Immutep Reports Promising New Data in Head and Neck Cancer at ESMO Immuno-Oncology 2024

- *Data shows strong overall survival, progression-free survival, and durability from novel combination of efti in combination with pembrolizumab in difficult-to-treat head and neck cancer patients with PD-L1 CPS <1*
- *Positively, median overall survival (OS) has not yet been reached and the 12-month OS rate is 67%, both well above historical controls*
- *Complete response rate increases to 12.9% and 16.1%, according to RECIST 1.1 and iRECIST, respectively*
- *Treatment continues to be well tolerated*

SYDNEY, AUSTRALIA – 12 December 2024 – Immutep Limited (ASX: IMM; NASDAQ: IMMP) ("Immutep" or "the Company"), a clinical-stage biotechnology company developing novel LAG-3 immunotherapies for cancer and autoimmune disease, today announces positive clinical results from Cohort B of the TACTI-003 (KEYNOTE-C34) Phase IIb trial. This study evaluates eftilagimod alpha (efti) in combination with MSD's (Merck & Co., Inc., Rahway, NJ, USA) anti-PD-1 therapy KEYTRUDA® (pembrolizumab) in first line recurrent/metastatic head and neck squamous cell carcinoma (1L HNSCC) patients with negative PD-L1 expression.

The new promising data presented by Martin Forster, M.D., Ph.D., at the ESMO Immuno-Oncology (IO) Annual Congress 2024 includes strong overall survival, progression-free survival, and durability. This adds to the high response rates and favourable safety data previously reported on 12 July 2024.

Prof. Martin Forster of the UCL Cancer Institute and University College London Hospital NHS Foundation Trust, London, UK, and TACTI-003 Investigator, stated, "The new survival and durability data, coupled with increasing complete responses, build on the strong response rates already established with this novel IO combination in head and neck squamous cell cancers with PD-L1 CPS <1. This difficult-to-treat disease places a high burden on patients who unfortunately have very limited treatment options that all include chemotherapy. Collectively, these impressive results build on the potential promise of efti to improve patient outcomes and expand populations that respond to anti-PD-1."

Results

Data as of the 31 October 2024 cut-off date in evaluable 1L HNSCC patients (N=31) whose tumours express PD-L1 below 1 (Combined Positive Score [CPS] <1) and who typically do not respond well to anti-PD-1 therapy alone shows:

- Positively, median overall survival (OS) has not yet been reached and the 12-month OS rate is 67%
- Promising progression-free survival (PFS) of 5.8 months
- Strong durability with interim median duration of response (DOR) of 9.3 months
- High 35.5% objective response rate (ORR) and 58.1% disease control rate (DCR), as reported on 12 July
- Complete response rate increases to 12.9% and 16.1%, according to RECIST 1.1 and iRECIST, respectively[1]
- Efti in combination with pembrolizumab continues to be well-tolerated with no new safety signals

This data compares favourably to historical results from anti-PD-1 therapy alone in 1L HNSCC patients with PD-L1 CPS <1 including a 7.9-month median OS, 12-month OS rate of 39%, 2.1-month median PFS, 2.6-month median DOR, 5.4% ORR and 32.4% DCR with no complete responses[2-3].

Marc Voigt, CEO of Immutep, noted, "Despite the significant progress of cancer immunotherapy over the past decade and the positive change in the therapeutic landscape it has brought to bear, head and neck cancer patients with PD-L1 expression of less than one continue to have limited treatment options that all include chemotherapy. We believe this data is an encouraging step in the right direction towards potentially bringing a new approach to this underserved population, representing up to 20% of patients with this difficult disease."

Next Steps

Patients with PD-L1 CPS <1 is an underserved patient population with limited treatment options. Immutep will continue to follow the maturing data from TACTI-003 and engage with regulatory authorities regarding potential paths forward.

The ESMO IO poster is attached and will be on the Posters & Publications section of Immutep's website.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

About Immutep

Immutep is a clinical-stage biotechnology company developing novel LAG-3 immunotherapy for cancer and autoimmune disease. We are pioneers in the understanding and advancement of therapeutics related to Lymphocyte Activation Gene-3 (LAG-3), and our diversified product portfolio harnesses its unique ability to stimulate or suppress the immune response. Immutep is dedicated to leveraging its expertise to bring innovative treatment options to patients in need and to maximise value for shareholders. For more information, please visit www.immutep.com.

1. *Complete response rate was 9.6%, according to RECIST 1.1 and iRECIST, respectively, at earlier cut-off date as previously reported on 12 July 2024*
2. *Burtness, B. et al. Pembrolizumab Alone or With Chemotherapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma in KEYNOTE-048: Subgroup Analysis by Programmed Death Ligand-1 Combined Positive Score. Journal of Clinical Oncology 2022 40:21, 2321-2332. Note, the 5.4% ORR and 32.4% DCR are calculated from the 37 evaluable patients with CPS <1.*
3. *Burtness B. et al. Abstract LB-258: Efficacy of first-line (1L) pembrolizumab by PD-L1 combined positive score <1, 1-19, and ≥20 in recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): KEYNOTE-048 subgroup analysis. Cancer Res 15 August 2020; 80 (16_Supplement): LB–258. https://doi.org/10.1158/1538-7445.AM2020-LB-258*

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This announcement was authorised for release by the Board of Immutep Limited.

TACTI-003 Cohort B: Eftilagimod Alpha (Soluble LAG-3) and Pembrolizumab in First-Line Recurrent or Metastatic Head & Neck Squamous Cell Carcinoma with CPS <1

Poster # 620

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BACKGROUND

Eftilagimod alpha (efti): a soluble LAG-3 protein and MHC Class II agonist that leads to an enhanced immune response by activating antigen presenting cells (APCs), leading to the activation/proliferation of CD8+ T cells[1] (**Figure 1**).

Pembrolizumab: current standard-of-care that antagonizes PD-1 receptor on T cells, enhancing the immune response against cancer cells.

Rationale for study: Efti activates APCs, leading to an increase in activated T cells (CD4/CD8), augmenting responses when combined with PD-(L)1 antagonists such as pembrolizumab.

Encouraging efficacy has been seen when efti was combined with pembrolizumab in 2nd line HNSCC patients after failure of 1st line chemotherapy[2] (**Table 1**) and in 1st line NSCLC regardless of PD-L1 TPS[3] (**Table 2**). Responses were observed irrespective of patients' CPS/TPS level.

Figure 1. Mechanism of action of efti when combined with pembrolizumab

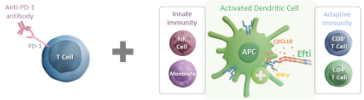


Table 1. Second line HNSCC, presented at ASCO 2023[2]

PD-L1 CPS	ITT, N=37	≥20, N=15	<20, N=17
Objective response rate (iRECIST), %	29.7	60.0	11.8

Table 2. First line NSCLC, presented at ESMO 2023[3]

PD-L1 TPS	<1%, N=32	1-49%, N=38	≥50%, N=20
Objective response rate (iRECIST), %	31.3	44.7	55.0

[1] Brignone C., Clin Cancer Res. 2009;15: 6225- 6231; [2] Doger B. et al, JCO. 2023;41: 6.29-6.29; [3] Carcereny E. et al, Ann of Onc 2023;34:S755-S851.

METHODS

Study Design and Patients

- **TACTI-003** (Two **AC**Tive Immunotherapies-003): Phase IIb, multinational, open label study. We present results from **first-line R/M HNSCC PD-L1 negative (CPS <1), Cohort B**.
- Efti administered as 30 mg subcutaneous injection Q2W for the first 6 months and then Q3W for max 2 years. Pembrolizumab administered as 400 mg intravenous infusion Q6W for max 2 years (**Figure 2**).

Results from Cohort A were published at ESMO 2024 (Kristensen CA et al, Ann of Onc 2024;35:S1227).

Assessments and Statistical Analyses:

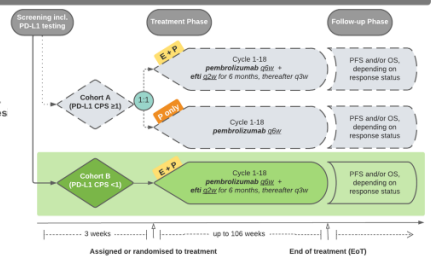
- Prospective assessment of tumor cell PD-L1 expression for enrollment (FDA-approved kit 22C3).
- Imaging performed Q9W (assessed according to RECIST 1.1 and iRECIST).
- Safety was analyzed in all patients who received at least one dose of study drug (N=33). Efficacy was analysed in all patients who were part of the safety population and had at least one evaluable post-baseline scan (N=31).

Safety data cut-off date: June 26, 2024. Efficacy data cut-off date: October 31, 2024.

Endpoints:

Primary Endpoint: ORR by RECIST 1.1.
Secondary Endpoints: ORR by iRECIST, DoR, safety, PFS and OS.

Figure 2. Study des



RESULTS

PATIENT DISPOSITION & BASELINE CHARACTERISTICS

- 33 patients were recruited at 14 sites across 6 countries between April 2022 until October 2023.
- Median age was 64 years (range: 23–83) & 74.2% of patients were male. Of the patients with primary oropharyngeal tumours, 36.4% were HPV positive (**Table 3**).

Table 3. Baseline characteristics

Baseline parameters	N=31
Median age, years (range)	64 (23-83)
Female / Male, %	25.8 / 74.2
ECOG 0 / 1, %	32.3 / 67.7
Current / Ex-smoker / Non-smoker, %	25.8 / 61.3 / 12.9
Primary tumour location, %	
Oral cavity	29.0
Oropharynx	35.5
Hypopharynx	3.2
Larynx	32.3
p16 (HPV) status[1]	
Positive / Negative	36.4 / 63.6
Disease status at study entry[2], %	
Primary only	22.6
Primary + distant	12.9
Distant only	64.5

[1] In patients with primary oropharyngeal tumours only.
[2]Primary only: local relapse at the site of primary tumor and possibly with or without cervical lymph nodes

- 25 patients discontinued treatment due to: disease progression (92.0%), adverse event (3.2%) and physician decision (3.2%).

SAFETY

- No treatment-related deaths occurred (**Table 4**).
- Local injection site reactions were observed in 18.2% of patients (all Grade 1).
- The most frequent AEs were fatigue and nausea (**Table 5**).

Table 4. General overview of AEs (N=33)

Safety parameter[1]	N=33
Adverse reactions with fatal outcome[2]	0
Serious adverse reactions[2]	0
Grade ≥3 adverse reactions[2]	15.2
Adverse reactions leading to discontinuation of treatment[2]	9.1[3]

[1] AEs rated according to NCI CTCAE (v5.0).
[2] relationship to efti and/or pembrolizumab could not be ruled out
[3] Immune thrombocytopenia (G4), Immune-mediated hepatitis (G3), Laryngeal obstruction (G4).

Table 5. Frequent AEs (incidence ≥15%) (N=33)

Adverse event (PT)[1]	Any grade, %	Grade 3, %	Grade 4/5, %
Fatigue	21.2	NA	NA
Nausea	21.2	NA	NA
Weight decreased	18.2	NA	NA
Hypothyroidism	18.2	NA	NA
Constipation	18.2	NA	NA
Pyrexia	15.2	NA	NA
Arthralgia	15.2	NA	NA
GGT increased	15.2	3.0	NA
Diarrhoea	15.2	NA	NA
Anaemia	15.2	NA	NA

[1] AEs rated according to NCI CTCAE (v5.0).
GGT: Gamma-glutamyltransferase.

EFFICACY

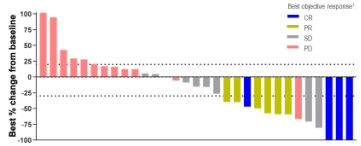
- ORR (RECIST 1.1) of 35.5% (95% CI: 19.2–54.6) and 38.7% (95% CI: 21.8–57.8) by iRECIST (**Table 6**).
- Responses confirmed in 91% of cases with a confirmed ORR by RECIST 1.1 of 32.3% (95% CI: 16.7–51.4).
- Responses were deep, had early onset (median time to response of 2.1 months) and included 4 confirmed complete responses by RECIST 1.1 (**Figure 3**).
- With a median follow up of 16.4 months, median (m) PFS by RECIST 1.1 was 5.8 months with a 6-month PFS rate of 48.4% (**Figure 5**).
- mDoR by RECIST 1.1 was 9.3 months with 50% events. 55% of patients on treatment >6 months and ~30% on treatment >12 months (**Figure 4**).
- mOS was not reached (**Figure 6**) and the 12-month survival rate was 66.8%.

Table 6. Best objective response[1] (N=31)

Response	RECIST 1.1, %	iRECIST, %
Complete Response	12.9	16.1
Partial Response	22.6	22.6
Stable Disease	22.6	25.8
Progressive Disease	41.9	35.5
ORR[1]; [95% CI][2]	35.5 [19.2–54.6]	38.7 [21.8–57.8]
DCR; [95% CI][2]	58.1 [39.1–75.5]	64.5 [45.4–80.8]

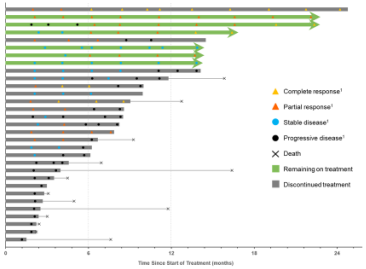
[1] Unconfirmed (local assessment).
[2] 95% confidence intervals calculated using Clopper-Pearson method.
Note:10/11 responses confirmed by RECIST 1.1 and 11/12 by iRECIST.

Figure 3. Waterfall plot (N=31)



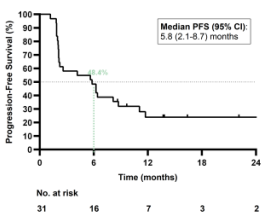
[1] by RECIST 1.1 (local assessment).
Includes one complete response (CR) with a best % change of -47%. This patient had one target lesion of the lymph node, which shrunk to <10 mm.

Figure 4. Swimmer plot (N=31)



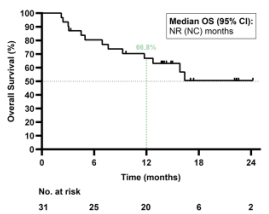
[1] by iRECIST.
Note: treatment decisions were made using iRECIST.

Figure 5. Progression free survival[1,2] (N=31)



[1] by RECIST 1.1.
[2] Note: figure has been cropped for visualization purposes.

Figure 6. Overall survival (N=31)



NC: non-calculable; NR: not reached.

SUMMARY & CONCLUSION

- Efti combined with pembrolizumab led to a high ORR (35.5% [95% CI: 19.2–54.6]) and DCR (58.1% [95% CI: 39.1–75.5]) in this PD-L1 CPS <1 population.
- Promising median PFS of 5.8 months, median DoR of 9.3 months and median OS not yet reached, with 67% of patients alive at 12 months.
- Treatment with efti plus pembrolizumab is safe and well-tolerated with no new safety signals.

Conclusion: Results are promising (mature 12-month OS rate of 67%), especially when considering the expected efficacy of anti-PD-1 alone in this population. Late-stage development is warranted.

ABBREVIATIONS

APC…antigen presenting cell
CPS…combined positive score
CR…complete response
DoR…duration of response
ECOG…Eastern Cooperative Oncology Group
(i)RECIST…(Immune) Response Evaluation Criteria in Solid Tumors
ITT…intention-to-treat
LAG-3…Lymphocyte Activation Gene-3
MHC…Major Histocompatibility Complex
NR…not reached
ORR…objective response rate
OS…overall survival
PD-L1… programmed death-ligand 1
PFS…progression free survival
PR…partial response
PT…preferred term
SD…stable disease
TPS…tumour proportion score
PD…progressive disease

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- We thank the dedicated clinical trial investigators & their team members.
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- This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

DISCLOSURES

Presenting Author: Dr. Martin Forster.
COI: Advisory board: Bayer, Merck, MSD, Takeda, Ultrahuman, Transgene, Immutep, Amgen, BMS, EQRS, Janssen, Oxford VacMedix, Pharmamar, Regeneron and Syncorp. Research grant: AstraZeneca (Inst), Boehringer Ingelheim (Inst), Merck Serono (Inst) and MSD Oncology (Inst). Invited speaker: Roches, Achilles, Oxford VacMedix, Apollomics, Takeda, Ellipsis, Moderna, Exscientia, Immutep, ALXOncology; Genmab and Janssen. Advisory role: Ruth Strauss Foundation.