemokines CCL17 and CCL22, which are produced by tumor cells, tumor-associated macrophages and dendritic cells, as well as by effector T cells (Teffs) in the setting of an inflammatory anti-tumor response. Preclinical studies with orally-available CCR4 antagonists have demonstrated potent inhibition of Treg migration into tumors, an increase in the intratumoral Teff/Treg ratio, and anti-tumor efficacy as a single agent and in combination with checkpoint inhibitors. In a first-in-human trial conducted in healthy volunteers, the oral CCR4 antagonist FLX475 was demonstrated to be well tolerated with outstanding PK properties. A robust PD assay measuring receptor occupancy on circulating Tregs demonstrated the ability to safely achieve exposure levels predicted to maximally inhibit Treg recruitment into tumors via CCR4 signaling. These human PK, PD, and safety data have enabled a streamlined design of a Phase III study of FLX475 in cancer patients both as monotherapy and in combination with checkpoint inhibitor.

Methods: This clinical trial is a Phase I/II, open-label, dose-escalation and cohort expansion study to determine the safety and preliminary anti-tumor activity of FLX475 as monotherapy and in combination with pembrolizumab. The study is being conducted in 2 parts, a dose-escalation phase (Part 1) and a cohort expansion phase (Part 2). In Part 1 (Phase I) of the study, at least 3 to 6 eligible subjects will be enrolled in sequential cohorts treated with successively higher doses of FLX475 as monotherapy (Part 1a) or in combination with pembrolizumab (Part 1b). In Part 2 (Phase II) of the study, expansion cohorts of both checkpoint-naive and checkpoint-experienced patients with tumor types predicted to be enriched for Tregs and/or CCR4 ligand expression (i.e., "charged tumors") -- including both EBV+ and HPV+ tumors and NSCLC, HNSCC, and TNBC -- will be enrolled using a Simon 2-stage design. As of January 2019, the first two cohorts have been completed without DLT.

REFERENCES
5. Talay et al., AACR 2018, P4752 (DOI: 10.1158/1538-7445.AM2018-4752)