**DART Study Part 1: Results of Dose Escalation and Expansion Cohorts of Dalantercept plus Axitinib in Advanced Renal Cell Carcinoma**

Martin H. Voss, Elizabeth R. Plimack, Brian I. Rini, Rupert S. Bhatt, Robert Altev, J. Thaddus Beck, Kristen M. Pappas, Dawn Wilson, Xiaohua Zhang, Chad E. Glasser, Matthew L. Sherman, Shuchi S. Pandya, Michael B. Atkin

**Background**
- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is selectively expressed on endothelial cells.
- When activated by ligands bone morphogenetic protein 9 (BMP9) and 10 (BMP10), ALK1 acts in a paracrine manner to stimulate vascular proliferation and maturation which are downstream from the proangiogenic steps of angiogenesis and which are involved in vascular morphogenesis.

**Study Design**
- This was a Phase I study to assess the safety and tolerability of dalantercept plus axitinib in advanced renal cell carcinoma patients who had 0 or 1 prior VEGFR TKI and ≤ 1 prior VEGFR inhibitor.
- Cohorts of 3–6 patients each received dalantercept (0.6, 0.9, or 1.2 mg/kg) subcutaneously (SC) and axitinib (5 mg BID) for up to 15 cycles.
- Imaging occurred every 2 cycles (8 weeks intervals) and was assessed by RECIST v1.1.
- A safety review team (SRT) reviewed safety data for all patients who received study drugs prior to each dose escalation and during the expansion.
- bulletin@tmdsl.com

**Study Results**
- In preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.
- When activated by ligands BMP9 and BMP10, ALK1 is a type I receptor of the TGFβ superfamily that is selectively expressed on endothelial cells. ALK1 acts in a paracrine manner to stimulate vascular proliferation and maturation which are downstream from the proangiogenic steps of angiogenesis and which are involved in vascular morphogenesis.
- Imaging occurred every 2 cycles (8 weeks intervals) and was assessed by RECIST v1.1.
- A safety review team (SRT) reviewed safety data for all patients who received study drugs prior to each dose escalation and during the expansion.
- Additional patients were enrolled in expansion cohorts at 0.9 and 1.2 mg/kg to further characterize safety and pharmacokinetics of the combination.
- Tumor response was assessed in all patients who received study drugs, and had at least 1 post-treatment scan.
- PFS was assessed for all patients who received study drugs.

**Durable Partial Response in 4th Line Patient**
- Patient progressed on 3 prior therapies: sorafenib (9 months), temsirolimus (1 month), and bevacizumab (2 weeks).
- Patient remains on dalantercept 0.9 mg/kg and axitinib 5 mg BID at 22 months post enrollment.

**Conclusions and Discussion**
In this pretreated advanced RCC population, combination of dalantercept and axitinib was well tolerated with a generally non-overlapping safety profile.
- The dose level was selected as RP2D for Part 2.
- The combination of dalantercept and axitinib was associated with clinically meaningful activity including partial responses (PR) and prolonged disease control (PD) in 1 patient to 3 prior lines of therapy. Dalantercept plus axitinib showed clinical safety in all patients previously treated with checkpoint inhibitors (n=3; 2 with PR and 1 with SD).
- The primary median PD of 2.8 months in all dose levels showed clinical efficacy comparable favorably to the historical mPFS with axitinib of 4.8 months in a VEGFR TKI pre-treated advanced RCC population.
- In Part 1 of the DART study, patients are randomized 1:1 to dalantercept plus axitinib vs. placebo plus axitinib (see Poster TPS4583).
- Part 2 of the DART study is currently recruiting patients who have received 1 prior mTOR inhibitor and/or any number of immune therapies.

**References**