The DART Study: Part 1 results of dalantercept plus axitinib dose escalation and expansion cohorts in advanced RCC

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Presented at the Genitourinary Cancers Symposium
Learning Objectives

After reading and reviewing this material, the participant should be able to:

• Distinguish the role of the ALK1 pathway from the VEGF pathway in the regulation of angiogenesis
• Describe the complementary action of dalantercept with VEGF targeted therapy in advanced RCC
• Assess the preliminary safety and activity of dalantercept plus axitinib from the open-label, dose-escalating cohorts in Part 1 of the DART study
• Describe the design and objectives of the randomized, placebo controlled Part 2 of the DART study

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ALK1: Novel Target in Angiogenesis

- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is selectively expressed on activated endothelial cells.
- ALK1 binds ligands, bone morphogenetic protein 9 (BMP9) and 10 (BMP10), and promotes vascular maturation and stabilization, which occur in later stages of angiogenesis subsequent to those regulated by VEGF.
- Inherited mutations in the ALK1 receptor result in hereditary hemorrhagic telangiectasia (HHT-2) which is characterized by a vascular dysplastic syndrome.

Shi Y, Massague J. Cell 2003;113:685-700
Oh SP, et al. Proc Natl Acad Sci USA 2000;97:2626-31
Dalantercept

- Dalantercept is an ALK1 receptor-Fc fusion protein that binds with high affinity to BMP9 and BMP10 and thereby acts as a ligand trap.
- Dalantercept inhibits the maturation of vascular cells and impairs VEGF-A and basic fibroblast growth factor (bFGF) stimulated angiogenesis both in vivo and in vitro.
- In preclinical models, dalantercept displays potent antitumor activity accompanied by decreased tumor vascularity in a variety of tumor models including RCC.

Dalantercept and ALK1 Signaling

- BMP9/10
- ALK1 Type I Receptor
- BMPRII Type II Receptor
- R-SMAD1/5/8
- SMAD4
- SRE (Smad Responsive Element)
- Vascular Maturation

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Dalantercept Monotherapy Phase 1 Summary

- 37 patients with variety of solid tumors, refractory to standard therapies
- Toxicities of fluid overload and anemia were seen at dose levels ≥ 1.6 mg/kg
  - Dependent edema was responsive to diuretics
- Non-overlapping toxicities with VEGF targeted drugs
  - Hypertension, proteinuria, hand-foot syndrome, and thromboembolic events were not reported
- Single agent activity observed
  - 3% PR, 45% SD
  - Prolonged stable disease (≥ 12 weeks) in 8 (27.6%) patients

DART Study Rationale

• The efficacy of anti-VEGF therapies in RCC is limited in duration
• Based on *in vivo* data, dalantercept may enhance and prolong the activity of agents that target the VEGF pathway in advanced RCC
• In multiple completed studies in patients with solid tumors, the expected side effect profile of dalantercept appears to be non-overlapping with the VEGFR TKI profile
Additive Efficacy of Dalantercept plus VEGFR TKI in RCC Xenograft Models

DART: Part 1 Study Schema

Open-Label, Dose Selection (n = 29)
Primary Endpoints: Safety, PK, RP2D
Secondary Endpoints: PFS, ORR, exploratory PD biomarkers in archived tissue and serum

Advanced RCC
≥ 1 prior VEGFR TKI, ≤ 3 lines of prior therapy

Dose-Escalation

Axitinib 5 mg BID + Dalantercept (0.6 mg/kg) (n = 6)

Axitinib 5 mg BID + Dalantercept (0.9 mg/kg) (n = 4)

Axitinib 5 mg BID + Dalantercept (1.2 mg/kg) (n = 5)

Expansion

Axitinib 5 mg BID + Dalantercept 0.9 mg/kg (n = 5)
1.2 mg/kg (n = 9)

Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study
Key Eligibility Criteria

• Predominantly clear cell advanced RCC
• Progression on at least 1 VEGFR TKI
  – Inclusive of adjuvant therapy
• No more than 3 prior lines of therapy
• Treated, stable CNS disease permitted
• ECOG performance status: 0 – 1
## Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>0.6 mg/kg (N = 6)</th>
<th>0.9 mg/kg (N = 9)</th>
<th>1.2 mg/kg (N = 14)</th>
<th>Overall n (%), (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5</td>
<td>7</td>
<td>11</td>
<td>23 (79.3)</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>3</td>
<td>5</td>
<td>7</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>3</td>
<td>4</td>
<td>7</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>1 site of disease ≥ 2 sites</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>9</td>
<td>11</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>MSKCC favorable</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>MSKCC intermediate</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>1 prior therapy ≥ 2 prior therapies</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7</td>
<td>7</td>
<td>18 (62.1)</td>
</tr>
<tr>
<td>Prior VEGFR TKI</td>
<td>6</td>
<td>9</td>
<td>14</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>Prior mTOR inhibitor</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Prior checkpoint inhibitor</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Prior other (bev, IL-2)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4 (13.8)</td>
</tr>
</tbody>
</table>
Safety Summary

• As of Jan 16, 2015, a total of 29 patients were enrolled
  • 15 patients were enrolled in Part 1 dose escalation cohorts (6 at 0.6 mg/kg, 4 at 0.9 mg/kg, and 5 at 1.2 mg/kg)
  • 1.2 mg/kg dose level was expanded to include 9 additional patients  
    – More edema events were reported compared to 0.6 and 0.9mg/kg dose levels
  • SRT recommended expanding the 0.9 mg/kg dose level with 5 additional patients
  • The 0.9 mg/kg dose level was overall well-tolerated with fewer edema related adverse events and was selected as the recommended phase 2 dose level for Part 2
  • Adverse event profile of both agents consistent with single agent experience
  • There were no grade 4/5 drug related adverse events

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## Adverse Events of Interest

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.6 mg/kg (N=6)</th>
<th>0.9 mg/kg (N=9)</th>
<th>1.2 mg/kg (N=14)</th>
<th>Overall (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
<td>6 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (66.7)</td>
<td>1 (16.7)</td>
<td>6 (66.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (33.3)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1 (16.7)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>0</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>0</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Note: there were no grade 4/5 drug related adverse events

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Laboratory Adverse Events of Interest

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>0.6 mg/kg (N=6)</th>
<th>0.9 mg/kg (N=9)</th>
<th>1.2 mg/kg (N=14)</th>
<th>Overall (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
<td>All grades n (%)</td>
<td>Grade = 3* n (%)</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>1 (16.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: there were no grade 4/5 lab adverse events*
# Disease Response and Preliminary PFS Analysis

<table>
<thead>
<tr>
<th>Response</th>
<th>0.6 mg/kg (N = 6)</th>
<th>0.9 mg/kg (N = 9)</th>
<th>1.2 mg/kg (N = 13)</th>
<th>Overall N = 28 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>2</td>
<td>6</td>
<td>9</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Disease Control Rate ≥ 8 cycles (~ 6 months)</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.5</td>
<td>NR</td>
<td>6.9</td>
<td>8.3 (4.1, NR)</td>
</tr>
</tbody>
</table>

Note: 1 patient not evaluable based upon ineligibility

NR = not reached
Best Overall Response and Duration of Treatment

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*Active on therapy

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Duration of Treatment (Months)

-100% -80% -60% -40% -20% 0% 20% 40% 60%

Maximum % Decrease (%Change from Baseline)

Best Overall Response

- PR
- SD
- PD

* Active on therapy
Durable Partial Response in 4th Line Patient

Dalantercept plus axitinib (20+ months): > 80% tumor regression in liver

6/6/13: Pre-treatment, left and right hepatic disease
7/22/13: Partial response after 2 cycles
7/29/14: Ongoing partial response > 1 year, disappearance of left and right inferior lesions, residual 1.2 cm in liver dome

Progressed on 3 prior therapies: 1st line sunitinib (8.9 months), temsirolimus (1.5 months), and bevacizumab (< 2 weeks)
Summary

- Dalantercept is a novel anti-angiogenic inhibitor of the ALK1 pathway and may complement the activity of VEGF pathway inhibitors in RCC
- Dalantercept plus axitinib is well tolerated in pre-treated advanced RCC patients
- Dalantercept plus axitinib is associated with clinically meaningful activity including an ORR of 25% and preliminary median PFS of 8.3 months for all three dose levels combined
- Part 2 of the DART study randomizes patients to dalantercept plus axitinib or placebo plus axitinib and is currently enrolling at approximately 50 centers in the US
DART: Part 2 Study Schema

Randomized, Double-Blind, Placebo-Controlled (N = 130)

Primary Endpoint: PFS
Secondary Endpoints: ORR, OS, Safety, PK, exploratory PD biomarkers

Advanced RCC
1 prior VEGFR TKI, may have also had 1 mTOR inhibitor and/or any prior immune therapy

Randomization

Dalantercept (0.9 mg/kg) + Axitinib (n = 65)

Placebo + Axitinib (n = 65)

NCT01727336

Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study

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Acknowledgements

• Patients and their families
• The DART Study investigators
• Research nurses and study teams
• Sponsor: Acceleron Pharma