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Abstract CT226

Phase 2 study of oral CCR4 antagonist FLX475 (tivumecirnon) plus pembrolizumab in subjects with head and neck squamous cell carcinoma (HNSCC) previously treated with checkpoint inhibitor

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ABSTRACT

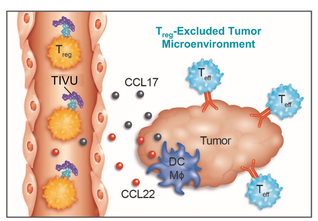
BACKGROUND: FLX475 (tivumecirnon, or TIVU) is a selective CCR4 antagonist designed to block the recruitment of immunosuppressive regulatory T cells (T_{reg}) into the tumor microenvironment. The FLX475-02 trial (NCT03674567) is a phase 1/2 study of FLX475 as monotherapy and in combination with pembrolizumab in subjects with advanced cancer. Early encouraging data on the biologic effects, safety and antitumor activity of FLX475 have previously been presented.[1-5] We now present the results from the Phase 2 cohort of combination therapy in subjects with head and neck squamous cell carcinoma (HNSCC) previously treated with checkpoint inhibitor (CPI- experienced).

METHODS: Subjects with CPI-experienced, recurrent or metastatic (R/M) HNSCC 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). Safety was evaluated as per CTCAE v4.03. Data cutoff was 04MAR2024.

RESULTS: For the 32 subjects with HNSCC evaluable for response, median follow-up was 14.8 months (range 2.2-40.1) and median lines of prior therapy were 3 (1-6). Median age of subjects was 59 yrs.; 94% were male and 75% were Caucasian. Primary tumor location was oropharynx in 56%. Consistent with previous disclosures,[3] the only adverse event determined to be treatment related was asymptomatic QTc prolongation, none of which required treatment discontinuation and was managed with dose reduction. Among the subjects evaluable for response regardless of HPV or PD-L1 status (n=32), confirmed partial response (cPR) was observed in 5 subjects (ORR: 15.6%, 95% CI 6-32%). Among the subgroup of subjects whose tumors were HPV positive (n=18), 8 (44%) experienced reduction from baseline in target lesion measurements and cPR was observed in 4 (ORR: 22.2%, 95% CI 9-46%). Among the subgroup of subjects whose tumors expressed PD-L1 (combined positive score [CPS] ≥1) (n=23), cPR was observed in 4 (ORR: 17.4%, 95% CI 5-39%). At data cutoff, the HPV-positive subgroup median PFS was 2.9 months (95% CI 2-10.3) and 2 subjects were still on treatment.

CONCLUSIONS: FLX475, an oral CCR4 antagonist, has previously demonstrated clear monotherapy activity in EBV+ extranodal NK/T-cell lymphoma and promising combination activity with pembrolizumab in EBV+ gastric cancer and CPI-naïve non-small cell lung cancer.[2,3,5] In this completed Phase 2 cohort of subjects with CPI-experienced R/M HNSCC, FLX475 (TIVU) in combination with pembrolizumab was shown to be well tolerated and has demonstrated encouraging clinical activity including in those with HPV-positive tumors, supporting the continued development of this combination therapy for CPI-experienced HNSCC.

INTRODUCTION



- TIVU is designed to prevent CCR4-mediated T_{reg} migration into tumors by selectively blocking the CCR4 ligand-receptor interaction.
- TIVU is designed to shift the T_{eff}/T_{reg} balance in favor of tumor elimination

- Clear monotherapy activity has been demonstrated (including complete responses) in subjects with EBV+ NK/T cell lymphoma.[3]
- In subjects with CPI-naïve, locally advanced or metastatic NSCLC, a confirmed ORR of 31%, and in the 20 subjects with PD-L1+ tumors, a confirmed ORR of 45% were observed with TIVU + pembrolizumab.[5]
- In subjects with EBV+ gastric cancer, an ORR of 66.7% was observed with TIVU + pembrolizumab.[2]
- Translational biomarker studies have shown beneficial changes in the tumor microenvironment consistent with the proposed MOA of TIVU.[4, 6-7]

METHODS

Tumor types selected based on **T_{reg}- and CCR4 ligand-enrichment** and studied in individual cohorts

Monotherapy (e.g., EBV+ NK/T cell lymphoma)

Combination w/ pembrolizumab (e.g., CPI-naïve NSCLC, and CPI-Experienced HNSCC)

- Design: Open-label Phase 2, Simon 2-Stage Design
- Treatment: TIVU 100 mg QD; pembrolizumab 200 mg Q3 weeks (for up to 2 years)

- Subjects with CPI-experienced, recurrent or metastatic HNSCC received TIVU 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 ORR, based on RECIST 1.1 criteria. Additional efficacy endpoints included progression-free survival (PFS).
- Data cutoff was 04Mar2024.

RESULTS

SAFETY SUMMARY FOR CPI-EXPERIENCED HNSCC PHASE 2 COHORT

N= Patients with TEAE (Highest Grade)	Subjects (N=32)	
	Any Grade	Grade 3-4
All-cause TEAEs	**N (%)**	**N (%)**
Serious	14 (43.8%)	
Led to discontinuation	4 (12.5%)	
Led to death	5 (15.6%)	
Any grade with incidence ≥15%		
Electrocardiogram QT prolonged	17 (53.1%)	2 (6.3%)
Dyspnoea	11 (34.4%)	2 (6.3%)
Fatigue	10 (31.3%)	0
Anaemia	9 (28.1%)	2 (6.3%)
Nausea	8 (25.0%)	0
Constipation	7 (21.9%)	0
Cough	6 (18.8%)	0
Dysphagia	6 (18.8%)	2 (6.3%)
Hypercalcaemia	6 (18.8%)	2 (6.3%)
Weight decreased	6 (18.8%)	0
Corona virus infection	5 (15.6%)	0
Diarrhoea	5 (15.6%)	0
Headache	5 (15.6%)	0
Hypophosphataemia	5 (15.6%)	1 (3.1%)
Productive cough	5 (15.6%)	0
Treatment-related TEAEs (to either drug, per investigator)		
Serious	2 (6.3%)	
Led to discontinuation	0	
Led to death	0	
Any grade with incidence ≥10%		
Electrocardiogram QT prolonged	14 (43.8%)	2[a] (6.3%)
Fatigue	5 (15.6%)	0
Nausea	5 (15.6%)	0
Pruritus	4 (12.5%)	0

TEAE = Treatment Emergent Adverse Events. [a]Both were Gr 3 and asymptomatic

RESULTS

DEMOGRAPHICS

	All CPI-Exp. (N=32)	HPV+ (N=18)
Age, Median (range), years	59 (34 - 77)	60 (47 -77)
Male, n (%)	30 (94%)	17 (94%)
ECOG PS, n (%)		
0	17 (53%)	10 (56%)
1	15 (47%)	8 (44%)
Primary Tumor Site		
Oropharynx	18 (56%)	17 (94%)
Not Oropharynx	13 (41%)	1 (6%)
Not known	1 (3%)	-
Previous Lines of Systemic Treatment		
1	2 (6%)	1 (6%)
2	8 (25%)	4 (22%)
3+	22 (69%)	13 (72%)
Best Overall Response to prior CPI treatment		
CR, PR	11 (34%)	5 (28%)
SD	9 (28%)	5 (28%)
PD	11 (34%)	7 (39%)
Not known	1 (3%)	1 (6%)
PD-L1 status[1]		
CPS <1	3 (9%)	3 (17%)
CPS ≥1	22 (69%)	10 (56%)
Unknown	7 (22%)	5 (28%)

[1]Fresh or archival result of PD-L1 IHC 22C3 pharmDx, if available
CPS: Combined Positive Score. ECOG PS: Eastern Cooperative Oncology Group Performance Status

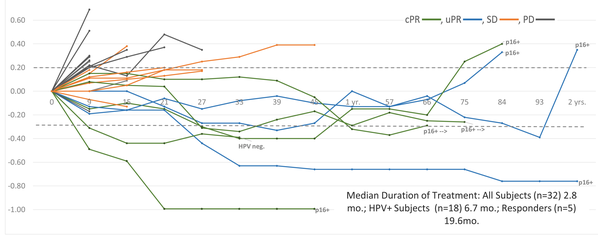
ACTIVITY BY SUBGROUPS

	All Subjects (N=32)[a]	HPV+ (N=18)
Responders with confirmation ORR, % (95% CI)	5/32; 15.6% (6-32%)	4/18; 22.2% (9-46%)
Responders with or without confirmation ORR, % (95% CI)	8/32; 25% (11-43%)	7/18; 38.9% (18-65%)
PR, n (%)	5 (15.6%)	4/18 (22.2%)
SD, n (%)	10 (31.3%)	5/18 (27.8%)
PD, n (%)	17 (53.1%)	9/18 (50.0%)
Median PFS, months (95% CI)	2.2 (2.0 – 6.0)	2.9 (2.0 – 10.3)
Median DoR[b], months (range)	4.8 (1.3 - 8.8)	5.5 (2.7 - 7.3)
By PD-L1 Status		
CPS ≥1: responders with confirmation; ORR % (95% CI)	4/23; 17.4% (5-39%)	3/10; 30.0% (7-65%)
CPS ≥1: responders with or without confirmation; ORR % (95% CI)	7/23; 30.4% (13-53%)	6/10; 60.0% (26-88%)
CPS <1: responders with confirmation; ORR % (95% CI)	1/3; 33% (0.8-99%)	1/3; 33.30% (0.8-91%)
CPS <1: responders with or without confirmation; ORR % (95% CI)	1/3; 33% (0.8-99%)	1/3; 33.30% (0.8-91%)

[a]Clinical Benefit Rate (CR, PR or Durable SD) = 9/32 (28.1%); [b]Includes confirmed and unconfirmed responses

RESULTS

LONGITUDINAL RESPONSE ASSESSMENT BY INVESTIGATOR (RECIST V1.1)



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CONCLUSIONS

- In this completed Phase 2 cohort of subjects with CPI-experienced R/M HNSCC, tivumecirnon (FLX475/TIVU) in combination with pembrolizumab was well tolerated and showed encouraging clinical activity including in those with HPV-positive tumors.
  - 69% subjects had received 3+ prior lines of treatment (up to 6)
  - Confirmed ORR 15.6% (5/32) in all, and 22.2% (4/18) HPV+ subjects
  - Median duration of treatment of 19.6 months in subjects with responses
- These data support the continued development of TIVU plus checkpoint inhibitor combination therapy for CPI-experienced HNSCC.

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.

References & Disclosures

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