Acceleron Drug Discovery Platform

*Targeting TGF-β superfamily yields robust pipeline of protein therapeutics*

TGF-β superfamily regulates the growth and repair of cells and tissues

- **TGF-β Family**
  - 30 ligands
  - 12 receptors
  - 10 ligand traps

- **in vivo Pharmacology**
- **Cell Biology**
- **Internal GMP Manufacturing Facility**
- **Protein Engineering**

Acceleron has unique knowledge of how to optimally design therapeutic candidates to regulate different cell types

- **Red Blood Cells** (Luspatercept)
- **Bone** (Sotatercept)
- **Vasculature** (Dalantercept)
- **Muscle** (ACE-083, ACE-2494, ACE-3891)
Building One of the Industry’s Most Robust Pipelines

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luspatercept – MDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luspatercept – Thalassemia</td>
<td></td>
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<tr>
<td>Sotatercept – CKD</td>
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<tr>
<td>Sotatercept – Myelofibrosis</td>
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<tr>
<td>Sotatercept – Myeloma</td>
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<tr>
<td>Sotatercept – DBA</td>
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<tr>
<td>Dalantercept – RCC</td>
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<tr>
<td>Dalantercept – HCC</td>
<td></td>
<td></td>
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<tr>
<td>ACE-083 – FSHD</td>
<td></td>
<td></td>
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<tr>
<td>ACE-2494</td>
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<td></td>
<td></td>
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<tr>
<td>ACE-3891</td>
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<tr>
<td>ACE-2798</td>
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<td></td>
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<tr>
<td>ACE-2536</td>
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<td></td>
<td></td>
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<tr>
<td>ACE-2395</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-1332</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Four internally discovered molecules in the clinic
- Phase 3 studies in MDS and beta-thalassemia started in 2015
- Fifth molecule expected to enter the clinic in 2016
- Several molecules expected to enter the clinic shortly thereafter
Dalantercept (ACE-041)

Novel Anti-Angiogenesis Agent Targeting the Activin Receptor-Like Kinase 1 (ALK1) / BMP9 Pathway
Dalantercept – ALK1-Fc Fusion Protein Binds BMP9

- Dalantercept is a soluble ALK1 receptor-Fc fusion protein
- Dalantercept binds BMP9 and BMP10 with high affinity, and thereby inhibits signaling via the ALK1 receptor
- Administered via SC injection q3 weeks in Phase 1 and 2 studies

Dalantercept
Soluble, Recombinant ALK1-Fc Fusion Protein

Note: **RAP-041** is the murine ortholog (murine ALK1: murine Fc) of ACE-041, that is used in studies in rodent models

Definitions: ALK1 = activin receptor-like kinase 1; BMP9 = bone morphogenetic protein 9
Dalantercept and ALK1 Signaling

- BMP9/10
- ALK1 (Type I Receptor)
- BMPRII (Type II Receptor)
- Endoglin (Accessory Receptor)

Dalantercept

R-SMAD1/5/8

- SMAD4

SRE (Smad Responsive Element)

Id1, Id3 and others: vascular maturation

Endothelial cell
Dalantercept – Novel Inhibitor of the ALK1 Pathway

- ALK1 is selectively expressed on vascular and lymphatic endothelial cells
- In mice, homozygous deletion of ALK1 (−/−) results in severe vascular defects and embryonic lethality
- Patients with hereditary hemorrhagic telangiectasia (HHT-2) have lost expression of a single ALK1 gene resulting in defective vasculature and a reduced ability to form a capillary bed following injury

Loss of Capillary Beds in Murine RCC Tumor Following ALK-1 Inhibition (Dalantercept)

Imaging of Vasculature with μCT Imaging of MicroFil-Perfused Tumor Samples

Vehicle

Dalantercept
Tumor secretes pro-angiogenic factors e.g. VEGF

Step 1
- VEGF induces EC proliferation

Step 2
- ALK1 mediates vessel maturation and pericyte coverage

Concept: Inhibit sequential steps in pathway to generate synergistic inhibition
ALK1 is Required for Tumor Angiogenesis and Growth

Genetic evidence in a spontaneous model of pancreatic islet cell cancer (RIP1-Tag2)

- RIP1-Tag2 mice spontaneously develop highly vascularized, pancreatic islet cell tumors
- ALK1 (+/-) mice crossed with RIP1-Tag2 mice develop fewer and smaller tumors with decreased vascularity

Dalantercept Enhanced Anti-Tumor Effects of VEGFR TKI in RCC

Dalantercept/Sunitinib Combination
Exceeds Activity of Either Alone
(Mouse Model of Renal Cell Carcinoma (A498))

Dalantercept/Sunitinib Combination
Slows Tumor Growth in a Sunitinib Resistant Model
(Mouse Model of Renal Cell Carcinoma (786O))

Collaboration with Drs. Wang, Bhatt, Mier, Atkins; Beth Israel Deaconess, Boston
Dalantercept Additive Efficacy with Chemotherapies

**MMTV-PyMT Breast Cancer Adenocarcinoma**

Monotherapy and combination with docetaxel

**RPMI2650 Squamous Carcinoma of Head and Neck**

Monotherapy and combination with cisplatin

Mean Tumor Volumes (mm$^3$)

Study Weeks


Additive Efficacy with Chemotherapies
Dalantarcept (ACE-041)

Clinical Program and Phase 1 Study Overview
## Completed/Ongoing Dalantercept Phase 1 and 2 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase 1</th>
<th>Phase 2 SCCHN</th>
<th>Phase 2 Endometrial (GOG/NRG-sponsored)</th>
<th>Phase 2 Ovarian (GOG/NRG-sponsored)</th>
<th>Phase 1b HCC</th>
<th>Phase 2 HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Recurrent or metastatic solid tumors</td>
<td>Recurrent or metastatic</td>
<td>Persistent or recurrent</td>
<td>Persistent or recurrent</td>
<td>Metastatic, first-line</td>
<td>Metastatic, second-line (failed either sunitinib or pazopanib)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Dalantercept monotherapy</td>
<td>Dalantercept monotherapy</td>
<td>Dalantercept monotherapy</td>
<td>Dalantercept monotherapy</td>
<td>Sorafenib + dalantercept</td>
<td>Axitinib +/- dalantercept</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Dose-escalation and expansion</td>
<td>Open-label, two-dose cohorts</td>
<td>Single-arm, open-label, two-stage study</td>
<td>Single-arm, open-label, two-stage study</td>
<td>Open-label, dose escalation and expansion</td>
<td>Part 1: dose-escalation and expansion, Part 2: randomized Ph2</td>
</tr>
<tr>
<td><strong>Study N</strong></td>
<td>37</td>
<td>46</td>
<td>28</td>
<td>30</td>
<td>21</td>
<td>Part 1: 29, Part 2: 130</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>Completed</td>
<td>Dose escalation completed, expansion ongoing</td>
<td>Dose escalation completed, Part 2 enrolling</td>
</tr>
</tbody>
</table>
Phase 1 Study Overview

- 37 patients with variety of solid tumors, refractory to standard therapies
- Dalantercept at 7 dose levels from 0.1 to 4.8 mg/kg
- Dose limiting toxicities of fluid overload and anemia
- Non-overlapping toxicities with VEGF targeted drugs
  - Hypertension, proteinuria, thrombo-embolic events, and wound-healing complications were not observed
- PK: $C_{\text{max}}$ and AUC demonstrated a dose linear relationship
  - $T_{1/2}$ 14-18 days, $T_{\text{max}}$ 4-7 days
- Single agent activity observed
  - 3% PR (n=1)
  - 45% SD (n=13)
  - Prolonged stable disease (≥12 weeks) in 8 patients
  - Responses correlated with PD effect seen by FDG-PET and DCE-MRI
## Phase 1 Summary of Patients with Disease Control

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Dose (mg/kg)</th>
<th>Tx Period (weeks)</th>
<th>RECIST Best Response</th>
<th>Max % Change</th>
<th>Lesion Size (CT)</th>
<th>FDG-PET SUV</th>
<th>DCE-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>605</td>
<td>NSCLC (Sq)</td>
<td>3.2 to 1.6</td>
<td>90</td>
<td>SD</td>
<td>-19.7</td>
<td>-29.9</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>807</td>
<td>SCCHN</td>
<td>1.6</td>
<td>33</td>
<td>SD</td>
<td>-28.9</td>
<td>-19.3</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>303</td>
<td>SCCHN</td>
<td>0.4</td>
<td>30</td>
<td>PR</td>
<td>-32.5</td>
<td>-44.4</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>702</td>
<td>Colorectal</td>
<td>4.8 to 1.6</td>
<td>27</td>
<td>SD</td>
<td>-9.4</td>
<td>-2.4</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>302</td>
<td>NSCLC (Non-Sq)</td>
<td>0.4</td>
<td>24</td>
<td>SD</td>
<td>-2.4</td>
<td>-22.7</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>811</td>
<td>Granulosa Cell</td>
<td>1.6</td>
<td>24</td>
<td>SD</td>
<td>5.2</td>
<td>N/A</td>
<td>-39.9</td>
<td></td>
</tr>
<tr>
<td>203</td>
<td>Carcinoid</td>
<td>0.2</td>
<td>18</td>
<td>SD</td>
<td>-3.2</td>
<td>-27.1</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>802</td>
<td>Small Bowel</td>
<td>1.6</td>
<td>18</td>
<td>SD</td>
<td>1.6</td>
<td>-52.8</td>
<td>-29.5</td>
<td></td>
</tr>
<tr>
<td>805</td>
<td>NSCLC (Sq)</td>
<td>1.6</td>
<td>18</td>
<td>SD</td>
<td>2.8</td>
<td>-40.6</td>
<td>-30.3</td>
<td></td>
</tr>
</tbody>
</table>
Effect of ACE-041 Treatment is Consistent with Phenotype Observed in Genetic ALK1 Deficiency HHT
Dalantercept (ACE-041)

Phase 2 RCC Study (DART)
Dalantercept in Renal Cell Carcinoma (RCC)

- Renal cell carcinoma is a highly angiogenic tumor
- Anti-angiogenesis therapies have shown and continue to show robust efficacy in RCC
- Substantial opportunity for a new drug to build upon, not compete with, large established base of numerous approved VEGF path inhibitors
## Phase 2 DART Study Schema – Advanced RCC

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label, dose escalation (N=29)</td>
<td>Randomized, double-blind, placebo-controlled (N=130)</td>
</tr>
<tr>
<td>≥1 prior VEGFR TKI</td>
<td>1 prior VEGF pathway inhibitor, may have also had 1 mTOR inhibitor and/or any prior immune therapy</td>
</tr>
<tr>
<td>≤3 lines of prior therapies</td>
<td></td>
</tr>
</tbody>
</table>

Primary Endpoints: Safety, PK and RP2D  
Secondary Endpoints: PFS, ORR, DCR (PR+SD), biomarkers

### 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

- **Randomization**
  - Axitinib 5 mg BID + Dalantercept (0.9 mg/kg) (n = 65)
  - Axitinib 5 mg BID + Placebo (n = 65)

Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study.
### Phase 2, Part 1 Adverse Events Regardless of Attribution

**As of June 3, 2015 (Presented at KCA, Nov 2015)**

<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>Grade 1-3 n (%)</td>
<td>Grade 3* n (%)</td>
<td>Grade 1-3 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>10 (71.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (66.7)</td>
<td>2 (33.3)</td>
<td>5 (55.6)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>4 (66.7)</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>0</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (50.0)</td>
<td>0</td>
<td>2 (22.2)</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>Nausea</td>
<td>2 (33.3)</td>
<td>0</td>
<td>5 (55.6)</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>Arthralgia</td>
<td>1 (16.7)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine increase</td>
<td>0</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (16.7)</td>
<td>0</td>
<td>4 (44.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (16.7)</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>2 (33.3)</td>
<td>0</td>
<td>1 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (16.7)</td>
<td>0</td>
<td>2 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (33.3)</td>
<td>0</td>
<td>3 (33.3)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (16.7)</td>
<td>0</td>
<td>3 (33.3)</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>
</tbody>
</table>

*No grade 4/5 related adverse events

**Note:** the rates of AEs with Dalantercept + axitinib treatment were consistent with the rates in the axitinib label.
## Phase 2, Part 1 Response Rates (RECIST v1.1)

*As of June 3, 2015 (Presented at KCA, Nov 2015)*

<table>
<thead>
<tr>
<th>Endpoint</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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response, n (%)</td>
<td>2 (33.3)</td>
<td>3 (33.3)</td>
<td>2 (15.4)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Stable Disease, n (%)</td>
<td>2 (33.3)</td>
<td>6 (66.7)</td>
<td>9 (69.2)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Progressive Disease, n (%)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>2 (15.4)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>DCR ≥ 8 cycles (~6 months), n (%)</td>
<td>3 (50.0)</td>
<td>6 (66.7)</td>
<td>7 (53.8)</td>
<td>16 (57.1)</td>
</tr>
</tbody>
</table>

*Note: 1 patient not evaluable for response based upon ineligibility*
Phase 2, Part 1 Best Overall Response (RECIST v1.1)
As of June 3, 2015 (Presented at KCA, Nov 2015)

Best Overall Response

- **PR**
- **SD**
- **PD**

*Active on Therapy*

Note: Duration of treatment listed in weeks above and below bars
Phase 2, Part 1 Treatment Duration

As of June 3, 2015 (Presented at KCA, Nov 2015)
## Phase 2, Part 1 Survival Analyses

*As of June 3, 2015 (Presented at KCA, Nov 2015)*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>0.9 mg/kg (N=9)</th>
<th>Overall (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Progression Free Survival (months)</td>
<td>Not reached</td>
<td>8.3</td>
</tr>
<tr>
<td>12 month progression free survival rate* (%)</td>
<td>50%</td>
<td>39%</td>
</tr>
<tr>
<td>12 month overall survival rate* (%)</td>
<td>89%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*Analysis includes all patients who received study drugs (N=29)*  
*Assessed by Kaplan-Meier Method*
Progression-Free Survival

Phase 2, Part 1 Median PFS in RCC vs. Competition

11 months for Sunitinib (1)

8.3 months for Dalantercept plus Axitinib

4.8 mos for Axitinib (2), 4.6 mos for Nivolumab (3)

3.6 months Sorafenib (4, 5)

Median PFS vs. Competition

Patients ≥ 1 Prior VEGFR TKI (2nd Line+ RCC Studies)

Dalantercept plus axitinib data demonstrate proof of concept

- Dalantercept + Axitinib (DART Part 1)*: 8.3 months
- Cabozantinib (METEOR): 7.4 months
- Axitinib (AXIS)**: 4.8 months
- Nivolumab (CheckMate-025)*: 4.6 months
- Everolimus (CheckMate-025)*: 4.4 months
- Everolimus (METEOR): 3.8 months
- Sorafenib (AXIS): 3.4 months

* PFS analyses were based on investigator assessment of radiologic progression (i.e. no central read)
** PFS in patients who received prior sunitinib

Dalantercept in combination with axitinib in Part 1 of the DART study produced clinical outcomes that exceed historical axitinib monotherapy results.

Dalantercept safety profile was generally non-overlapping with VEGFR TKI and well-tolerated.

Development strategy is to combine with VEGF path inhibitors to improve outcomes beyond VEGFR TKI monotherapy.

Enrollment ongoing in Part 2 of the DART study (130 patient, randomized, double-blind, placebo-controlled trial).

PFS data from Part 2 of the DART study projected to be available end of 2016.
Dalantercept (ACE-041)

Indications and Combination Regimens of Interest
Combination Regimens and Indications to Consider

- **Dalantercept + VEGFR TKIs**
  - Dal + pazopanib, sunitinib or cabozantinib in mRCC
  - Dal + sunitinib in pancreatic neuroendocrine tumors
  - Dal + pazopanib in soft tissue sarcoma
  - Dal + cabozantinib or lenvatinib in medullary thyroid cancer
  - Dal + regorafenib in mCRC

- **Dalantercept + chemotherapy**
  - Dalantercept + chemo in triple-negative breast cancer

- **Dalantercept + Immune Oncology Therapies**
  - Dal + nivolumab in mRCC
  - Dal + atezolizumab + bevacizumab in mRCC

- **Dalantercept + bevacizumab +/- chemotherapy**
  - Dal + bevacizumab + taxane in platinum-resistant ovarian
  - Dal + bev + chemo in mCRC
  - Dal + bev + chemo in NSCLC
  - Dal + bev in GBM
  - Dal + ramucirumab +/- chemo in gastric or GEJ adenocarcinoma