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Phase 2 Study of Dalantercept Monotherapy in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

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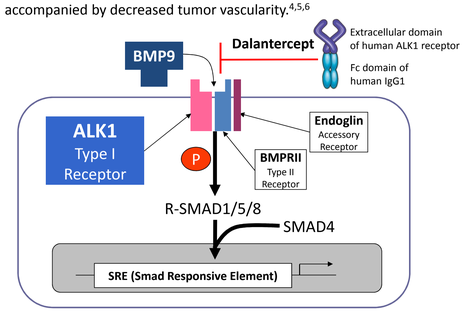
Dalantercept Background

- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is expressed on endothelial cells.[1]
- When activated by its ligands, bone morphogenetic protein 9 (BMP9) and 10 (BMP10), ALK1 signals via phosphorylation of SMAD 1/5/8 to activate genes involved in vascular morphogenesis.[2]
- ALK1/BMP9 signaling promotes vascular stabilization and maturation which are downstream events from the proliferative stages of angiogenesis that are driven primarily by vascular endothelial growth factor (VEGF).[3]
- Dalantercept is an ALK1 receptor:Fc fusion protein that binds with high affinity to BMP9 and BMP10 and thereby acts as a ligand trap.
- In preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.[4,5,6]



Study Rationale

- Limited treatments exist for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN) after platinum therapy, especially for patients already treated with cetuximab.
- Cetuximab is the only approved agent in RM-SCCHN and in the platinum refractory setting, the monotherapy response rate is 13% with a disease control rate (DCR) of 46% and median overall survival of 178 days (5.9 months).[7]
- Angiogenesis remains an area of active research in RM-SCCHN. However, VEGF-directed therapies tested, including sunitinib and sorafenib, have limited clinical activity and significant toxicity.[8,9]
- Based on immunohistochemistry of human tumor samples, BMP9 is over-expressed in SCHHN.[10]
- In preclinical SCCHN models, dalantercept caused tumor growth inhibition as a monotherapy and in combination with cisplatin.[10]
- In a completed phase 1 study, dalantercept monotherapy demonstrated anti-tumor activity in patients with a variety of diseases including two patients with RM-SCCHN, one of whom had a partial response (33% reduction from baseline) and another with prolonged stable disease (29% reduction from baseline).[11]
- The study objectives were to assess the efficacy, safety, and tolerability of dalantercept monotherapy in patients with RM-SCCHN.

Study Design

- This is a single arm phase 2 trial evaluating dalantercept monotherapy administered subcutaneously (SC) every 3 weeks for a 21 day cycle.
- After the first two patients were enrolled at 80 mg, the protocol was amended to use weight-based dosing (mg/kg) and two dose levels were evaluated (0.6 mg/kg and 1.2 mg/kg).
- The primary endpoint was objective response rate (ORR). Imaging occurred every 2 cycles (6 week intervals), assessed by RECIST v1.1.
- Secondary endpoints included safety and tolerability, progression free survival (PFS), overall survival (OS), pharmacokinetic (PK) and pharmacodynamic (PD) testing on serum and tumor specimens.
- Per the current statistical analysis plan, efficacy analyses used a modified intent-to-treat population consisting of patients who received at least one dose of dalantercept (either 0.6 or 1.2 mg/kg) and had one on-treatment tumor assessment. Safety analyses included all patients who received at least one dose of dalantercept.

Key Eligibility Criteria

- Patients with RM-SCCHN of mucosal origin (oral cavity, oropharynx, hypopharynx, or larynx) or patients with an unknown primary SCC presumed to be of head and neck mucosal origin
- ≥ 1 one prior platinum regimen
- ECOG performance status of 0 or 1
- No prior anti-angiogenic therapy

Patient Demographics by Cohort

Demographic	80 mg (N = 2)	0.6 mg/kg (N = 13)	1.2 mg/kg (N = 31)	Overall (N = 46)
Median age, years (range)	56.5 (47-66)	60 (50-68)	61 (45-78)	60.5 (45-78)
Gender, n (%)				
Male	0	13 (100)	26 (83.9)	39 (84.8)
Female	2 (100)	0	5 (16.1)	7 (15.2)
ECOG, n (%)				
0	0	8 (61.5)	8 (25.8)	16 (34.8)
1	2 (100)	5 (38.5)	23 (74.2)	30 (65.2)
Site of primary tumor, n (%)				
Oropharynx	0	11 (84.6)	9 (29.0)	20 (43.5)
Oral cavity	2 (100)	2 (15.4)	12 (38.7)	16 (34.8)
Larynx	0	0	6 (19.4)	6 (13.0)
Unknown	0	0	4 (12.9)	4 (8.7)
HPV status, n (%)				
Positive	0	9 (69.2)	11 (35.5)	20 (43.5)
Negative	2 (100)	4 (30.8)	13 (41.9)	19 (41.3)
Unknown	0	0	7 (22.6)	7 (15.2)
Median number prior regimens	4	5	4	4
Prior cetuximab, n (%)	2 (100)	7 (53.8)	19 (61.3)	28 (60.9)

Results: Response Rate

- 46 patients were enrolled and 40 were evaluable for response (13 at 0.6 mg/kg, 27 at 1.2 mg/kg).
- One patient in the 1.2 mg/kg cohort achieved a PR (49% reduction in tumor measurements from baseline) and was on treatment for 9.7 months (HPV-positive, 2 prior lines of therapy).
- Another patient in the 1.2 mg/kg cohort (HPV-negative, 4 prior lines of therapies including cetuximab) remains active on therapy for 9 months with stable disease (21.6% reduction in tumor measurements from baseline).
- The overall rate of disease control (PR + SD) was 45%, and was numerically superior at 1.2 mg/kg (48.1%) compared to 0.6 mg/kg (38.5%).
- 37% of patients at 1.2 mg/kg had disease control lasting ≥ 4 cycles (3 months) compared to 23.1% of patients at 0.6 mg/kg.
- The disease control rate was greater in HPV-positive patients (57.9%) compared to HPV-negative (20%).

Objective Response Rate Data
Patients receiving one dose of dalantercept (0.6 or 1.2 mg/kg) and one post-baseline investigator assessed RECIST scan

Endpoint	0.6 mg/kg (N = 13)	1.2 mg/kg (N = 27)	Overall (N = 40)
Partial Response, n (%)	0	1 (3.7)	1 (2.5)
Stable Disease, n (%)	5 (38.5)	12 (44.4)	17 (42.5)
Disease Control Rate, n (%)	5 (38.5)	13 (48.1)	18 (45.0)
Disease Control Rate ≥ 3 mos., n (%)	3 (23.1)	10 (37.0)	13 (32.5)
Progressive Disease, n (%)	8 (61.5)	14 (51.9)	22 (55.0)

Response Data by HPV Status
Patients receiving one dose of dalantercept (0.6 or 1.2 mg/kg) and one post-baseline investigator assessed RECIST scan

Endpoint	HPV Positive (N = 19)	HPV Negative (N = 15)	HPV Unknown (N = 6)*
Partial Response, n (%)	1 (5.3)	0	0
Stable Disease, n (%)	10 (52.6)	3 (20.0)	4 (66.7)
Disease Control Rate, n (%)	11 (57.9)	3 (20.0)	4 (66.7)
Disease Control Rate ≥ 3 mos., n (%)	7 (36.8)	3 (20.0)	3 (50.0)
Progressive Disease, n (%)	8 (42.1)	12 (80.0)	2 (33.3)

* All patients with HPV status unknown were in the 1.2 mg/kg cohort

Results: Survival

- In the overall study population, the median PFS was 1.4 months (95% CI 1.3 – 2.7), and median OS (n = 44) was 8.9 months (95% CI 5.8 – 11.1).
- Ten (22.7%) patients survived at least 1 year and 14 (31.8%) patients remain in active follow-up.
- In the HPV-positive population, the median OS was 7.6 months (95% CI 5.1 – not reached), and in the HPV-negative population the median OS was 6.7 months (95% CI 3.7 – 10.0).
- Among the HPV positive patients, the median OS was numerically superior at 1.2 mg/kg (11.1 months, 95% CI 5.2 – not reached) compared to 0.6 mg/kg (6.1 months, 95% CI 4.6 – 15.5).

Survival Data
Patients receiving one dose of dalantercept (0.6 or 1.2 mg/kg)

Endpoint	0.6 mg/kg (N = 13)	1.2 mg/kg (N = 31)	Overall (N = 44)
Median PFS, months (95% CI)	1.3 (1.3 – 2.7)	1.4 (1.3 – 2.7)	1.4 (1.3 – 2.7)
Median OS, months (95% CI)	7.1 (4.6 – 10.5)	9.5 (5.8 – not reached)	8.9 (5.8 – 11.1)
1 year survival rate, n (%)	3 (23.1)	7 (22.6)	10 (22.7)

Pharmacokinetics and Pharmacodynamics

- The PK profile of dalantercept in patients with RM-SCCHN was consistent with the phase 1 PK analyses.
- No patient had positive anti-drug antibody results on study.
- Pharmacodynamic analyses of serum biomarkers and IHC on archived and fresh tumor biopsies are ongoing.

Safety Summary

- The most common treatment related adverse events occurring in > 15% of patients were anemia, fatigue, peripheral edema, headache, and hyponatremia.
- There were no related thromboembolic events, and bleeding events were grade 1 and infrequent, occurring in 3 patients.
- 2 patients discontinued due to adverse events.
- There were no treatment associated deaths.

Treatment-Emergent Dalantercept-Related Adverse Events (> 5% Patients)
All Patients Enrolled

Preferred Term	80 mg (N = 2)		0.6 mg/kg (N = 13)		1.2 mg/kg (N = 31)		Overall (N = 46)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Patients with ≥ 1 AE	1 (50.0)	1 (50.0)	13 (100.0)	1 (7.7)	27 (87.1)	4 (12.9)	41 (89.1)	6 (13.0)
Anemia	0	0	2 (15.4)	0	9 (29.0)	0	11 (23.9)	0
Fatigue	1 (50.0)	0	3 (23.1)	0	7 (22.6)	1 (3.2)	11 (23.9)	1 (2.2)
Edema peripheral	0	0	2 (15.4)	0	8 (25.8)	0	10 (21.7)	0
Headache	0	0	3 (23.1)	0	5 (16.1)	0	8 (17.4)	0
Hyponatremia	1 (50.0)	1 (50.0)	0	0	6 (19.4)	2 (6.5)	7 (15.2)	3 (6.5)
Pleural effusion	0	0	1 (7.7)	1 (7.7)	4 (12.9)	1 (3.2)	5 (10.9)	2 (4.3)
Decreased appetite	0	0	2 (15.4)	0	2 (6.5)	0	4 (8.7)	0
Dyspnea	0	0	1 (7.7)	0	3 (9.7)	0	4 (8.7)	0
Edema	1 (50.0)	0	2 (15.4)	0	1 (3.2)	0	4 (8.7)	0
Telangiectasia	0	0	1 (7.7)	0	3 (9.7)	0	4 (8.7)	0
Vomiting	1 (50.0)	1 (50.0)	2 (15.4)	0	1 (3.2)	0	4 (8.7)	1 (2.2)
Weight increased	0	0	0	0	4 (12.9)	0	4 (8.7)	0
Constipation	0	0	2 (15.4)	0	1 (3.2)	0	3 (6.5)	0
Nausea	1 (50.0)	1 (50.0)	1 (7.7)	0	1 (3.2)	0	3 (6.5)	1 (2.2)

Treatment-Emergent Dalantercept-Related Serious Adverse Events
All Patients Enrolled

Preferred Term	80 mg (N = 2) n (%)	0.6 mg/kg (N = 13) n (%)	1.2 mg/kg (N = 31) n (%)	Overall (N = 46) n (%)
Patients with at least 1 SAE	0	1 (7.7)	2 (6.5)	3 (6.5)
Pleural effusion	0	1 (7.7)	1 (3.2)	2 (4.3)
Pulmonary edema	0	0	1 (3.2)	1 (2.2)
Tracheal obstruction	0	0	1 (3.2)	1 (2.2)

Conclusions and Discussion

- In this heavily pretreated (median 4 prior regimens) RM-SCHHN population, dalantercept monotherapy demonstrated modest dose-dependent activity with an overall disease control rate of 45% and mPFS of 1.4 months (95% CI 1.3-2.7).
  - 1 patient receiving 1.2 mg/kg achieved a PR (RR = 3.7%) and was on treatment for 9.7 months.
  - 1 patient receiving 1.2 mg/kg remains on study for 9 months.
- Despite the majority of patients receiving prior cetuximab (60.9%) in this study, the median OS (8.9 months, 95% CI: 5.8 – 11.1) compares favorably to the historical OS (5.9 months) in the SCCHN patient population receiving cetuximab after platinum based therapy.[7]
  - The median OS appeared to be dose dependent and was higher in the 1.2 mg/kg cohort (9.5 months, 95% CI: 5.8 – not reached) compared to the 0.6 mg/kg cohort (7.1 months, 95% CI: 4.6 – 10.5).
- Dalantercept was associated with an overall favorable safety profile in RM-SCCHN including a low bleeding risk that is relatively distinct from VEGF pathway inhibitors.[8,9]
- Given the disease control rate and overall favorable safety profile of dalantercept in RM-SCCHN, further study with dalantercept combinations should be considered.
- Study design details are at www.clinicaltrials.gov/show/NCT01458392.

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