SITC 2023
Abstract 629-C

Phase 2 safety and efficacy of oral CCR4 antagonist FLX475 (tivumecirnon) plus pembrolizumab in subjects with non-small cell lung cancer not previously treated with checkpoint inhibitor

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ABSTRACT

Background: FLX475 (tivumecirnon) is a selective CCR4 antagonist designed to block the recruitment of immunosuppressive regulatory T cells (T_{reg}) into the tumor microenvironment. The FLX475-02 trial (NCT03674567) is a phase 1/2 study of FLX475 as monotherapy and in combination with pembrolizumab in subjects with advanced cancer. Early encouraging data on the biologic effects, safety and antitumor activity of FLX475 have previously been presented [1-4]. We now present the results from the fully enrolled Phase 2 cohort of combination therapy in subjects with non-small cell lung cancer (NSCLC) not previously treated with checkpoint inhibitor (CPI-naive).

Methods: Subjects with CPI-naïve, locally advanced or metastatic NSCLC received FLX475 100 mg orally once daily with pembrolizumab (200 mg IV Q3 weeks). The primary study objectives were safety and tolerability, and antitumor activity. The primary efficacy endpoint was objective response rate (ORR), based on RECIST 1.1 criteria. Additional efficacy endpoints included progression-free survival (PFS). Data cutoff was 06OCT2023.

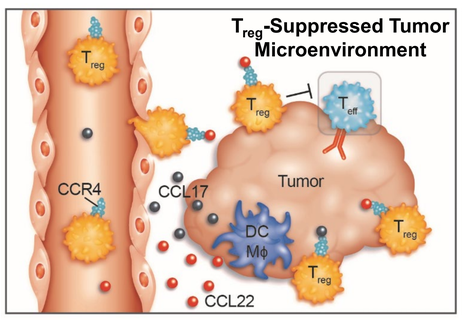
Results: Of the 36 subjects with relevant NSCLC histologies evaluable for response, median follow-up was 250 days (9 – 883 days) and median lines of prior therapy was 1 (0-5). As previously described [3], the only adverse event determined to be specifically related to FLX475 treatment was asymptomatic and reversible QT prolongation (managed by dose reduction). Across all the subjects evaluable for response regardless of PD-L1 status (n=36), confirmed partial response (cPR) was observed in 10 (ORR: 28%). Amongst the subgroup of subjects whose tumors expressed PD-L1 (tumor proportion score [TPS] ≥1%) (n=20), cPR was observed in 8 (ORR: 40%), with an ORR of 38% (6/16) and 50% (2/4) in subjects with tumors expressing low and high levels of PD-L1 (TPS 1-49% or ≥50%), respectively. As of the data cutoff, the PD-L1 TPS ≥ 1% subgroup had a median PFS of 6.3 months with 7 subjects still on treatment.

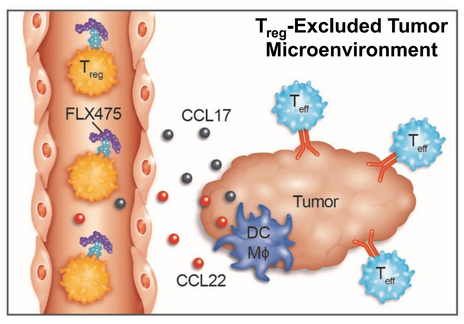
Conclusions: FLX475, an oral CCR4 antagonist, has previously demonstrated clear monotherapy and encouraging combination activity with pembrolizumab [2,3]. In this fully enrolled Phase 2 cohort of subjects with CPI-naïve NSCLC, FLX475 in combination with pembrolizumab was shown to be well tolerated and has demonstrated encouraging clinical activity compared to pembrolizumab monotherapy in PD-L1+ NSCLC (based on historical results) – in both subjects with low (TPS 1-49%) and those with high (TPS ≥50%) PD-L1 expression – supporting the continued development of this combination therapy for NSCLC.

Trial Registration: NCT03674567

BACKGROUND

FLX475: Designed to Enhance the Antitumor 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

Previous Findings with FLX475

- FLX475-01 Phase 1 SAD/MAD Study in Healthy Volunteers[1]
  - Once-daily oral FLX475 demonstrated robust PK, with a mean $T_{1/2}$ of ~72 hours
  - Able to achieve/exceed target drug concentration and receptor occupancy with once-daily oral dosing of 100 mg
  - Well-tolerated safety profile, with no safety findings associated with FLX475 beyond low-grade, reversible, asymptomatic QT prolongation
- Translational Biomarker Studies[4,5]
  - FLX475 treatment results in beneficial changes in the tumor microenvironment (TME) consistent with the proposed mechanism of action (MOA), including
    - Small increase in proportion of circulating T_{reg}
    - Increase in the intratumoral CD8/T_{reg} ratio
    - Increase in the distance between CD8 and T_{reg} in the TME
  - FLX475/pembrolizumab combination treatment also results in similar beneficial changes in the TME consistent with the proposed MOA of FLX475
- Studies of FLX475 as Monotherapy and in Combination with Pembrolizumab in Advanced Cancer
  - Once-daily oral dose of 100 mg selected as recommended Phase 2 dose of FLX475 (monotherapy and combination with pembrolizumab) based on robust PK, PD (receptor occupancy), and well-tolerated safety profile[3]
  - Clear FLX475 monotherapy activity demonstrated (including complete responses) in subjects with EBV+ NK/T cell lymphoma[3]
  - In a Phase 2 study of FLX475 + pembrolizumab, 6/10 confirmed responses were observed in subjects with EBV+ gastric cancer (vs historical data suggesting ~33% ORR expected with CPI alone)[2]
  - Stage 1 data from the FLX475-02 Phase 2 cohort of FLX475 + pembrolizumab in CPI-naïve NSCLC demonstrated early encouraging data[3]
    - Confirmed ORR of 31% (4/13) in all CPI-naïve subjects
    - Confirmed ORR of 38% (3/8) in those with PD-L1+ (TPS ≥1%) tumors

Historical CPI Efficacy in CPI-naïve Advanced/Metastatic NSCLC Subgroups

Published Pembrolizumab Efficacy Data Provide Historical Context for FLX475 + Pembrolizumab Combination Results

Treatment	Line of Tx	PD-L1 Subgroup	ORR (mPFS)	Study/Reference
Pembrolizumab	1L	PD-L1+ (TPS ≥1%)	27% (5.4 mo)	KEYNOTE-042[6]
	1L	PD-L1hi (TPS ≥50%)	39% (6.9 mo) 45% (10.3 mo)	KEYNOTE-042[6] KEYNOTE-024[6]
	1L	PD-L1low (TPS 1-49%)	19.2%	KEYNOTE-001[7]
	2L+	PD-L1+ (TPS ≥1%)	18% (4 mo)	KEYNOTE-010[6]
	2L+	PD-L1hi (TPS ≥50%)	30% (5.2 mo)	KEYNOTE-010[6]
	2L+	PD-L1low (TPS 1-49%)	15.6%	KEYNOTE-001[7]
Pembrolizumab/ Vibostolimab (anti-TIGIT)	Mixed (#12)	PD-L1+ (TPS ≥1%)	33% (9 mo)*	MK-7684-001[8]

1L = First line; 2L+ = previously treated; PD-L1 status as assessed by PD-L1 IHC 22C3 pharmDx
*Median duration of follow-up: 24 mo
Primary subpopulations represented in the FLX475/pembrolizumab CPI-naïve cohort

Anti-TIGIT Benefit may be Limited to the PD-L1hi (TPS ≥50%) Subpopulation

CITYSCAPE Phase 2[9]				
Treatment	Line of Tx	PD-L1 Subgroup	Atezolizumab ORR (mPFS)	Atezolizumab/ Tiragolumab (anti-TIGIT) ORR (mPFS)
Atezolizumab	1L	PD-L1+ (TPS ≥1%)	20.6% (3.9 mo)	38.8% (5.6 mo)
		PD-L1hi (TPS ≥50%)	24.1% (4.1 mo)	69% (16.6 mo)
		PD-L1low (TPS 1-49%)	18% (3.6 mo)	16% (4.0 mo)

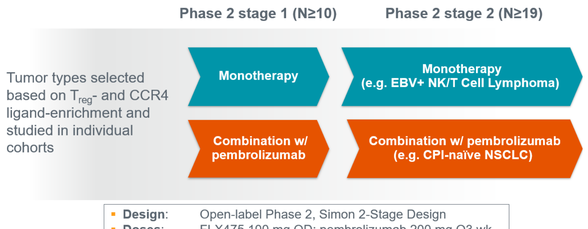
16Aug2021 cutoff date, median duration of follow-up 30.4 mo

METHODS

FLX475-02 Study Design

- Phase 1/2, open-label, sequential-group, dose-escalation and cohort expansion study to determine the safety 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; recommended Phase 2 dose (RP2D) of 100 mg PO QD selected
  - Monotherapy: 25 mg (n=3), 50 mg (n=3), 75 mg (n=7), 100 mg (n=6)
  - Combination: 50 mg (n=3), 75 mg (n=4), 100 mg (n=11)
- Phase 2: Expansion Cohorts
  - Simon 2-stage design

Phase 2 Dose Expansion: Monotherapy and Combination



- **Design**: Open-label Phase 2, Simon 2-Stage Design
- **Doses**: FLX475 100 mg QD; pembrolizumab 200 mg Q3 wk
- **Endpoints**: Safety, PK, Biomarkers, Objective Response Rate

- **CPI-Naïve NSCLC Cohort:** Subjects with Stage IIIB/IV squamous or non-squamous NSCLC with no prior treatment with anti-PD-1 or anti-PD-L1 therapy

RESULTS

Safety Summary for CPI-naïve NSCLC Phase 2 Cohort

N= Patients with TEAE (Highest Grade)	FLX475 + Pembrolizumab, N=40[a]	
	Any Grade	Grade 3[b]
All-cause TEAEs	N(%)	N(%)
Serious	19 (48%)	
Let to discontinuation	4 (10%)	
Led to death	2 (5%)	
Any grade with incidence ≥15%		
QT prolongation	21 (53%)	3[c] (8%)
Rash	12 (30%)	1 (3%)
Decreased appetite	9 (23%)	1 (3%)
Pruritus	9 (23%)	0
Dyspnoea	7 (18%)	2 (5%)
Fatigue	7 (18%)	0
Nausea	8 (20%)	0
Abdominal pain	6 (15%)	1 (3%)
Constipation	6 (15%)	0
Dizziness	6 (15%)	0
Hypothyroidism	6 (15%)	0
Treatment-related TEAEs (to either drug, per investigator)		
Serious	1 (3%)	
Let to discontinuation	1 (3%)	
Led to death	0	
Any grade with incidence ≥10%		
QT prolongation	20 (50%)	3[c] (8%)
Rash	10 (25%)	1 (3%)
Pruritus	7 (18%)	0
Hypothyroidism	6 (15%)	0

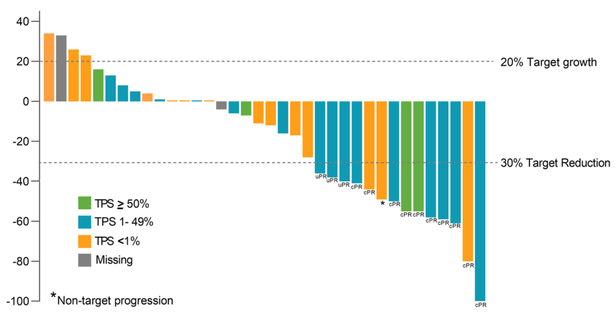
TEAE = Treatment-Emergent Adverse Event
[a]40 total safety-evaluable CPI-naive NSCLC subjects enrolled
[b]None were Grade 4 or 5 TEAEs
[c]All asymptomatic and reversible

Overall Phase 1/2 Safety Summary as of 06OCT2023

- Well-tolerated safety profile, with >300 patients with advanced cancer dosed (including several up to 2-year maximum time on study)
  - Representative data from CPI-naïve NSCLC cohort summarized
- No immune-related AEs observed related to FLX475 monotherapy
  - Consistent with MOA; no depletion of T_{reg}; expected only to affect CCR4-mediated recruitment of T_{reg} into tumors
- No observed increased/new immune toxicity over pembrolizumab alone
- No FLX475-related laboratory changes or target-related toxicities
- Only FLX475-related AE observed has been asymptomatic and reversible low-grade QT prolongation in minority (<20%) of patients
  - Managed with dose reduction from 100 mg to 50 mg PO QD

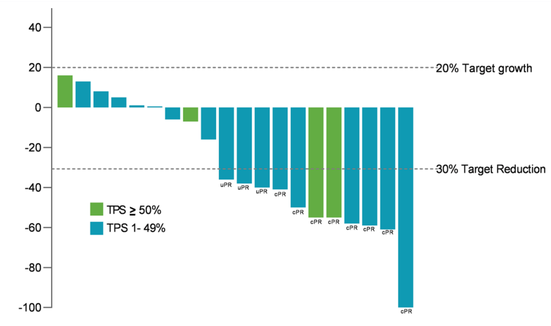
FLX475 + Pembrolizumab Efficacy Data from Phase 2 CPI-naïve NSCLC Cohort (Stages 1 & 2)

Best Change From Baseline in Target Lesions All Evaluable CPI-naïve Subjects (n=36)



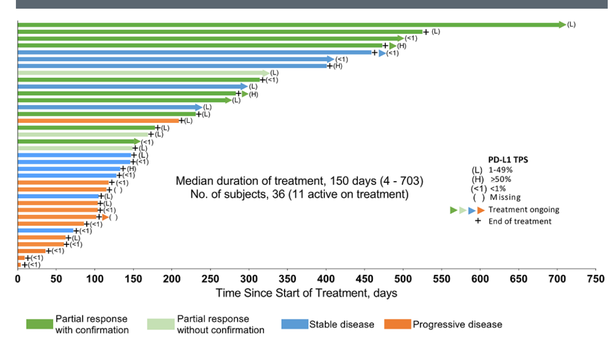
- n=36 CPI-naïve evaluable
- 10 (28%) confirmed PRs as best overall response (BOR)
- PD-L1 status as determined by PD-L1 IHC 22C3 pharmDx

Best Change From Baseline in Target Lesions PD-L1+ (TPS ≥1%) CPI-naïve Subjects (n=20)

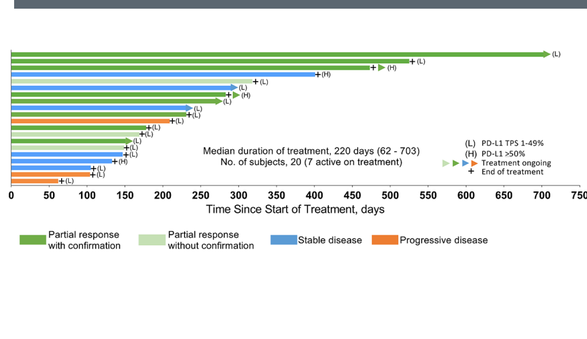


- n=20 PD-L1+ (TPS ≥1%) evaluable
- 8 (40%) confirmed PRs as BOR (plus 1 additional uPR awaiting confirmation scan)
  - 6/16 (38% ORR) in PD-L1 low (TPS 1-49%)
  - 2/4 (50% ORR) in PD-L1 high (TPS ≥50%)

Response Duration All Evaluable CPI-naïve Subjects (n=36)



Response Duration PD-L1+ (TPS ≥1%) CPI-naïve Subjects (n=20)



Demographics and Activity by Subgroup

	All CPI-Naive (N = 36)	PD-L1+ (N = 20)
Age, mean (range), years	69 (47-87)	67 (58-87)
Male, n (%)	29 (81%)	15 (75%)
ECOG PS, n (%)		
0	8 (22%)	4 (20%)
1	28 (78%)	16 (80%)
Previous Lines of Therapy for Advanced Disease, n (%)		
0	10 (28%)	7 (35%)
1	13 (36%)	7 (35%)
2	6 (17%)	2 (10%)
3+	7 (19%)	4 (20%)
Histology, n (%)		
Squamous	16 (44%)	9 (45%)
Non-squamous	20 (56%)	11 (55%)
PD-L1 Status*, n (%)		
TPS <1%	14 (39%)	--
TPS ≥1%	20 (56%)	20 (100%)
TPS 1-49% / TPS ≥50%	--	16 (80%) / 4 (20%)
Unknown	2 (5%)	--

	FLX475 + Pembrolizumab (N=36)	
All CPI-Naïve Patients	With Confirmation^	Without Confirmation
Responders, n	10	13
ORR, % (95% CI)	28% (16-44%)	36% (22-52%)
PR, n (%)	10 (28%)	13 (36%)
SD, n (%)	14 (39%)	11 (31%)
PD, n (%)	12 (33%)	12 (33%)
Median PFS, months (95% CI)	3.5 (2.1-8.9)	--
Median DoR, months (range)	10.2 (2-20.6+)	--
By PD-L1 Status	With Confirmation^	Without Confirmation
TPS ≥1%: responders; ORR % (95% CI)	8/20; 40% (22-61%)	11*/20; 55% (34-74%)
Median PFS, months (95% CI)	6.3 (3.4-NR)	--
Median DoR, months (range)	10.2 (2-20.6+)	--
TPS 1-49%: responders; ORR % (95% CI)	6/16; 38% (18-61%)	9*/16, 56% (33-77%)
TPS ≥50%: responders; ORR % (95% CI)	2/4; 50% (15-85%)	2/4; 50% (15-85%)
TPS <1%: responders; ORR % (95% CI)	2/14; 14% (3-42%)	2/14; 14% (3-42%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status
TPS: Tumor Proportion Score
*Fresh or archival result of PD-L1 IHC 22C3 pharmDx, if available
Data Cutoff: 06OCT2023

ORR: Overall Response Rate; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease
PFS: Progression-free Survival; DoR: Duration of Response: NR: Not Reached
^Response confirmation per RECIST v1.1
*Includes 1uPR awaiting confirmatory scan results
Data cutoff 06OCT2023; median duration of follow-up 8.3 months (0.3 - 29.4 mo)

Distribution of Efficacy-Evaluable Subjects by Line of Therapy and PD-L1 Status:
Responders to FLX475 + Pembrolizumab Include a Substantial Proportion in those with Previously-Treated and PD-L1 Low NSCLC

	PD-L1 Unknown	TPS <1% (Negative)	TPS 1-49% (Low)	TPS ≥50% (High)
1L NSCLC	-	3 (1 PR)	7 (2 PR)	-
2L+	2	11 (1 PR)	9 (4 PR)	4 (2 PR)

1L: First line; 2L+: Previously treated

- Efficacy by CPI-naïve NSCLC subgroup (confirmed responses)
  - PD-L1+ (TPS ≥1%): 40% ORR (8/20)
  - PD-L1 low (TPS 1-49%): 38% ORR (6/16)
  - PD-L1+, 2L+ (previously treated, but CPI naïve): 46% (6/13)

CONCLUSIONS

- FLX475, an oral CCR4 antagonist, has previously demonstrated clear monotherapy and encouraging combination activity with pembrolizumab in various tumor types
  - In addition, translational biomarker studies with FLX475 both as monotherapy and in combination with pembrolizumab have demonstrated beneficial changes in the TME consistent with the proposed MOA of FLX475
- In this fully enrolled Phase 2 cohort of subjects with CPI-naïve NSCLC (data cutoff 06OCT2023), FLX475 in combination with pembrolizumab was shown to be well tolerated and has demonstrated encouraging clinical activity compared to pembrolizumab monotherapy in PD-L1+ NSCLC (based on historical results) – in both subjects with low (TPS 1-49%) and those with high (TPS ≥50%) PD-L1 expression
  - Confirmed 40% ORR (8/20) in PD-L1+ (TPS ≥1%)
  - Confirmed 38% ORR (6/16) in PD-L1 low (TPS 1-49%)
  - Confirmed 50% ORR (2/4) in PD-L1 high (TPS ≥ 50%)
- These data support the continued development of FLX475 plus checkpoint inhibitor combination therapy for PD-L1 positive NSCLC

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This study was sponsored by RAPT Therapeutics.

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.