ESMO-IO 2022
Presentation 187P
(ID 479)

Phase 1/2 study of the oral CCR4 antagonist, FLX475, as monotherapy and in combination with pembrolizumab in advanced cancer

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ABSTRACT

Background: Preclinical studies with oral CCR4 antagonists have demonstrated inhibition of suppressive regulatory T cell (T_{reg}) migration into the tumor microenvironment and antitumor efficacy. The FLX475-02 trial is a Phase 1/2, open-label, dose-escalation and cohort expansion study to determine the safety and antitumor activity of the oral CCR4 antagonist FLX475 as monotherapy and in combination with pembrolizumab in subjects with several types of advanced cancer.

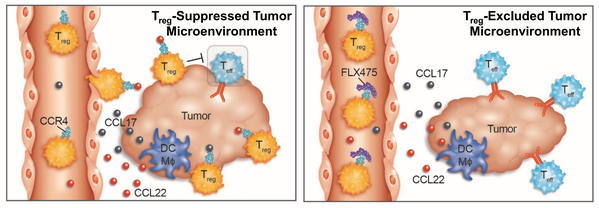
Methods: A standard 3+3 design was used in Phase 1 testing FLX475 given orally once daily as monotherapy or in combination with pembrolizumab (200 mg IV Q3 weeks). In Phase 2, expansion cohorts of subjects both naïve to and pretreated with checkpoint inhibitor with tumor types predicted to be enriched for T_{eff}, T_{reg}, and CCR4 ligand expression (i.e. "charged tumors") – including EBV+ tumors and NSCLC – are being enrolled using a Simon 2-stage design.

Results: Phase 1 dose escalation has been completed and a recommended Phase 2 dose of 100 mg once daily was selected for FLX475. The safety profile of FLX475 was consistent with that previously described in healthy volunteers, and there has been no evidence of increased severity or frequency of adverse events in combination therapy vs either FLX475 or pembrolizumab given alone. In Phase 2 expansion, FLX475 monotherapy has induced complete responses in the first two subjects of five evaluable enrolled with EBV+ NK/T cell lymphoma. In addition, enrollment of the Stage 1 portion has been completed in several Phase 2 expansion cohorts for the combination of FLX475 and pembrolizumab. In a cohort enrolling subjects with non-small-cell lung cancer (NSCLC) not previously treated with checkpoint inhibitor, 4/13 subjects (31%) have had confirmed partial responses (PRs), including several ongoing for over 6 months, meeting criteria to proceed to Stage 2 enrollment.

Conclusions: In this ongoing Phase 1/2 trial of the oral CCR4 antagonist, FLX475, as monotherapy and in combination with pembrolizumab, antitumor activity including complete responses to FLX475 monotherapy and encouraging combination activity have been observed with an acceptable safety profile. (NCT03674567)

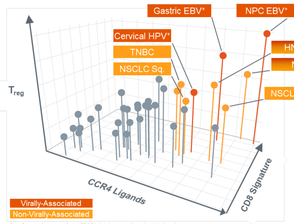
BACKGROUND

FLX475: Designed to Enhance the Anti-Tumor Immune Response



- CCR4 is the predominant chemokine receptor expressed on human regulatory T cells (T_{reg})
- In response to inflammation, cells in the tumor microenvironment express the ligands for CCR4 (CCL17 and CCL22), inducing the migration of T_{reg} into tumors, which can suppress the antitumor activity of effector T cells (T_{eff})
- 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

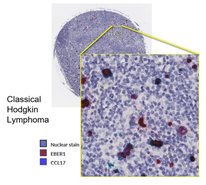
Patient Selection: "Charged Tumors" Including Those Associated with EBV



Data from in-house analysis of TCGA database combined with other data sets;
Confirmed in >400 tumor microarrays
The graph above reflects a logarithmic scale on each axis
NPC:Nasopharyngeal; HNSCC:Head & Neck Squamous Cell Carcinoma; NHL:Non-Hodgkin Lymphoma; NSCLC:Non-Small Cell Lung Cancer; TNBC:Triple Negative Breast Cancer

- "Charged" tumors express high levels of CCR4 ligands, T_{reg} and CD8 T cells[1]
  - Expected to be "hot" with high levels of effector CD8 cells but also with high levels of T_{reg} that limit the antitumor immune response
- Blocking CCR4-mediated T_{reg} recruitment would thus be more likely to shift the T_{eff}/T_{reg} ratio toward an enhanced antitumor microenvironment in these tumors
- The EBV LMP1 protein can directly upregulate CCR4 ligand expression[2]
  - Thus recruiting immunosuppressive T_{reg}
- EBV and other virally-associated tumors are among those with the highest "charged" score
  - EBV-associated tumors include ~95% of NPC and subsets of lymphoma and gastric cancer

EBV Drives T_{reg} Recruitment via CCR4



METHODS

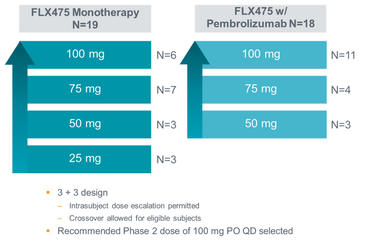
FLX475-02 Study Design

- Phase 1/2, open-label, sequential-group, dose-escalation and cohort expansion study to determine the safety (MTD and/or RP2D) and preliminary antitumor 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
- Phase 1: Dose Escalation
  - 3+3 design
  - Parallel, staggered enrollment to monotherapy (Part 1a) and combination therapy (Part 1b)
- Phase 2: Expansion Cohorts
  - Monotherapy and combination therapy at RP2D (100 mg)
  - Simon 2-stage design:
    - Stage 1: At least 10 evaluable subjects
    - Stage 2: Enroll at least 19 additional subjects if activity criteria are met in Stage 1
- ClinicalTrials.gov Identifier: NCT03674567

Major Eligibility Criteria

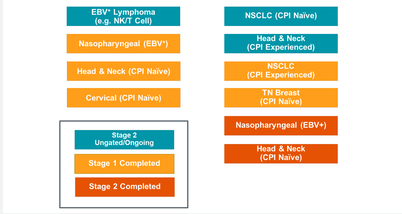
- All subjects must have histologically or cytologically confirmed, advanced or metastatic tumors and (1) have disease progression after treatment with other available therapies for metastatic disease that are known to confer clinical benefit or (2) do not tolerate or refuse standard treatment(s).
- For Phase 1, subject must have one of the following diagnoses to be eligible for enrollment into a dose escalation cohort:
  - 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: Monotherapy and Combination



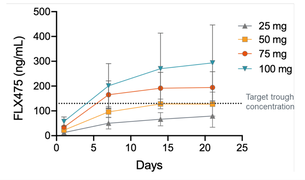
- 3 + 3 design
  - Intrasubject dose escalation permitted
  - Crossover allowed for eligible subjects
- Recommended Phase 2 dose of 100 mg PO QD selected

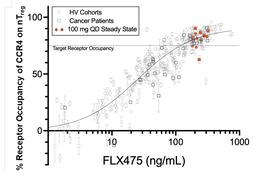
Phase 2 Expansion Cohort Status



RESULTS

Phase 1 PK and PD Data Support RP2D of 100 mg





(Left)
- Exposures were dose proportional, and comparable between monotherapy and combo cohorts
- Doses of 75 mg and above achieved/exceeded the minimum target concentration, with nearly all patients at 100 mg achieving/exceeding minimum target concentration by day 7

(Right)
- Tight PK/PD relationship observed in healthy volunteers (HV) and patients with cancer
- Target CCR4 receptor occupancy on T_{reg} achieved at ≥ 75 mg QD
- **100 mg chosen as the RP2D as it achieved/exceeded target drug concentration and receptor occupancy (orange squares) in the most patients and was well tolerated**

Interim Safety Summary

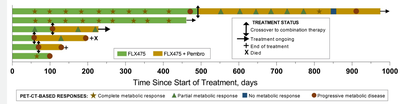
N = Patients with TEAE (Highest Grade)	FLX475 Monotherapy N = 25*	
	Any Grade	Grade 3 (no Grade 4 or 5)
All-cause TEAEs	N (%)	N (%)
Serious	5 (20%)	
Led to discontinuation	0	
Led to death	0	
Any grade with incidence ≥15%		
QT prolongation	8 (32%)	2 (8%)
Nausea	8 (32%)	0
Anemia	5 (20%)	2 (8%)
Cough	5 (20%)	0
Decreased appetite	5 (20%)	0
Pruritis	5 (20%)	0
Tumor flare/pain	4 (16%)	1 (4%)
Rash	4 (16%)	0
Fatigue	4 (16%)	0
Diarrhea	4 (16%)	0
Elevated creatinine	4 (16%)	0
Treatment-related TEAEs (per investigator)		
Serious	0	
Led to discontinuation	0	
Led to death	0	
Any grade with incidence ≥10%		
QT prolongation	6 (24%)	2 (8%)
Pruritus	5 (20%)	0
Rash†	4 (16%)	0

*19 Phase 1 patients + 6 Phase 2 NK/T cell lymphoma patients
†None were deemed definitely related to study treatment

N = Patients with TEAE (Highest Grade)	FLX475 + Pembrolizumab N = 39*	
	Any Grade	Grade 3 (unless otherwise noted)
All-cause TEAEs	N (%)	N (%)
Serious	19 (49%)	
Led to discontinuation	1 (3%)	
Led to death	3 (8%)	
Any grade with incidence ≥15%		
Anemia	11 (28%)	3 (8%)
Fatigue	11 (28%)	0
Rash	10 (26%)	0
QT prolongation	9 (23%)	3 (8%)
Decreased appetite	9 (23%)	1 (3%)
Dyspnea	8 (21%)	0
Cough	8 (21%)	0
Abdominal pain	7 (18%)	2 (5%)
Hyponatremia	6 (15%)	3 (8%)
Back pain	6 (15%)	2 (5%)
Nausea	6 (15%)	1 (3%)
Dizziness	6 (15%)	0
Urinary tract infection	6 (15%)	0
Pruritis	6 (15%)	0
Constipation	6 (15%)	0
Treatment-related TEAEs (to either drug, per investigator)	N (%)	N (%)
Serious	2 (5%)	
Led to discontinuation	0	3‡ (8%)
Led to death	0	
Any grade with incidence ≥10%		
QT prolongation	8 (21%)	3‡ (8%)
Rash	6 (15%)	0
Pruritus	4 (10%)	0
Fatigue	4 (10%)	0

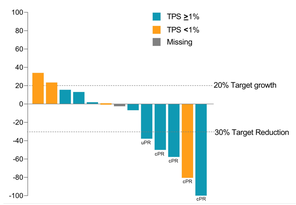
*22 Phase 1 patients (including 4 crossover) + 13 Phase 2 CPI-Naïve NSCLC and 4 EBV+ NK/T Cell Crossover Patients
‡Includes one Grade 4; all were reversible and asymptomatic

FLX475 Monotherapy Activity in EBV+ NK/T Cell Lymphoma



- 4 of 6 subjects with EBV+ NK/T cell lymphoma enrolled to date have had responses to FLX475 monotherapy
  - 2 durable complete metabolic responses to FLX475 monotherapy
  - 1 unconfirmed CMR and 1 unconfirmed PMR as best overall response to FLX475 monotherapy
  - 4 have crossed over to combination therapy, with responses as noted above
- Response assessments by Lugano criteria
  - Data cutoff 21Nov2022

FLX475 + Pembrolizumab Combination CPI-Naïve NSCLC Stage 1 Cohort: Best Change From Baseline in Target Lesions



- 5 of 13 subjects with CPI-naïve NSCLC had responses to FLX475 + pembrolizumab combination therapy
  - 4 confirmed PRs, 1 unconfirmed PR as best overall response

FLX475 + Pembrolizumab Combination CPI-Naïve NSCLC Stage 1 Cohort: Demographics and Responses

	FLX475 + Pembrolizumab (N = 13)
Age, mean (range), years	66 (47-85)
Male, n (%)	10 (77%)
ECOG PS, n (%)	
0	2 (15%)
1	11 (85%)
Previous Lines of Therapy for Advanced Disease, n (%)	
0	3 (23%)
1	4 (31%)
2	3 (23%)
3+	3 (23%)
PD-L1 Status*, n (%)	
TPS <1%	4 (31%)
TPS ≥1%	8 (61%)
Unknown	1 (8%)

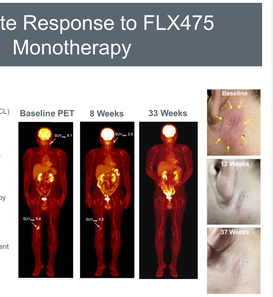
ECOG PS: Eastern Cooperative Oncology Group performance Status
TPS: Tumor Proportion Score
*Fresh or archival result of PD-L1 IHC 22C3 pharmDx, if available

	FLX475 + Pembrolizumab (N = 13)	
All Patients	With Confirmation†	Without Confirmation
Responders, n	4	5
ORR, % (90% CI)	31% (11-57%)	38% (17-65%)
PR, n (%)	4 (31%)	5 (38%)
SD, n (%)	3 (23%)	2 (15%)
PD, n (%)	6 (46%)	6 (46%)
Patients with PD-L1 Data	With Confirmation*	Without Confirmation
TPS ≥1%: responders, n	3	4
TPS ≥1%: ORR, % (90% CI)	38% (11-71%)	50% (19-81%)
TPS <1%: responders, n	1	1
TPS <1%: ORR, % (90% CI)	25% (1-75%)	25% (1-75%)

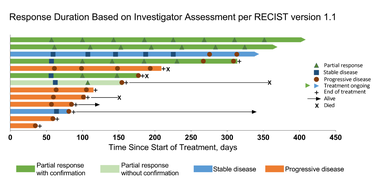
ORR: Overall Response Rate; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease
†Responses confirmed per RECIST v1.1
‡2 subjects had TPS ≥50%, neither qualified as a responder

Complete Response to FLX475 Monotherapy

- EBV+ NK/T Cell Lymphoma (ENTCL)
  - 53 y/o, 1 line of prior chemotherapy 1H 2019
  - 2 primary lesions
    - L posterior auricular (target), R distal anterior thigh (non target)
- Deep Durable Response
  - 8-week scan with complete metabolic response (Deauville score of 5 reduced to 2) and target lesion visibly improving by 12 weeks
  - Disease continued to improve; patient remained in complete metabolic response for 16 months
  - After disease progression, patient also responded to FLX475 + pembrolizumab combination therapy after crossover



FLX475 + Pembrolizumab Combination CPI-Naïve NSCLC Stage 1 Cohort: Response Duration



- Based on investigator assessment per RECIST v1.1
- Data cutoff 21Nov2022

References & Disclosures

1) Okal *et al., J Immunother Cancer (2017) 5(Suppl 2):P44 (SITC 2017)*
2) Nakayama *et al., J Virol (2004) 78(4): 1665-74.*

The first and presenting author has no conflicts of interest to declare.

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This study is sponsored by RAPT Therapeutics.

CONCLUSIONS

- This Phase 1/2 trial of the oral CCR4 antagonist, FLX475, has demonstrated good PK and target engagement with once-daily oral dosing and a well-tolerated safety profile to date, both as monotherapy and in combination with pembrolizumab.
- Clear monotherapy activity has been demonstrated in the highly "charged" tumor type of EBV+ NK/T cell lymphoma.
- Early encouraging activity of the combination of FLX475 with pembrolizumab has been observed in Phase 2 Stage 1 patients with CPI-naïve NSCLC, including a confirmed ORR of 31% in all subjects and 38% in those with PD-L1 TPS ≥1% tumors. Stage 2 enrollment is ongoing.

Acknowledgments

- Thank you to the patients participating in the study, and to their families and caregivers.
- Over 30 sites in the United States, Australia, South Korea, Taiwan, Thailand, and Hong Kong have been participating in this study.
  - ClinicalTrials.gov Identifier: NCT03674567
- Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is providing pembrolizumab for the study.