A Phase 2 Study of Evorpacept (ALX148) in Combination with Pembrolizumab and Chemotherapy in Patients with Advanced Head and Neck Squamous Cell Carcinoma (HNSCC); ASPEN-04

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Background

- Anticancer immunity relies on the release of tumor antigens and subsequent activation of the innate and adaptive immune systems. After cytotoxic chemotherapy induces neoantigen release, myeloid checkpoint inhibitors can help potentiate innate immune cell activity including antigen presentation by dendritic cells.
- CD47 is a marker of self that interacts with SIRPα on myeloid immune cells and is upregulated by tumors to evade immune responses.
- Evorpacept is a high affinity CD47-blocking fusion protein with an inactive Fc region (Figure 1) designed to safely enhance standard anticancer therapeutics.

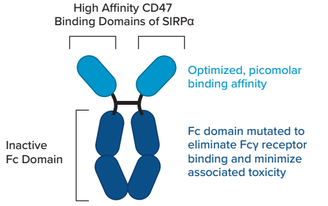


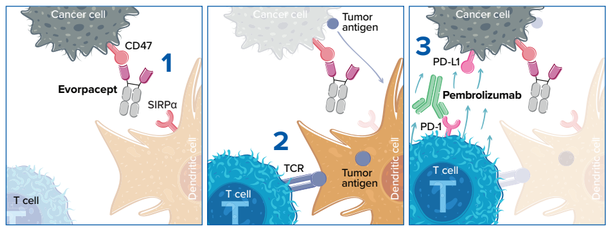
Figure 1. Evorpacept Potently and Selectively Binds CD47 to Block Interaction with SIRPα

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

Evorpacept, Pembrolizumab, and Chemotherapy Have Complementary Mechanisms of Action

- Pembrolizumab, a T cell checkpoint inhibitor that activates cytotoxic lymphocytes, is a standard option for patients with previously untreated recurrent/metastatic (R/M) HNSCC, both as a monotherapy for patients with PD-L1-positive disease and in combination with 5FU + platinum for a PD-L1-unselected population.
- Through increased activation of the immune system, a combination of evorpacept + pembrolizumab + 5FU/platinum might have more antitumor activity in R/M HNSCC than current standard therapeutic approaches (Figure 2).
- This combination approach could be particularly beneficial to patients with PD-L1-low HNSCC, where anti-PD-(L)1 therapy historically has diminished efficacy.

Figure 2. Evorpacept, Pembrolizumab, and Chemotherapy Combine to Activate the Antitumor Immune Response



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

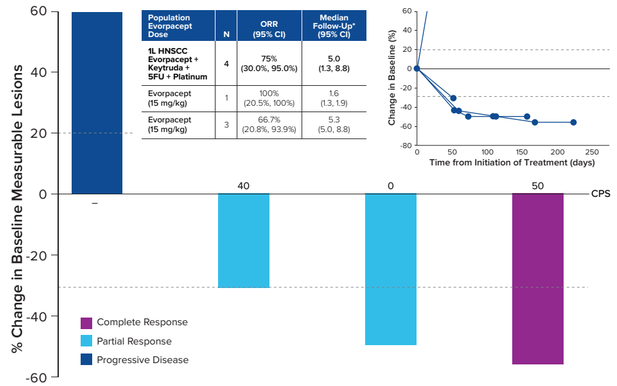
2 Activated dendritic cells cross-present tumor antigens (including tumor antigens released in response to treatment with chemotherapy) to cytotoxic T cells

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

Evorpacept, Pembrolizumab, and Chemotherapy Have Shown Initial Antitumor Activity in the ASPEN-01 Study

- The combination of evorpacept + pembrolizumab + 5FU/platinum has undergone preliminary testing in the ongoing Phase 1 ASPEN-01 study[1], demonstrating initial clinical response and tolerability. In initial data from patients with previously untreated, PD-L1-unselected R/M HNSCC treated with evorpacept + pembrolizumab + 5FU/platinum, patients experienced objective responses including complete response (Figure 3).
- The **ASPEN-04** study will assess the efficacy and safety of evorpacept in combination with pembrolizumab and chemotherapy in previously untreated patients with PD-L1-unselected R/M HNSCC.

Figure 3. Evorpacept + Pembrolizumab + 5FU + Platinum Preliminary Activity in Patients with First-Line HNSCC (ASPEN-01 Study)



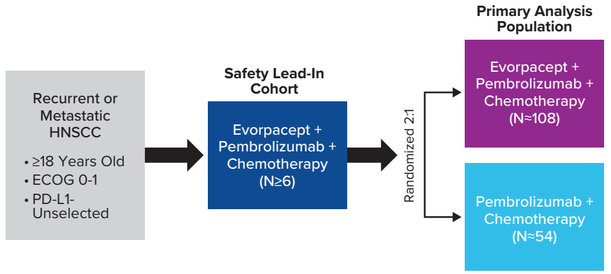
Population Evorpacept Dose	N	ORR (95% CI)	Median Follow-Up* (95% CI)
1L HNSCC Evorpacept + Keytruda + 5FU + Platinum	4	75% (30.0%, 95.0%)	5.0 (1.3, 8.8)
Evorpacept (15 mg/kg)	1	100% (20.5%, 100%)	1.6 (1.3, 1.9)
Evorpacept (15 mg/kg)	3	66.7% (20.8%, 93.9%)	5.3 (5.0, 8.8)

Notes: Data Cutoff October 1, 2020; *Intent to treat population: HNSCC (10 + 15 mg/kg) N=5; HNSCC (15 mg/kg) N=2
Lee KW, et al. SITC Annual Meeting; 2020. Abstract #404.

Study Methods

- **ASPEN-04** (Figure 4) is an ongoing non-comparative, open-label, randomized Phase 2 global study of evorpacept + pembrolizumab + chemotherapy (5FU + either carboplatin or cisplatin) or pembrolizumab + chemotherapy in patients with PD-L1-unselected metastatic or unresectable recurrent HNSCC who have not yet been treated for their advanced disease.
- After an initial safety lead-in cohort, **ASPEN-04** will randomize ~162 patients 2:1 to receive evorpacept + pembrolizumab + chemotherapy or pembrolizumab + chemotherapy.
- Key minimization factors used to randomize patients include geography, PD-L1 combined positive score, and HPV (p16) status.
- Patients in the evorpacept treatment arm will receive evorpacept 45 mg/kg IV Q3W.
  - All patients will receive pembrolizumab 200 mg IV Q3W (maximum of 35 cycles), 5FU (1000 mg/m^2/day continuous infusion Days 1, 2, 3, 4 Q3W x 6 cycles) and either carboplatin (AUC 5 mg/ml/min as a 60 min infusion Day 1 Q3W x 6 cycles) or cisplatin (100 mg/m^2 as a 60 min infusion Day 1 Q3W x 6 cycles).

Figure 4. ASPEN-04 Study Schema



Eligibility Criteria

Key Inclusion Criteria

- Patients with metastatic or unresectable, recurrent HNSCC 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 53% for the Pembrolizumab + Chemo arm[2].
  - To detect 12-month OS rate of 66.3% for the Evorpacept + Pembrolizumab + Chemotherapy 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, NCT04675333
- Presented at the 2021 Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 10-14, 2021. Abstract #433.

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