Final results from TACTI-002 Part C: A Phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with metastatic 2nd line head and neck squamous cell carcinoma unselected for PD-L1

Poster # 21

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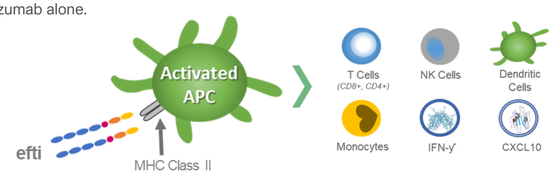
BACKGROUND

Mechanism of action: eftilagimod alpha (efti) is soluble LAG-3 protein (LAG-3 domains fused to human IgG backbone (1). Activating antigen presenting cells (APCs) with efti leads to a broader immune response to fight cancer, including increases in activated T cells (CD4/CD8) (**Figure 1**).

Difference to anti-LAG-3 mAbs: efti is an MHC-Class II agonist and not a LAG-3 antagonist.

Rationale for study: Stimulation of the dendritic cell network and the resulting T cell recruitment/activation may lead to stronger anti-tumor responses than observed with pembrolizumab alone.

Figure 1. Mechanism of action of efti



METHODS

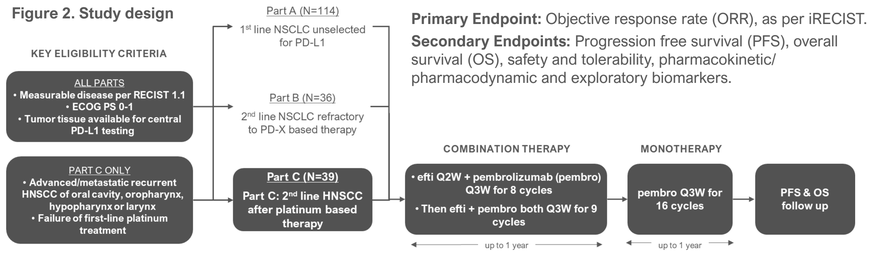
Study Design and Patients

- **TACTI-002** (**T**wo **ACT**iv**e** **I**mmunotherapies-002): Phase II, non-randomized, multinational, open label, PD-L1 all-comer, multiple indications, presenting results from **2nd line head and neck squamous cell carcinoma (HNSCC)** patients **unselected for PD-L1 expression**.
- Efti administered as 30 mg subcutaneous injection Q2W for the first 8 cycles (1 cycle: 3 weeks) and Q3W for the following 9 cycles. Pembrolizumab (pembro) administered at standard dose of 200 mg intravenous infusion every Q3W for max 2 yrs (**Figure 2**).

Assessments and Statistical Analyses:

- Central assessment of tumor cell PD-L1 expression (by Dako PD-L1 IHC 22C3 pharmDx), performed retrospectively.
- Imaging performed Q9W (reported according to iRECIST and RECIST 1.1).
- Safety and efficacy analyzed in all patients who received at least one dose of study drug.
- Data cut-off date was March 31, 2023.

Figure 2. Study design



Primary Endpoint: Objective response rate (ORR), as per iRECIST.

Secondary Endpoints: Progression free survival (PFS), overall survival (OS), safety and tolerability, pharmacokinetic/ pharmacodynamic and exploratory biomarkers.

RESULTS

BASELINE CHARACTERISTICS

- 39 patients (pts) were recruited in Part C in 9 sites across 4 countries between Mar 2019-Jan 2021. Baseline characteristics are reported in **Table 1**.
- Two patients were excluded from the efficacy dataset due to covid-related fatality prior to first post-baseline radiological assessment.

Table 1. Baseline characteristics

Baseline parameters, n (%)	Part C (N=37)
Median age, years (range)	63 (48–84)
Female / Male, n (%)	4 (10.8) / 33 (89.2)
ECOG 0 / ECOG 1, n (%)	13 (35.1) / 24 (64.9)
Current or Ex-smoker Non-smokers	32 (86.5) 5 (13.5)
Primary tumor location Oral cavity Oropharynx Hypopharynx Larynx	 11 (29.7) 13 (35.1) 7 (18.9) 6 (16.2)
Metastatic disease	34 (91.9)
Prior chemotherapy Prior cetuximab	37 (100) 15 (40.5)
PD-L1 (CPS)[1] <20 ≥20 ≥1	 17 (53.1) 15 (46.9) 25 (78.1)

[1] N=32; Central assessment of PD-L1 CPS using Dako IHC 22C3 pharmDx.

EXPOSURE

- Median efti exposure was 2.7 mo (range: 0.02–12.9) and 2.7 mo for pembro (range 0.02–24.6).
- 4 patients completed 2 years of treatment.
- 33 patients discontinued treatment due to death (18.2%), disease progression (57.6%), adverse event (15.2%) and withdrawal of consent (3.0%).

SAFETY

- No treatment-related deaths occurred (**Table 2**).
- Immune-related AEs (irAEs[1]) >5%: hypothyroidism (20.5%) and pruritus (10.3%) (**Table 3**).

[1] relationship to efti and/or pembrolizumab could not be ruled out.

Table 2. General overview of AEs

Safety parameter[1]	n (%)
Adverse reactions with fatal outcome[2]	0
Serious adverse reactions[2]	*3 (7.7)*
Grade ≥3 adverse reactions[2]	*5 (12.8)*
Adverse reactions leading to discontinuation of treatment[2]	*2 (5.1)*

[1]AEs rated according to NCI CTCAE (v5.0).
[2]relationship to efti and/or pembrolizumab could not be ruled out.

Table 3. Frequent AEs (incidence ≥10%) related to study treatment[2]

Adverse event (PT)[1]	Any grade N (%)	Grade 3 N (%)	Grade 4/5 N (%)
Hypothyroidism	8 (20.5)	*1 (2.6)*	*0*
Pruritus	4 (10.3)	*0*	*0*
Fatigue	4 (10.3)	*0*	*0*

[1] AEs rated according to NCI CTCAE (v5.0).
[2] relationship to efti and/or pembrolizumab could not be ruled out.

EFFICACY

- ORR (iRECIST) of 29.7% (95% CI: 15.9–47.0) in the ITT and 35.5% (95% CI: 19.2–54.6) in the EVAL population (**Table 4**). RECIST 1.1 results were comparable.
- Responses confirmed in 91% of cases (confirmed ORR by iRECIST: 27% (95% CI: 13.8–44.1).
- Response onset was early (median: 1.9 mo) and responses were long-lasting with <10% of responding pts progressing within 6 mo (**Figure 3**).
- Median (m)PFS of 2.1 mo (95% CI: 2.0–4.3) (**Figure 4**) and median OS of 8.7 mo (95% CI: 4.8–15.6) (**Figure 5**).
- ORR, mPFS and mOS were higher for pts with CPS ≥20 with 60%, 13.6 mo and 15.5 mo, respectively (**Table 5**). For pts for CPS ≥1, mOS was 12.6 mo (95% CI: 4.8–24.8).
- mDoR (iRECIST) not reached with 4 events (40%) at median follow-up of 38.8 mo (95% CI: 28.0–44.5) (**Figure 6**).

Table 4. Best overall response, ITT (N=37)

Response	iRECIST[4] n (%)	RECIST 1.1[4] n (%)
Complete Response	5 (13.5)	5 (13.5)
Partial Response	6 (16.2)	5 (13.5)
Stable Disease	3 (8.1)	3 (8.1)
Progression	17 (46.0)	18 (48.6)
Not Evaluable[1]	6 (16.2)	6 (16.2)
ORR, (ITT=37); [95% CI][2]	11 (29.7) [15.9–47.0]	10 (27.0) [13.8–44.1]
ORR (EVAL[3]=31); [95% CI][2]	11 (35.5) [19.2–54.6]	10 (32.3) [16.7–51.4]

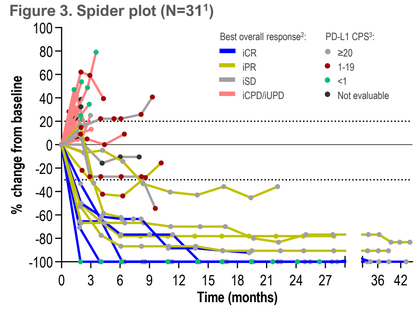
[1] Pts with no on-study post-baseline tumor staging for any reason.
[2] 95% confidence intervals calculated using Clopper-Pearson method.
[3] All pts with ≥1 on-study post-baseline tumor staging.
[4] Unconfirmed (local assessment).

Table 5. Overview of efficacy endpoints

PD-L1 CPS[1]	ITT (N=37)	≥20 (N=15)	<20 (N=17)	≥1 (N=25)
Overall response rate (ORR)[2]				
ORR, % [95% CI][3]	29.7 [15.9–47.0]	60.0 [32.3–83.7]	11.8 [1.5–36.4]	38.5 [20.2–59.4]
Progression-free survival (PFS)[2]				
Median, mo [95% CI][4]	2.1 [2.0–4.3]	13.6 [1.6–24.8]	2.0 [1.3–2.7]	2.3 [1.6–13.6]
6-mo PFS rate, %	32.4	53.3	17.7	40.0
Overall survival (OS)				
Median, mo [95% CI][4]	8.7 [4.8–15.6]	15.5 [4.9–31.1]	7.5 [1.9–18.8]	12.6 [4.8–24.8]
12-mo OS rate, %	46.0	66.7	35.3	52.0
Duration of response (DoR)[2]				
Median, mo	NR	NR	16.2	NR
12-mo DoR rate, %	80.0	87.5	50.0	77.8
24-mo DoR rate, %	60.0	62.5	50.0	55.6

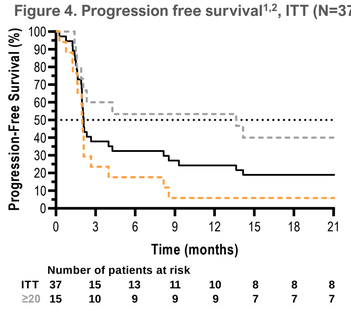
[1] Central assessment of PD-L1 TPS using Dako IHC 22C3 pharmDx for 32 pts.
[2] By iRECIST (local assessment).
[3] 95% confidence intervals calculated using Clopper-Pearson method.
[4] 95% confidence intervals calculated using Kaplan Meier survival analysis method.
NR: not reached; NC: not calculated.

Figure 3. Spider plot (N=31[1])



[1] All pts with ≥1 post-baseline CT scan with evaluable response; n=31. Pts listed with iPR/iCR whether confirmed or unconfirmed.
[2] Best overall response by iRECIST (local assessment).
[3] Central PD-L1 assessment with Dako kit.

Figure 4. Progression free survival[1,2], ITT (N=37)



[1] by iRECIST (local assessment).
[2] Note: figure has been cropped for visualization purposes.

Figure 5. Overall survival (N=37)

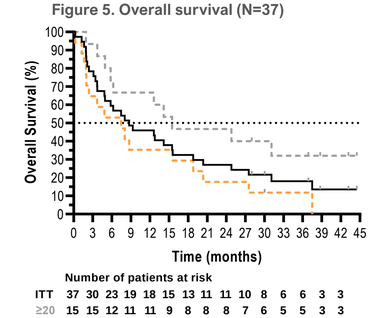
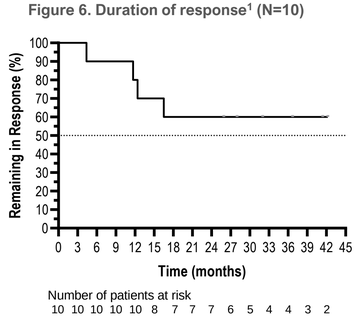


Figure 6. Duration of response[1] (N=10)



[1] by iRECIST including only pts with confirmed response (local assessment).

SUMMARY & CONCLUSION

- Encouraging ORR (iRECIST) of 29.7% (95% CI: 15.9–47.0) in 2nd line HNSCC pts responding to combination therapy of efti + pembrolizumab.
- Early onset of responses (median ~2 mo) that were deep (13.5% CRs) and durable (median DoR not reached despite a median FU of ~39 mo).
- Promising ORR of 60%, median PFS of 13.6 mo and median OS of 15.5 mo in patients with CPS ≥20.
- Treatment with efti plus pembrolizumab is safe and well-tolerated with no new safety signals.

Conclusion: efti in combination with pembrolizumab is safe, showing encouraging antitumor activity in 2nd line HNSCC patients.

TACTI-003 (NCT04811027), a randomized study in 1st line HNSCC unselected for PD-L1, is currently recruiting.

ABBREVIATIONS

APC…antigen presenting cell
(i)CR…complete response
DoR…duration of response
ECOG…Eastern Cooperative Oncology Group
(i)RECIST…(Immune) Response Evaluation Criteria In Solid Tumors
IFNg…interferon-gamme
irAE…immune-related adverse event
ITT…intention-to-treat
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
NK…natural killer cell
NR…not reached
ORR…overall response rate
OS…overall survival
PFS…progression free survival
(i)PR…partial response
PT…preferred term
(i)SD…stable disease
(i)UPD…unconfirmed progressive disease

REFERENCES

1. Brignone C, Clin Cancer Res. 2009;15: 6225- 6231.

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DISCLOSURES

Presenting Author: Dr. Bernard Doger
COI: This author has no relationships to disclose.