A first-in-human Phase 1 study of the anti-cancer stem cell agent OMP-54F28 (FZD8-Fc), a decoy receptor for WNT ligands, in patients with advanced solid tumors

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Presented by: Antonio Jimeno MD PhD, University of Colorado, Aurora, CO
Therapeutic promise of targeting CSCs

CSCs have been implicated in tumor progression, recurrence, and metastasis

Frank et al., J Clin Inv 120:41-50 (2010)

CSC = cancer stem cell

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The WNT pathway

WNT as an anti-cancer stem cell target

- Cancer Stem Cells (CSCs) may be responsible for resistance to anti-cancer therapies
- Activated WNT pathway is strongly associated with CSCs
- OMP-54F28 (FZD8-Fc)
  - Recombinant fusion protein (immunoadhesin)
    - Extracellular ligand binding domain of human frizzled (FZD) 8 receptor + human IgG1 Fc fragment
- Potent antagonist of WNT signaling
- Single-agent and combination efficacy in many patient-derived xenograft models
- Promotes differentiation
- Inhibits metastatic growth
- Reduces CSC frequency

OMP-54F28 structure

Extracellular WNT binding domain of FZD8
Immunoglobulin Fc domain

WNT-activated β-catenin reporter gene assay
Single-agent activity of OMP-54F28 in pancreatic cancer PDX model

PN4: adenocarcinoma of pancreas
FZD8-Fc (OMP-54F28): 15 mg/kg, weekly
PDX = patient-derived xenograft

Reduction in CD44+ frequency

Increase in Mucin-producing cells

Control Ab
FZD8-Fc

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OMP-54F28 reduces tumor-initiating cell frequency in pancreatic cancer PDX model

PN4: adenocarcinoma of pancreas
FZD8-Fc (OMP-54F28): 15 mg/kg, weekly
Gemcitabine: 10 mg/kg, weekly
PDX = patient-derived xenograft
CSC = cancer stem cell

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OMP-54F28 and bone biology

- WNT pathway fosters bone formation and inhibits bone resorption
- Phase 1a for anti-Frizzled antibody vantictumab:
  - Grade 3 compression fracture after minor fall on Day 110
- Increases in bone turnover marker \( \beta \)-CTX reflect bone loss
- Zoledronic acid (ZA) protects from OMP-54F28 effects on bone in preclinical in vivo models
- \( \beta \)-CTX monitoring and ZA administration in case of \( \beta \)-CTX doubling were incorporated into the OMP-54F28 Phase 1 trial

Control 54F28 54F28 + ZA

ZA (100 µg/kg) 54F28 (20 mg/kg) 2 weeks 2 weeks

Analysis

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Study objectives

• Primary objectives
  – Safety of OMP-54F28 in patients with previously treated solid tumors

• Secondary objectives
  – Pharmacokinetics of OMP-54F28
  – Immunogenicity of OMP-54F28
  – Preliminary efficacy of OMP-54F28

• Exploratory objectives
  – Biomarkers
    – Blood RNA, hair follicles
    – Tumor (optional)
Study design

OMP-54F28 intravenously every 3 weeks (until progressive disease, unacceptable toxicity or withdrawal of consent)

1 mg/kg

2.5 mg/kg

5 mg/kg

10 mg/kg

15 mg/kg

20 mg/kg

Every 7 days
- Safety assessments, including standard laboratories

Every 28 days
- Bone turnover markers

Every 56 days
- Tumor assessments and DEXA scans

Advanced solid tumors
3+3 design

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Key eligibility criteria

• Inclusion Criteria
  – Age ≥18 years
  – Histologically confirmed, metastatic or unresectable malignancy
  – No remaining standard therapy options of proven benefit
  – ECOG PS 0-1
  – Adequate organ and marrow function

• Exclusion criteria
  – Brain metastases
  – Bleeding disorder or coagulopathy
  – Therapeutic anticoagulation
  – Heart failure (NY Heart Association Classification III or IV)
  – T-score ≤ -2.5 (diagnostic for osteoporosis)
  – Bone metastases AND prior pathologic fracture, need for orthopedic intervention or NOT receiving a bisphosphonate or denosumab
  – Glucocorticoids for ≥4 weeks (daily dose equivalent of ≥5 mg oral prednisone)
  – β-CTX >1000 pg/mL (bone turnover marker)
Dose-limiting toxicity (DLT) criteria

• Assessment window
  – From 1st dose to 28 days after 1st dose

• Type of adverse event (AE)
  – Any related Grade ≥3 adverse event
    – Except for Grade 3 infusion reaction that resolves within 24 hours

Version 4.02 of Common Toxicity Criteria for Adverse Events
### Patient characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>26</td>
</tr>
<tr>
<td><strong>Median age, yr (range)</strong></td>
<td>54 (26-79)</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td>17 (65%)</td>
</tr>
<tr>
<td><strong>ECOG score</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>1</td>
<td>15 (58%)</td>
</tr>
<tr>
<td><strong>Number of prior systemic therapies, median (range)</strong></td>
<td>3 (0-9)</td>
</tr>
<tr>
<td><strong>Tumor types</strong></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Desmoid tumor</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (41%)</td>
</tr>
</tbody>
</table>
Dose escalation, DLTs and Grade ≥3 AEs

- 20 mg/kg q3w as highest dose level
  - Estimated to be double the target efficacious dose
- No DLTs encountered
- Maximum tolerated dose not determined
- One related Grade ≥3 AE total
  - Grade 3 increase in serum phosphorus (20 mg/kg)
## Related Grade 1 and 2 adverse events (≥10%)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>1 (n=3)</th>
<th>2 (n=3)</th>
<th>3 (n=3)</th>
<th>4 (n=5)</th>
<th>5 (n=3)</th>
<th>6 (n=3)</th>
<th>7 (n=6)</th>
<th>Total (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level (mg/kg, q3w)</td>
<td>0.5</td>
<td>1</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td><strong>10 (38.5%)</strong></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td><strong>9 (34.6%)</strong></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td><strong>9 (34.6%)</strong></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td><strong>8 (30.8%)</strong></td>
</tr>
<tr>
<td>Alopecia</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td><strong>5 (19.2%)</strong></td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td><strong>5 (19.2%)</strong></td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td><strong>4 (15.4%)</strong></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td><strong>4 (15.4%)</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
<tr>
<td>Nail disorder</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td><strong>3 (11.5%)</strong></td>
</tr>
</tbody>
</table>
OMP-54F28 and β-CTX doubling (6 of 26 patients)

- Return of β-CTX to baseline for all 5 patients treated with zoledronic acid (one patient * went to hospice)
- No significant changes in DEXA scans

Zoledronic acid administered

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Pharmacokinetics

- Linear PK between 2.5 and 20 mg/kg (clearance: 1.45 L/day)
- Terminal half life of 4.3 days (within linear range)
- The volume of distribution was larger than for typical antibody (due to lower MW)
  - 82 KDa without oligosaccharides, 96 KDa with oligosaccharides (IgG ~150 KDa)
- 2 of 26 patients with anti-drug antibodies (preliminary immunogenicity analysis)
  - Late-emerging, no impact on drug exposure
Pharmacodynamics
OMP-54F28 affects WNT-related gene expression patterns in hair follicles

- Decreased expression of WNT pathway target genes (e.g. LGR6, DKK1)
- Increased expression of differentiation genes (NRCAM)
- No significant changes in same genes for control subjects
Thyroid cancer
Non-squamous NSCLC
Time on study

Progressive disease as off-study reason, except 16 (patient decision), 23 (2nd β-CTX doubling) and 24 (adverse event)

As of 23 May 2014

Non-seminoma germ cell tumor
Basal cell carcinoma
Thyroid cancer
Non-squamous NSCLC
Desmoid tumor
Desmoid tumor
Renal cell carcinoma
Pancreatic cancer

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Patient 14 (desmoid tumor)

- 44 year-old male diagnosed in 2010 with chest wall tumor
- Resected with positive margins
- Relapsed in chest wall in April 2012
- Tumor increased from 3 to 5 cm over ~1 year (with observation)

2 April 2012
14 May 2013 Baseline
18 April 2014 C16
Patient 21 (non-seminoma germ cell tumor)

- 27 year-old male diagnosed in 2004 with lung and brain metastases
- Relapsed in lung and bone in 2011, as teratoma with adenocarcinoma differentiation
- Genetic testing showed beta-catenin exon 3 mutation (D32N)

1 April 2013 20 Sep 2013 26 Mar 2014
Baseline Cycle 8
Summary data for OMP-54F28

• First-in-class decoy receptor inhibiting WNT pathway and with anti-cancer stem cell properties
• Adverse events almost exclusively Grade 1 and 2
  • Dysgeusia, fatigue, muscle spasms and decreased appetite most common
• 20 mg/kg q3w was the highest dose level evaluated (no DLTs)
  • Twice the estimated target efficacious dose
  • One clinically significant Grade 2 bone event after 6 cycles
• β-CTX doubling in 6 of 26 patients, reversed with zoledronic acid in 5 of 5
• PD effects on hair follicles consistent with WNT pathway inhibition
• Several patients with prolonged stable disease
• Three Phase 1b studies are ongoing
  • Hepatocellular cancer (1st-line, with sorafenib)
  • Ovarian cancer (recurrent platinum-sensitive, with carboplatin + paclitaxel)
  • Pancreatic cancer (1st-line, with nab-paclitaxel + gemcitabine)

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