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Phase 1/2 dose escalation and expansion study of FLX475 alone and in combination with pembrolizumab in advanced cancer

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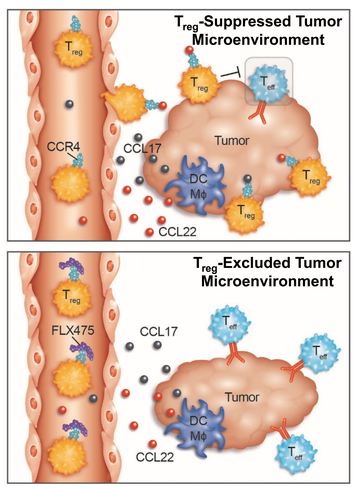
ABSTRACT

Background: Regulatory T cells (T_{reg}) can dampen anti-tumor immune responses in the tumor microenvironment (TME). The predominant chemokine receptor on human T_{reg} 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 (T_{eff}) in the setting of an inflammatory anti-tumor response. 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 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 T_{reg} demonstrated the ability to safely achieve exposure levels predicted to maximally inhibit T_{reg} recruitment into tumors via CCR4 signaling. These human PK, PD, and safety data have enabled a streamlined design of a Phase 1/2 study of FLX475 in cancer patients both as monotherapy and in combination with checkpoint inhibitor.

Methods: This clinical trial is a Phase 1/2, 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 1) of the study, at least 3 to 6 eligible subjects are being 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 2) of the study, expansion cohorts of both checkpoint-naïve and checkpoint-experienced patients with tumor types predicted to be enriched for T_{reg} 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 February 4, 2020, Phase 1 dose escalation has been completed and a recommended Phase 2 dose chosen for both FLX475 monotherapy and combination therapy with pembrolizumab. Enrollment into Phase 2 expansion cohorts has been initiated.

BACKGROUND

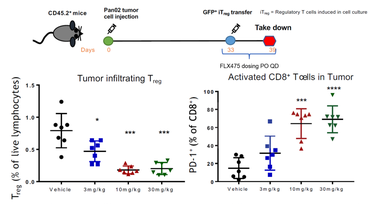
FLX475: Designed to Enhance the Anti-Tumor Immune Response



- Immune cells follow chemokines to migrate into target tissues
- CCR4 is the predominant chemokine receptor expressed on human regulatory T cells (T_{reg})
- In response to inflammation, tumor cells and other cells in the tumor microenvironment (TME) 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 Data[a]

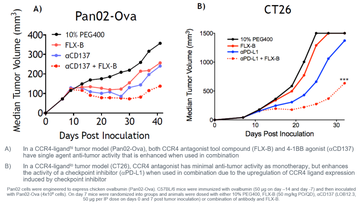
CCR4 Antagonists Block the Recruitment of T_{reg} and Increase the Number of Activated CD8$^+$ T Cells in Tumors



Murine pancreatic tumor cells (Pan02) were subcutaneously inoculated into C57BL/6 mice. Tumor-bearing mice were dosed with increasing doses of FLX475 or vehicle prior to transfer of in vitro-induced T_{reg} (iT_{reg}) (I.V.).

Analysis of TILs: Dose-dependent inhibition of T_{reg} trafficking into tumor but not in periphery (data not shown). Activated CD8$^+$ T cell numbers (measured by PD-1$^+$ staining) increased with higher dose of FLX475.

CCR4 Antagonists Potentiate Anti-Tumor Effects of Immune Modulators



A) In a CCR4-ligand^a tumor model (Pan02-Ova), both CCR4 antagonist tool compound (FLX-B) and 4-1BB agonist (αCD137) have single agent anti-tumor activity that is enhanced when used in combination

B) In a CCR4-ligand^a tumor model (CT26), CCR4 antagonist has minimal anti-tumor activity as monotherapy, but enhances the activity of a checkpoint inhibitor (αPD-L1) when used in combination due to the upregulation of CCR4 ligand expression induced by checkpoint inhibitor

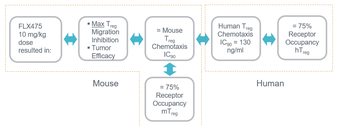
Pan02 cells were engineered to express chicken ovalbumin (Pan02-Ova). C57BL/6 mice were immunized with ovalbumin (50 μg po day -14 and day -7) and then inoculated with Pan02-Ova (4x10^5 cells). On day 7 mice were randomized into groups and animals were dosed with either 10% PEG400, FLX-B (50 mg/kg PO/QD), αCD137 (LOB12.3, 50 μg per IP dose on days 0 and 7 post tumor inoculation) or combination of antibody and FLX-B.

CT26 cells inoculated into BALB/c mice and grown for 7 days and randomized into groups (40-70 mm^3). PD-L1 antibody treatment (10F.9G2; 100 μg each dose) on days 7, 10, 14, FLX-B treatment (50 mg/kg QD/PO) starting at day 7.

Phase 1 Healthy Volunteer Data[b]

Foundation for Target PK and PD in Humans: Efficacy Linked to Exposure

75% Receptor Occupancy is Required for Maximal Inhibition of T_{reg} Migration



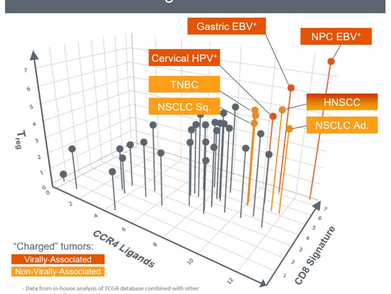
- IC_{90} = [FLX475] inhibiting 90% *of in vitro* T_{reg} chemotaxis
- IC_{90} at trough = 75% Receptor Occupancy (RO) in mice which achieved maximal inhibition of T_{reg} migration and anti-tumor efficacy
- In healthy volunteers, IC_{90} at trough = 130 ng/ml, which was achieved with 75 mg PO QD dosing

Phase I Healthy Volunteer Study Established Well-Tolerated Potentially Therapeutic Dose

- First-in-human, randomized, double-blind, placebo-controlled study examined safety, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy volunteers of single and repeat dosing of FLX475
- Seven cohorts (8 subjects each: 6 drug, 2 placebo) were administered single doses ranging from 5 mg to 1000 mg. Six cohorts were administered daily doses of FLX475 for 14 days ranging from 25 mg to 150 mg, including two highest dose cohorts evaluating a loading dose of 300 mg administered on Day 1.
- Plasma FLX475 levels increased in a dose-proportional manner, with low peak-to-trough ratios, and a mean $T_{1/2}$ of ~72 hours in healthy volunteers
- A strong PK/PD correlation was observed between plasma drug levels and CCR4 receptor occupancy (RO)
- Doses of 75 mg PO QD and above exceeded the target RO of 75% corresponding to the human T_{reg} chemotaxis IC_{90}
- Consistent with the mechanism of action of FLX475 which specifically blocks the recruitment of tumor T_{reg} without cellular depletion or nonspecific immune activation, no autoimmunity or immune-related AEs were observed
  - No significant clinical AEs or laboratory changes were noted
  - No significant QTcF prolongation was observed at projected efficacious exposures

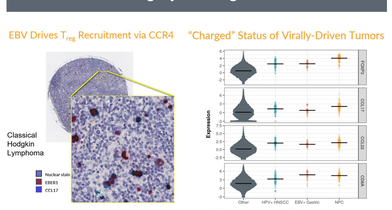
Patient Selection: “Charged” and Virally-Driven Tumors

Identification and Characterization of “Charged” Tumors[c]



- “Charged” tumors: express high levels of CCR4 ligands, T_{reg} and CD8 cells
- “Charged” tumors tend to be “hot” with high levels of T_{reg} likely holding back antitumor immune response
- Blocking CCR4-mediated T_{reg} recruitment is more likely to shift the T_{eff}/T_{reg} ratio toward an enhanced anti-tumor microenvironment in these tumors

Virally-Driven Tumors are Among the Most Highly “Charged”



TCGA RNA-Seq data from UCSC Xena was normalized with NPC data (GSE102349 and GSE68799). HPV and EBV annotation for HNSCC and gastric carcinoma was obtained from cBioPortal. Expression values are log2(TPM).

(Left)
- The EBV LMP1 protein has been shown to directly upregulate CCR4 ligand expression in lymphoma cells via NFκB[b]
- CCR4 ligands are co-expressed with EBV genes in Hodgkin lymphoma (HL) and nasopharyngeal carcinoma (NPC)[a]
- The immunosuppressive recruitment of T_{reg} by EBV may be co-opted by EBV$^+$ tumors (~95% of NPC, ~40% of HL)
  - Similar mechanisms may also take place in HPV$^+$ malignancies (e.g. cervical and oropharyngeal cancer)

(Right)
- Virally-associated tumors such as NPC (~100% EBV$^+$), HPV$^+$ HNSCC, and EBV$^+$ gastric carcinomas show significantly increased levels of FOXP3, CCL17, CCL22, and CD8 expression compared to all other solid tumors in TCGA.

METHODS

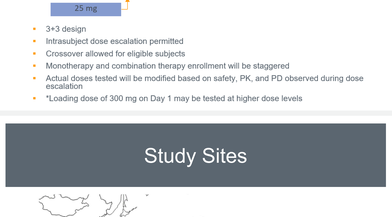
FLX475-02 Study Design

- Phase I/II, open-label, sequential-group, dose-escalation and cohort expansion study to determine the safety (MTD and/or RP2D) and preliminary anti-tumor activity of FLX475 as monotherapy and in combination with pembrolizumab
- Treatment (until progression or toxicity, up to 2 years)
  - Monotherapy: FLX475 PO QD, 21-day cycles
  - Combination Therapy: FLX475 PO QD + pembrolizumab 200 mg IV D1, 21-day cycles
- Two-part study
  - Part 1: Dose Escalation (Phase I)
    - 3+3 design
    - Parallel, staggered enrollment to monotherapy (Part 1a) and combination therapy (Part 1b)
  - Part 2: Expansion Cohorts (Phase II)
    - Monotherapy and combination therapy
    - Simon 2-stage design; 10 subjects in Stage 1, plus 19 additional subjects in Stage 2 should activity criteria be met in Stage 1
- ClinicalTrials.gov Identifier: NCT03674567

Major Eligibility Criteria

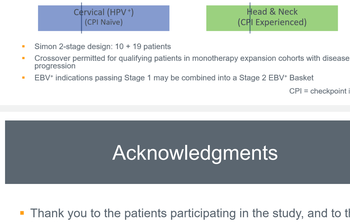
- All subjects must have histologically or cytologically confirmed, advanced or metastatic tumors and (1) have disease progression after treatment with other available therapies for metastatic disease that are known to confer clinical benefit or (2) do not tolerate or refuse standard treatment(s).
- Subject must have one of the following diagnoses to be eligible for enrollment into a dose escalation cohort (Parts 1a and 1b):
  - Stage IIIB/IV squamous or non-squamous non-small cell lung carcinoma (NSCLC)
  - Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC; specifically of the oral cavity, oropharynx, hypopharynx, or larynx; and nasopharyngeal carcinoma)
  - Metastatic triple-negative breast cancer
  - Locally advanced or metastatic urothelial carcinoma (UC)
  - Locally advanced, recurrent, or metastatic gastric cancer (GC)
  - Locally advanced, recurrent, or metastatic esophageal or esophagogastric junction cancer
  - Recurrent or metastatic cervical squamous cell carcinoma or endocervical adenocarcinoma
  - Metastatic melanoma
  - Recurrent classical Hodgkin lymphoma
  - Others with approval
- (See schema for Part 2 Expansion Cohort indications)
- Willing and able to provide newly obtained tissue biopsies
- No prior systemic anticancer therapy including investigational agents within 4 weeks (or < 5 half-lives for investigational/noncytotoxic agents, whichever is shorter) prior to first dose of study treatment
- For Part 2 expansion cohorts limited to “checkpoint-experienced” patients = “documented disease progression or relapse more than 3 months after initiation of prior anti-PD-1 or anti-PD-L1 therapy”

Phase 1 Dose Escalation (Original Schema)



- 3+3 design
- Intrasubject dose escalation permitted
- Crossover allowed for eligible subjects
- Monotherapy and combination therapy enrollment will be staggered
- Actual doses tested will be modified based on safety, PK, and PD observed during dose escalation
- *Loading dose of 300 mg on Day 1 may be tested at higher dose levels

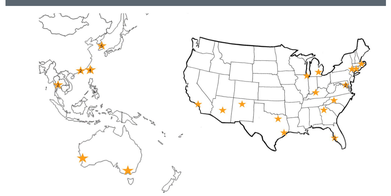
Phase 2 Expansion Cohorts



- Simon 2-stage design: 10 + 19 patients
- Crossover permitted for qualifying patients in monotherapy expansion cohorts with disease progression
- EBV$^+$ indications passing Stage 1 may be combined into a Stage 2 EBV$^+$ Basket

CPI = checkpoint inhibitor

Study Sites



- 32 sites in the United States, Australia, South Korea, Taiwan, Hong Kong, and Thailand

Acknowledgments

- Thank you to the patients participating in the study, and to their families and caregivers.
- Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA is providing pembrolizumab for the study.

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