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Abstract TIP 548

Phase 2 study of FLX475 in combination with ipilimumab in advanced melanoma

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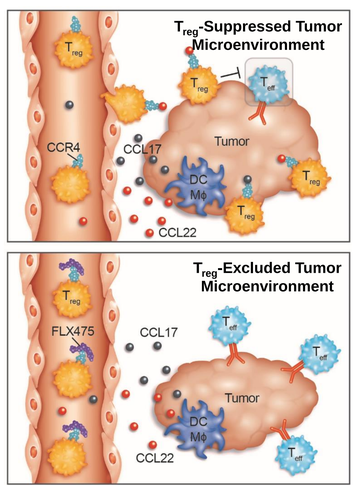
ABSTRACT

Background: Regulatory T cells (T_{reg}) can dampen antitumor immune responses in the tumor microenvironment (TME) and have been shown to correlate with poor clinical outcome. Translational studies have demonstrated an accumulation of T_{reg} in tumors after treatment with immunotherapies including CAR-T cells and anti-CTLA-4, which could potentially reflect a mechanism of adaptive immune resistance[a-b]. CCR4, the receptor for the chemokines CCL17 and CCL22, is the predominant chemokine receptor on human T_{reg} and is responsible for the migration and accumulation of T_{reg} in the TME. Preclinical studies with orally available CCR4 antagonists have demonstrated potent inhibition of T_{reg} migration into tumors, an increase in the intratumoral T_{eff}/T_{reg} ratio, and antitumor efficacy as a single agent and in combination with checkpoint inhibitors, including anti-CTLA-4[c]. In a first-in-human trial conducted in healthy volunteers, the oral CCR4 antagonist FLX475 was demonstrated to be well tolerated with outstanding pharmacokinetic and pharmacodynamic properties[d]. An ongoing Phase 1/2 clinical trial of FLX475 is examining the safety and preliminary antitumor activity of FLX475 as monotherapy and in combination with pembrolizumab in subjects with several types of advanced cancer[e]. Given the preclinical data demonstrating a significant enhancement of the antitumor activity of anti-CTLA-4 when combined with FLX475, a Phase 2 study investigating the combination of FLX475 and ipilimumab is now being conducted in subjects with advanced melanoma.

Methods: This clinical trial is a Phase 2, multicenter, open-label, single-arm study to determine the antitumor activity of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent. The primary objectives of the study are to evaluate objective response rate, and the safety and tolerability of this combination. The study will first examine the safety of the combination of the 100 mg PO QD recommended Phase 2 dose of FLX475 and the approved 3 mg/kg IV Q3W dose of ipilimumab as part of a safety run-in phase, prior to examining the degree of antitumor activity in approximately 20 subjects. Evidence of an overall response rate (ORR) notably greater than the expected ORR of ipilimumab monotherapy alone in such subjects, which has been shown to be approximately 14%[f], would provide preliminary clinical evidence in support of the clinical hypothesis that CCR4 blockade by FLX475 can significantly enhance the antitumor activity of an anti-CTLA-4 checkpoint inhibitor.

BACKGROUND

FLX475: Designed to Enhance the Anti-Tumor Immune Response

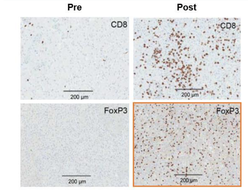


- Immune cells follow chemokines to migrate into target tissues
- CCR4 is the primary chemokine receptor expressed on human T_{reg}
- In response to inflammation, tumor cells and other cells in the TME highly express the chemokines CCL17 and CCL22 (ligands for CCR4), inducing the migration of T_{reg} into tumors
- T_{reg} can suppress the anti-tumor activity of effector T cells
- FLX475 is a potent, orally-available, small molecule antagonist of CCR4 designed to specifically block the recruitment of T_{reg} into tumors
  - With a goal of shifting the T_{eff}/T_{reg} balance in favor of tumor elimination

PRECLINICAL RATIONALE

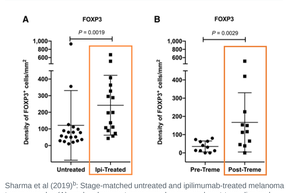
Accumulation of T_{reg} in the TME is a General Adaptive Immune Resistance Mechanism to Treatment

Localization of glioblastoma-specific CAR-T cells is accompanied by a large influx of FoxP3$^+$ T_{reg}



O'Rourke et al (2017)[a]: Immunohistochemistry of the TME showing CD8 T cells and FoxP3 expressing T_{reg} cells before (left panel) and after (right panel) CART-EGFRvIII infusion

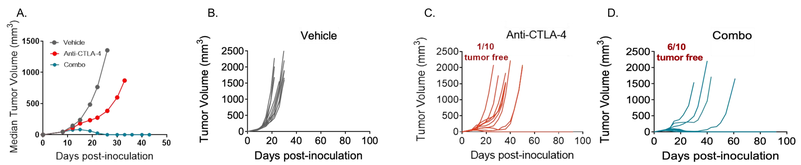
Melanoma tumors show an increase of FoxP3$^+$ T_{reg} after anti-CTLA-4 mAb treatment



Sharma et al (2019)[b]: Stage-matched untreated and ipilimumab-treated melanoma tumor samples (A), and melanoma tumor samples pre- and post-tremelimumab treatment (B) analyzed by IHC for the presence of FOXP3$^+$ cells. Each plot shows mean with SD, and each symbol represents an individual patient. Statistical significance is defined as P <0.05.

PRECLINICAL DATA

CCR4 Inhibition in Combination with Anti-CTLA-4 Treatment Can Significantly Improve Antitumor Efficacy vs Anti-CTLA-4 Alone



Marshall et al (2020)[c]: CT26 tumor-bearing mice were dosed daily with CCR4 antagonist daily and with anti-CTLA-4 antibody on days 0, 4, 8 and 12 post randomization. Median tumor volume (A) or individual tumor growth plots (B, C and D) are shown (n=10 mice). This is representative data from 3 independent in vivo efficacy studies.

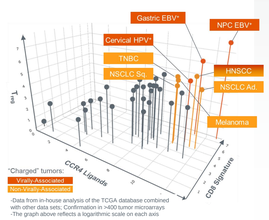
FLX475 CLINICAL PROGRAM

Phase 1 Healthy Volunteer Study Established Well-Tolerated Potentially Therapeutic Dose[d]

- FLX475 was first tested in a healthy volunteer study (FLX475-01; single dose and daily oral doses for 2 weeks)
- Dose-dependent increases in exposure were observed with a half-life of approximately 72 hours
- A dose of 75 mg PO QD and above achieved/exceeded target drug concentration
- FLX475 was well-tolerated, with no significant lab abnormalities or dose-limiting clinical adverse events (including no irAEs, consistent with mechanism of action)
- Only drug-related finding was asymptomatic, reversible low-grade QTc prolongation at exposures 3-5-fold beyond target therapeutic exposure level

Phase 1/2 Study of FLX475 Monotherapy and Combination with Pembrolizumab is Ongoing in Patients with Cancer[e]

- Currently in Phase 2 of the Phase 1/2 study (FLX475-02)
  - Phase 1 dose escalation as monotherapy and in combination with pembrolizumab
  - Phase 2 monotherapy and combination expansion cohorts in selected "charged" tumor types
- Study focusing on "charged" tumor types, i.e. those more likely to be enriched for high levels of CCR4 ligands, T_{reg} and CD8 cells
  - Hypothesized to be more likely to respond to CCR4 antagonism
  - Melanoma is not currently included as one of the indications being studied in the Phase 2 expansion cohorts of the FLX475-02 study



METHODS

FLX475-03 Study Rationale

- Ipilimumab is an approved treatment for advanced melanoma with a reported best overall response rate (ORR) ranging from 10.9% in previously-treated patients[g] to 19% in previously untreated patients[h], thus there remains room for clinical improvement
- Regulatory T cells (T_{reg}) may play a role in limiting the efficacy of immunotherapies, including checkpoint inhibitors such as anti-CTLA-4
- FLX475 administration may block the CCR4-mediated recruitment of suppressive T_{reg} into tumors, thus enhancing the anti-tumor immune response when given in combination with ipilimumab, thus increasing the clinical activity of ipilimumab

FLX475-03 Study Objectives

- Primary Objectives
  - To evaluate the objective response rate, defined as confirmed complete or partial response per RECIST 1.1, of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
  - To evaluate the safety and tolerability of FLX475 in combination with ipilimumab in subjects with advanced melanoma previously treated with an anti-PD-1 or anti-PD-L1 agent
- Secondary Objectives
  - Progression-free survival, overall survival, duration of response
  - FLX475 pharmacokinetics, pharmacodynamic markers
  - Tumor biomarkers

Study Design

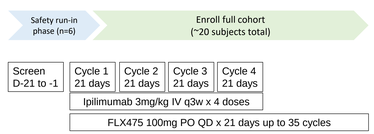
- Phase 2, single arm, open-label Phase 2 study exploring the efficacy of the combination of FLX475 and ipilimumab in patients with advanced/metastatic melanoma that has progressed on or recurred after anti-PD-(L)1 therapy
- Approx. 20 subjects
- Using the recommended Phase 2 dose from Phase 1/2 study of FLX475 (100 mg PO QD) + full-standard dose of ipilimumab (3 mg/kg q3w x 4 doses)
- Enrollment will start with safety run-in phase
  - -6 subjects will be enrolled and treated for at least 3 weeks (1 cycle)
  - -If no more than 1/6 have a dose-limiting toxicity(DLT), a full cohort of ~20 subjects will be enrolled

ClinicalTrials.gov Identifier: NCT04894994

Major Eligibility Criteria

- Pathologically confirmed melanoma (stage IV or unresectable Stage III)
- Subjects must have had prior treatment with anti-PD-1 or anti-PD-L1 agents, with at least 2 months of therapy followed by documented disease progression
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- Subjects must have measurable disease per RECIST 1.1
- Tumor available for biopsy
- No prior history of discontinuing prior treatment due to Grade 3–4 immune related adverse events of colitis or pneumonitis.
- No prior treatment with ipilimumab or other CTLA-4 antagonists

Study Schema



Study Sites

- MD Anderson Cancer Center, Houston, Texas (Hussein Tawbi)
- Moffitt Cancer Center, Tampa, Florida (Zeynep Eroglu)
- University of California, Los Angeles, California (Bartosz Chmielowski)
- Washington University School of Medicine St. Louis, St. Louis, Missouri (Tanner Johanns)

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[a] *O'Rourke et al., Sci Transl Med.2017; 9:eaaa0984*
[b] *Sharma et al., Clin Cancer Res. 2019;25:1233-1238*
[c] *Marshall et al., J Immunother Cancer. 2020;8:e000764*
[d] *van Marle et. al, J Immunother Cancer. 2018, 6 (Suppl 1): P484 (SITC2018)*
[e] *Powderly et al, J Clin Oncol 2020;38(15_suppl):TPS3163 (ASCO 2020)*
[f] *Long et al, Society for Melanoma Research 2016 Congress. Pigment Cell & Melanoma Research.2017;30:76-156*
[g] *Hodi et al, N Engl J Med. 2010 Aug 19;363(8):711-23*
[h] *Larkin et al, N Engl J Med. 2015 Jul 2; 373(1): 23-34*