A Phase 2 Study of Evorpacept (ALX148) in Combination with Pembrolizumab in Patients with Advanced Head and Neck Squamous Cell Carcinoma (HNSCC); ASPEN-03

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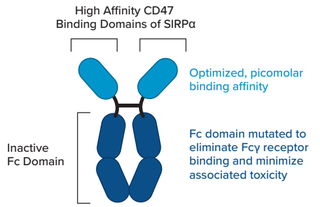
Background

- Both innate and adaptive immune responses are important components of anticancer immunity.
- CD47 is a marker of self that interacts with SIRPα on myeloid immune cells, inhibiting their function. CD47 is upregulated by tumors to evade immune responses and its expression is associated with poor prognosis in hematologic and solid tumors including HNSCC.
- Evorpacept is a high affinity CD47-blocking fusion protein with an inactive Fc region (Figure 1) designed to be safely combined with and to enhance the efficacy of standard anticancer therapeutics.

Figure 1. Evorpacept Potently and Selectively Binds CD47 to Block Interaction with SIRPα

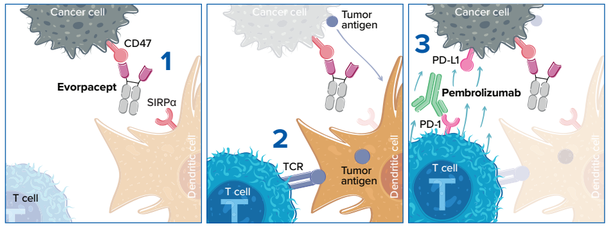


- Fc domain enables antibody-like PK.
- Molecular weight half the size of typical antibody.

Evorpacept and Pembrolizumab Have Complementary Mechanisms of Action

- Anti-PD-1 immune checkpoint inhibitor pembrolizumab has demonstrated antitumor efficacy through activation of tumor-infiltrating lymphocytes. Pembrolizumab as a single agent is a standard treatment option for patients with previously untreated recurrent or metastatic (R/M) HNSCC with PD-L1-positive tumors (combined positive score (CPS) ≥1).
- Evorpacept used in combination with pembrolizumab has the potential to augment both innate and adaptive antitumor immune responses (Figure 2).

Figure 2. The Combination of Evorpacept and Pembrolizumab Can Bridge the Innate and Adaptive Immune Responses



1 Evorpacept binds to CD47 expressed by cancer cells to block the CD47-SIRPα myeloid checkpoint leading to enhanced phagocytosis and activation of dendritic cells

2 Activated dendritic cells cross-present tumor antigens to cytotoxic T cells

3 Pembrolizumab binds to PD-1, relieving PD-1/PD-L1-mediated inhibition of activated T cells

Evorpacept + Pembrolizumab Has Demonstrated Initial Antitumor Activity from the ASPEN-01 Study

- The combination of evorpacept + pembrolizumab has shown preliminary antitumor activity and acceptable tolerability in patients with ≥2nd line advanced HNSCC in the ongoing Phase 1 ASPEN-01 study[1].
- PD-L1-unselected immune checkpoint naïve patients whose disease progressed on platinum-based therapy (n=10) were treated with evorpacept + pembrolizumab and experienced a 40% ORR and 4.6 months median PFS, comparing favorably with historical controls (Figure 3).
- Based on these encouraging results, the **ASPEN-03** study will assess the efficacy and safety of evorpacept in combination with pembrolizumab in previously untreated patients with metastatic or unresectable recurrent PD-L1-positive HNSCC.

Figure 3. Initial Activity of Evorpacept + Pembrolizumab in Patients with HNSCC (ASPEN-01 Study)

Response Evaluable Patients

N=20: Recurrent/metastatic HNSCC, at least one prior systemic therapy

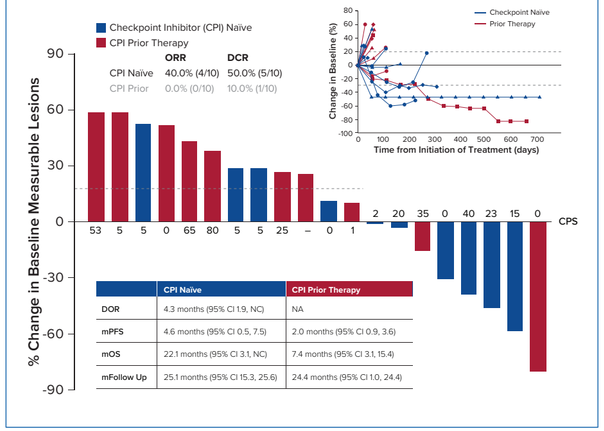
→ **N=10:** Checkpoint inhibitor naïve patients

Treatment

Evorpacept 10 mg/kg once a week (QW) + **Pembrolizumab** 200 mg every three weeks (Q3W)

Endpoints

- Maximum tolerated dose
- Anti-cancer activity



	CPI Naïve	CPI Prior Therapy
DOR	4.3 months (95% CI 1.9, NC)	NA
mPFS	4.6 months (95% CI 0.5, 7.5)	2.0 months (95% CI 0.9, 3.6)
mOS	22.1 months (95% CI 3.1, NC)	7.4 months (95% CI 3.1, 15.4)
mFollow Up	25.1 months (95% CI 15.3, 25.6)	24.4 months (95% CI 1.0, 24.4)

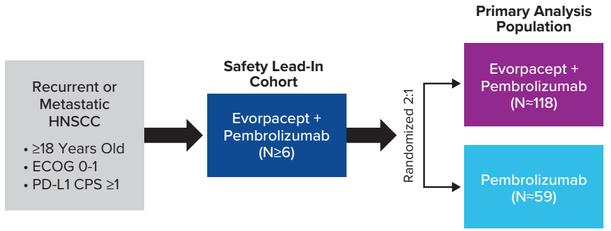
Notes: Data Cutoff October 1, 2020; Patients who received at least one dose of ALX148 in the expansion phase, had a baseline assessment, and at least one post-baseline disease assessment; **ORR** – Overall Response Rate; **DCR** – Disease Control Rate; **CPS** – Combined Positive Score.

Lee KW, et al. SITC Annual Meeting; 2020. Abstract #404.

Study Methods

- **ASPEN-03** (Figure 4) is an ongoing non-comparative, open-label, randomized Phase 2 global study of evorpacept + pembrolizumab or pembrolizumab alone in patients with metastatic or unresectable recurrent, PD-L1-positive (CPS ≥1) HNSCC who have not yet been treated for their advanced disease.
- After an initial safety lead-in cohort, **ASPEN-03** will randomize ~177 patients 2:1 to receive evorpacept + pembrolizumab or pembrolizumab alone.
- Key minimization factors used to randomize patients include geography, CPS, and HPV (p16) status.
- Patients in the evorpacept + pembrolizumab treatment arm will receive evorpacept 45 mg/kg IV Q3W.
- All patients will receive pembrolizumab 200 mg IV Q3W (for a maximum of 35 cycles).

Figure 4. ASPEN-03 Study Schema



Eligibility Criteria

Key Inclusion Criteria

- Patients with metastatic or unresectable, recurrent HNSCC that is PD-L1-positive (CPS ≥1) and who have not received prior systemic therapy for their advanced disease.
  - Prior systemic therapy for the treatment of locoregionally advanced disease is allowed if it was completed more than 6 months prior to enrollment.
- Measurable disease per RECIST v1.1.
- Adequate bone marrow, renal, and liver function.
- Age ≥18 years, except in regions in which the minimum age for subject participation is >18 years.
- ECOG performance status 0 or 1.

Key Exclusion Criteria

- HNSCC suitable for local therapy.
- Progressive disease within 6 months of completion of systemic therapy for the treatment of locoregionally advanced HNSCC.
- Nasopharyngeal carcinoma (NPC).
- Prior treatment with any anti-CD47 or anti-SIRPα agent.
- Prior treatment with a PD-1, PD-L1, or PD-L2 agent, or with an agent directed to another stimulatory or co-inhibitory T cell receptor (e.g., CTLA-4, OX40, CD137).

Study Endpoints

Co-Primary Endpoints

- 12-month overall survival rate
- Objective response rate

Key Secondary Endpoints

- Duration of response
- Progression-free survival
- Overall survival
- Safety

Exploratory endpoints will characterize pharmacodynamic properties.

Sample Size Determination

- Statistical assumptions used for the sample size determination:
  - 1-sided α = 2.5% and 80% power.
  - 12-month OS rate of 51% for the Pembrolizumab arm[2].
  - To detect 12-month OS rate of 63.7% for the Evorpacept + Pembrolizumab arm.
- Testing strategy: Fixed sequence procedure will be used for the testing of co-primary endpoints.

References

1. Keun-Wook Lee, Hyun Cheol Chung, Won Seog Kim, et al. ALX148, a CD47 blocker, in combination with standard chemotherapy and antibody regimens in patients with gastric/gastroesophageal junction (GC) cancer and head and neck squamous cell carcinoma (HNSCC); ASPEN-01. Poster presented at: Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 11-14, 2020. Abstract #404.
2. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab Alone or With Chemotherapy Versus Cetuximab With Chemotherapy for Recurrent or Metastatic Squamous Cell Carcinoma Of The Head And Neck (Keynote-048): A Randomised, Open-Label, Phase 3 Study. *The Lancet*. 2019 Nov 23; 394 (10212): 1915-1928.

Acknowledgments

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- This study is being conducted in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
- **Contact email:** info@alxoncology.com
- Trial Registration: ClinicalTrials.gov identifier, NCT04675294
- Presented at the 2021 Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 10-14, 2021. Abstract #439.

*Dr. Ruffner was employed by ALX Oncology Inc during the reporting period.