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The DASH STUDY: A Phase 1b Study of Dalantercept Plus Sorafenib in Advanced Hepatocellular Carcinoma

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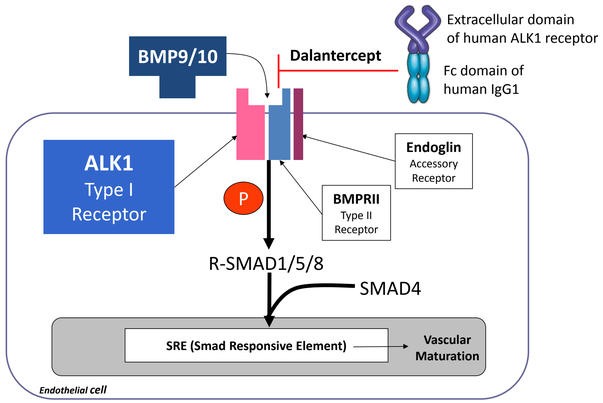
ALK1 Pathway Background

- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is selectively expressed on endothelial cells.[1]
- When activated by 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] [Figure 1]
- ALK1/BMP9 signaling promotes vascular stabilization and maturation, which are downstream from the proliferative stages of angiogenesis that are driven primarily by vascular endothelial growth factor (VEGF).[3]

Dalantercept Background

- Dalantercept is an ALK1 receptor fusion protein that binds BMP9 and 10 and acts as a ligand trap. [Figure 1]
- Dalantercept inhibits the maturation of vascular cells and impairs basic fibroblast growth factor (bFGF) and VEGF-A stimulated angiogenesis both *in vivo* and *in vitro*.[4]
- In a variety of preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.[4,5,6]
- In a completed Phase 1 study in thirty-seven subjects with advanced solid tumors, dalantercept monotherapy demonstrated anti-tumor activity. The safety profile was generally non-overlapping with VEGFR TKIs as the most common toxicities included fatigue, peripheral edema, and anemia.[7]

Figure 1: ALK1/BMP9/BMP10 Signaling Pathway



BEL-7402 HCC Xenograft Tumor Models

- The BEL-7402 cell line is derived from a primary human hepatocellular carcinoma (HCC) tumor from a patient with no prior chemotherapy. The cell line is AFP+ and has epithelial-like morphology.
- In a study of dalantercept monotherapy, dalantercept (15 mg/kg 3x week) completely inhibited tumor growth compared to vehicle. [Figure 2a]
- In a study of dalantercept (10 mg/kg 2x week) in combination with sorafenib, a multi-kinase and vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) (5 to 15 mg/kg QD), there was additive tumor growth inhibition, compared to either agent alone. [Figure 2b]

Figure 2a: Dalantercept monotherapy inhibited BEL-7402 tumor growth

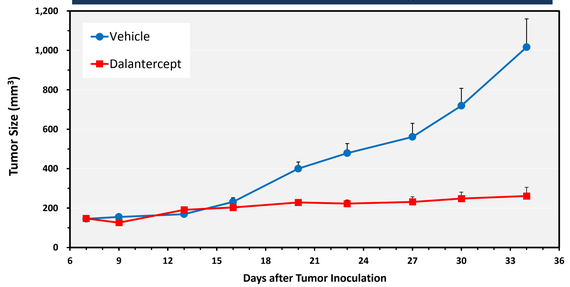
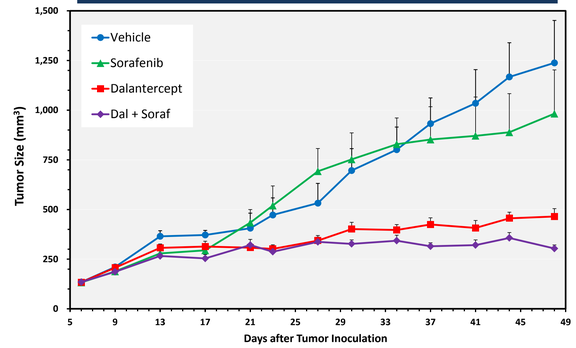


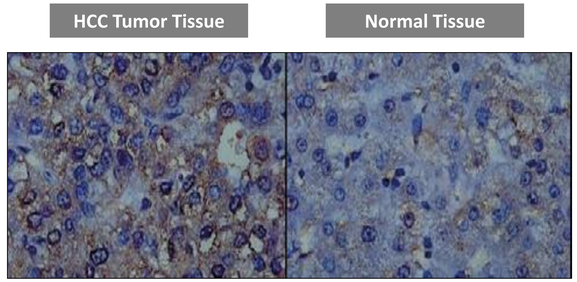
Figure 2b: Additive tumor growth inhibition by treatment with dalantercept + sorafenib



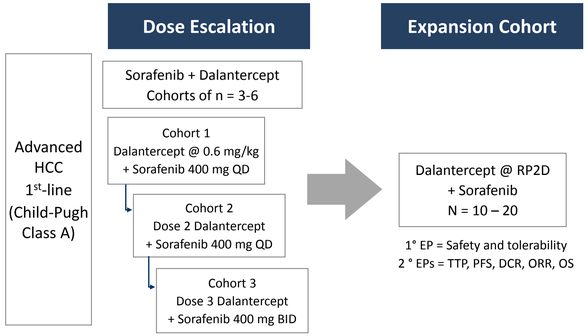
DASH Study Rationale

- BMP9 is overexpressed in HCC compared to normal hepatocytes.[8] [Figure 3]
- BMP9 is a proliferative and survival factor in HepG2 HCC cells.[8]
- ALK1-Fc (analogous to dalantercept) reduces proliferation rates in Huh7, Hep3B, and HepG2 cell lines.[8]
- Sorafenib is the standard therapy for advanced HCC.
- In the BEL-7402 preclinical model of HCC, simultaneous blockade of ALK1 and VEGF signaling with dalantercept and sorafenib resulted in additive tumor growth inhibition. [Figure 2b]

Figure 3: BMP9 Expression is Elevated in HCC



DASH Study Schema



Additional study design details are available at www.clinicaltrials.gov/show/NCT02024087

Methods

- A open label, multi-center, dose escalating, phase 1b study to evaluate dalantercept plus sorafenib in subjects with advanced HCC is ongoing.
- Primary endpoint: safety and tolerability of dalantercept plus sorafenib and determine the recommended Ph2 dose levels of the combination.
- Secondary endpoint: pharmacokinetic profile of the combination, preliminary activity including response rate using RECIST 1.1 and time to progression, and pharmacodynamic biomarkers in the serum and tissue including ALK1 and BMP9 expression by immunohistochemistry.
- The starting dose level of dalantercept is 0.6 mg/kg subcutaneously Q3W in combination with sorafenib 400 mg PO QD on a 21 day schedule.
- Sorafenib can be titrated to 400 mg BID at cycle 3 in cohorts 1 and 2.
- An expansion cohort will enroll 10-20 subjects at or below the maximum tolerated dose level.

Key Eligibility Criteria

- Histologically confirmed advanced HCC
- Child-Pugh Class A liver disease
- ECOG 0 – 1
- No prior systemic therapy in the advanced setting

Summary

- Dalantercept inhibits signaling through the ALK1 receptor by binding BMP9, and disrupts the formation of mature blood vessels through a mechanism that is distinct from the VEGF pathway.
- In a preclinical model of HCC, the combination of dalantercept and sorafenib demonstrated additive efficacy.
- The DASH study is evaluating the safety and tolerability of dalantercept and sorafenib in combination in patients with previously untreated advanced HCC.
- Enrollment to cohort 1 is complete and cohort 2 is open for enrollment.

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