A Phase I study of PF-06647020, an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in patients with advanced cancers including heavily pretreated ovarian cancer (OVCA)

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Pfizer Oncology Early Clinical Development

World ADC Summit, 20 -22 Feb 2017
PTK7 (Protein Tyrosine Kinase 7)

- PTK7 is a catalytically inactive protein tyrosine kinase
  - Functions in developmental biology (Wnt signaling and planar cell polarity)
  - Over-expressed in variety of human cancers including ovarian, breast, colon, lung, gastric, esophageal and AML
    - Expression linked to poor prognosis in patients with TNBC and NSCLC
  - Enriched on cancer stem cells (CSCs), which may contribute to treatment resistance and relapse

Chen R et al, Cancer Res; 74 (10); 2892, 2014
PTK7-ADC: PF-06647020

- Conventional conjugation at cysteines
- Cleavable linker
- Membrane-permeable payload auristatin-0101

**Stemcentrx**

**TNBC PDX**

**NSCLC PDX**

**OVCA PDX**
Phase I Study Scheme for PF-06647020

**Part 1**
- RP2D/MTD
  - 0.2 mpk, Q3W
  - 0.5 mpk, Q3W
  - 1.25 mpk, Q3W
  - 2.1 mpk, Q3W
  - 2.8 mpk, Q3W

**Part 2**
- Multiple types of cancers; mono-Tx
- Arm 1: TNBC
  - M-H/H PTK7 expression pre-selection; N=22 pts
- Arm 2: NSCLC
  - M/H PTK7 expression pre-selection; N=20 pts
- Arm 3: OVCA
  - non-PTK7-selective, retrospective target expression/efficacy analysis; N=27 pts

**RP2D: 2.8 mg/kg, Q3W, 21-day/cycle**

PTK7, Q3W, IV, 21-day/cycle
- Advanced solid tumors
- No PTK7 expression pre-selection at baseline
Key Enrollment Criteria

Inclusion Criteria
• Patients with advanced/metastatic solid tumors resistant to standard therapy or for which no standard therapy is available (during dose expansion: OVCA, TNBC and NSCLC)
• 18 years or older
• ECOG performance status 0 or 1
• Adequate bone marrow, renal, liver and cardiac function
• Dose escalation: Measurable or non-measurable disease
• OVCA dose expansion: Platinum resistant/refractory with measurable or assessable according to the Gynecological Cancer Intergroup (GCIG, 2011)17 CA-125 criteria and require chemotherapy treatment

Exclusion Criteria
• Symptomatic brain metastases
• Active and clinically significant bacterial, fungal or viral infection
• Presence of Grade ≥2 peripheral neuropathy
• Previous high dose chemotherapy requiring stem cell rescue
### Treatment-Emergent Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade in ≥10% of Patients (All Doses, All Cycles, in Total N=76 Patients Treated)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEs</td>
<td>20 (26)</td>
<td>16 (21)</td>
<td>19 (25)</td>
<td>6 (8)</td>
<td>62 (82)</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (29)</td>
<td>13 (17)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>35 (46)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8 (11)</td>
<td>18 (24)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>26 (34)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (13)</td>
<td>10 (13)</td>
<td>4 (5)</td>
<td>0 (0)</td>
<td>24 (32)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (13)</td>
<td>10 (13)</td>
<td>3 (4)</td>
<td>0 (0)</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td>9 (12)</td>
<td>7 (9)</td>
<td>20 (26)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (7)</td>
<td>10 (13)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>17 (22)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6 (8)</td>
<td>7 (9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (9)</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (8)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>8 (11)</td>
</tr>
</tbody>
</table>

- Safety and tolerability assessed at increasing dose levels of PF-06647020 ranging between 0.2 mg/kg to 3.7 mg/kg
- DLTs reported in two patients at 3.7 mg/kg (G3 fatigue and G3 headache)
- G3 febrile neutropenia reported in 2 pts (2.6%) at 2.8 mg/kg
- Majority of common adverse events were Grade 1&2, they were self-limited and didn’t require intervention
(Data cutoff : May 31 2016)
PTK7-ADC Clinical Activity in OVCA: Best Change in Target Lesions from Baseline

### Best Overall Response by RECIST

<table>
<thead>
<tr>
<th>Response Type</th>
<th>OVCA (n=27)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable*</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>5</td>
<td>(4+1uPR)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Objective response rate (ORR)</td>
<td>27.3%</td>
<td>(13% - 48%)</td>
</tr>
</tbody>
</table>

- 5 patients not yet assessed for disease at the time of data cutoff (May 31 2016)
Complete Response in Ovarian Cancer

• 52 yo woman with advanced ovarian cancer (serous papillary carcinoma)
  • Previously treated with multiple lines of chemotherapies including carboplatin/taxol, cisplatin/gemcitabine, carboplatin/pegylated liposomal doxorubicin, and nab paclitaxel
PTK7-ADC Clinical Activity in OVCA: Time to and Duration of Response

Data cutoff: May 31 2016
PTK7-ADC Exposure and Reasons for Discontinuation in Patients with OVCA

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of exposure, wks</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6 (1-38)</td>
</tr>
<tr>
<td>No. of cycles received</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (1-13)</td>
</tr>
<tr>
<td>No. of dose reduction (2.8 → 2.1 mg/kg) (%)</td>
<td>1** (4%)</td>
</tr>
</tbody>
</table>

** Dose reduced after Cycle 1 due to G4 neutropenia

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>8 (29.6)</td>
</tr>
<tr>
<td>Adverse event*</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lack of clinical benefit</td>
<td>2 (7.2)</td>
</tr>
</tbody>
</table>

* Pulmonary embolism (unrelated to study drug)
PTK7-ADC Pharmacokinetics

Cycle 1 Mean (±SE) Serum Concentration-Time Profiles at 2.8 mg/kg Q3W

- At 2.8 mg/kg Q3W, the serum concentration-time profiles for PTK7 ADC and total antibody were comparable; the mean terminal half-lives for PTK7 ADC and total antibody were 2.8 and 3.5 days, respectively.
- Serum concentrations of Auristatin-0101 were substantially lower compared to those of PTK7 ADC and total antibody, terminal half-life was 2.9 days.
Retrospective Assessment of PTK7 Expression

*Validated PTK7 IHC LDT in one central CLIA-certified lab*

- PTK7 digital H-scores range from 1 to 198, with average H-score of 105 and median H-score of 116 (n=12)
- Partial Responder (PR) patients PTK7 H-scores range from 110 to 166, with an average H-score of 133 (n=4)
- Stable Disease (SD) patients PTK7 H-scores range from 43 to 154, with an average H-score of 88 (n=6)
- Progressive Disease (PD) patients PTK7 H-scores range from 1 to 198, with an average H-score of 99.5 (n=2)
PTK7 Expression in Tumor Stroma

PTK7 Expression by IHC

(Primary NSCLC)

HUVEC ex vivo Sprout Assay

Control

PTK7-ADC : 1 µg/mL

Damelin M et al, Sci Transl Med, 2017
PTK7 is Expressed on Dendritic Cells

Whole blood: Flow cytometry

PTK7

mDC
pDC

CD123
CD303
DNA

Primary NSCLC

Damenlin M et al, Sci Transl Med, 2017
Payload-Dependent Effects on ICD and DC Activation

Immunogenic Cell Death
Calreticulin at cell surface

Dendritic Cell Activation
CD80 surface expression

CT26 murine colon cancer cells
C57BL/6 murine bone marrow-derived cells

Doses:
0.1X 1X 10X of 2-day IC₅₀

Doses:
1000 0.05 nM

Damelin M et al, Sci Transl Med, 2017
ADC Increases Tumor-Infiltrating T-cells in PDX Models

Untreated control  
Her2-vc0101, 6mg/kg

H&E

CD8/nuclei

Damelin M et al, Sci Transl Med, 2017

4T1-8A6-3x; 24 hrs after Q4Dx2
Potential Synergy of PTK7-ADC in Combination with IO for Cancer Treatment?

• Emerging clinical data of PTK7-ADC
  • Acceptable safety profile and encouraging anti-tumor activity as a single agent therapy

• Stimulate anti-tumor immunity via tumor cells
  • Auristatin-0101 induces Immunogenic Cell Death (ICD)

• Stimulate anti-tumor immunity via dendritic cells
  • Auristatin-0101 activates dendritic cells
  • PTK7 is expressed on dendritic cells (mDC and pDC)

• Stimulate anti-tumor immunity via vasculature remodeling
  • Auristatin-0101 increases TIL infiltration
  • PTK7-ADC has anti-angiogenic activity, could promote TIL infiltration
Conclusions

• Encouraging clinical activity of PTK7-ADC as single agent treatment demonstrated in an ongoing Phase I study in patients with advanced cancers including heavily pretreated OVCA
• PF-06647020 has an acceptable and manageable safety profile
• Further clinical development of PTK7-ADC is being considered
Acknowledgements

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