Novel RCC Targets from Immuno-Oncology and Antibody-Drug Conjugates

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### Celldex Pipeline

<table>
<thead>
<tr>
<th>CANDIDATE</th>
<th>INDICATION</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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</thead>
<tbody>
<tr>
<td>Glembatumumab Vedotin (gpNMB)</td>
<td>Triple Negative Breast Cancer</td>
<td>METRIC Trial (registrational)</td>
<td>+/- Varililumab</td>
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<td></td>
<td>Metastatic Melanoma</td>
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<td>Uveal Melanoma</td>
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<td></td>
<td>Osteosarcoma</td>
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<tr>
<td></td>
<td>Squamous Cell Lung Cancer</td>
<td>(with PrECOG)</td>
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<td>Varililumab (CD27)</td>
<td>Multiple Solid Tumors (incl RCC)</td>
<td>+ Nivolumab (with BMS)</td>
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<td></td>
<td>Renal Cell Carcinoma</td>
<td>+ Sunitinib</td>
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<td></td>
<td>Multiple Solid Tumors (incl RCC)</td>
<td>+ Atezolizumab (Roche)</td>
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<td>CDX-1401 (NY-ESO-1)</td>
<td>Metastatic Melanoma</td>
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<td></td>
<td>Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma</td>
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<td>CDX-301 (FLT3L Pathway)</td>
<td>B-cell Lymphomas</td>
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<td>CDX-014 (TIM-1)</td>
<td>Renal Cell Carcinoma</td>
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<td>CDX-1140 (CD40)</td>
<td>Multiple Tumor Types</td>
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**Other Indications:**
- Renal Cell Carcinoma
- Multiple Tumor Types
- Ongoing Investigator Sponsored Trial

**CDX-1140 (CD40)**

**Cellnex therapeutics**

**Fifteenth International Kidney Cancer Symposium**
November 4-5, 2016
Marriott Miami Biscayne Bay, Miami, Florida, USA

www.kidneycancersymposium.com
Varlilumab: Immune Modulating mAb Targeting CD27
Varlilumab: Immune Modulating mAb Targeting CD27

- Induces activation and proliferation of human T cells when combined with T-cell receptor stimulation\(^1\)

- In lymphoid malignancies that express CD27 at high levels, varlilumab has an additional mechanism through a direct anti-tumor effect\(^2\)

- Has potential to augment a patient’s immune response in combination with:
  - Checkpoint inhibitors (anti-CTLA-4, anti-PD-1)
  - APC targeting combinations (CDX-1401)
  - Vaccines/Immunotherapy
  - Other immune modulators (CDX-301)
  - Chemo or ADC that reduce tumor burden and provide source of tumor antigen (glembatumumab vedotin; sunitinib)

Mechanism of Action

- Varilumab is an agonist anti-CD27 mAb:
- Binds to the CD27 (TNFRSF member) expressed on the cell surface and blocks CD70 binding
- Through its binding with CD27, valilumab:
  - Results in proliferation, survival, and maturation of effector capacity and memory T cells
  - Potential to activate B cells and promote generation of plasma cells and production of immunoglobulin and induce NK cell cytolytic activity

Preclinical Activity

- Based on preclinical data, anti-tumor efficacy of CD27 mAbs is likely to involve multiple mechanisms:
  - Expansion and maintenance of tumor-specific CD8+ T cells
  - Enhancement of NK cell function
  - Reducing immune suppression mechanisms mediated by regulatory T cells and negative co-stimulatory molecules.
  - Direct effector function via antibody-dependent cell-mediated cytotoxicity
- Varilumab has been shown effective in syngeneic murine tumor models alone, in CD27 expressing tumors and in combination with chemotherapy or check-point inhibitors
Varilumab Proof of Concept Data

• Safety profile appears favorable in its class; minimal toxicities; no indication of high grade immune-mediated AEs; most common AE is fatigue\(^1\)

• Potent immunologic activity consistent with MOA\(^1\)
  – Rapid induction of pro-inflammatory cytokines
  – Activation of T cells as assessed by increased HLA-DR expression and antigen specific responses
  – Marked decrease in T regs without evidence of broad T cell depletion

• Single-agent antitumor activity demonstrated in advanced, refractory patients (n=90)\(^2\)
  – Two patients experienced significant objective responses
    – Complete response in Hodgkin lymphoma, continues at 33.1+ months
    – Partial response in renal cell carcinoma continues at 27.7+ months
  – Thirteen patients experienced stable disease
    – Renal cell carcinoma, 47.3+ months
    – Follicular lymphoma, 14 months
    – Uveal melanoma, 11.5 months

• Less frequent dosing may provide optimal immunologic effects

2. Publications- submitted (solid tumors) and in preparation (heme)
Partial Response in RCC Patient in Varlitumab Phase 1 Study

- 67 year old male with stage IV RCC
  - Progressed through 3 prior regimens
  - Lenalidomide and Sutent treated for 11 months before PD
  - Everolimus treated for 25 months before PD
  - Sonepcizumab/LT1009 treated for less than 1 month before PD and 7 weeks prior to varlitumab

- Partial Response (PR) after 1 cycle of varlitumab (3 mg/kg)
  - Decrease in all target lesions (-31% end of cycle 1, -52% end of cycle 2, -67% end of cycle 3)
  - Lung nodule completely resolved (shown in scans above)

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Use of Varlilumab in Combination with Checkpoint Inhibitors to Augment Anti-tumor Activity
Rationale for Combination Immunotherapy Regimens

- Targeted therapy of multiple non-redundant molecular pathways regulating immune responses may enhance antitumor immunotherapy without unexpected toxicity.

- In RCC patients with high CD70 expression, blockade of tumor induced CD27 signaling by anti-CD27 antibody, an antibody which competes for the ligand binding site, could reduce apoptosis of effector T cells and survival of Tregs.

- Antitumor immune responses enhanced by mAb mediated CD27 ligation still must contend with regulatory mechanisms designed to dampen immunity.

- Combining varilumab with anti-PD-L1 mAb enhanced tumor antitumor activity and survival in 2 different tumor models.

**Combining PD-1 Signaling Blockade with Varilumab Results in Increased Survival**

BCL1 Lymphoma Model

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<tr>
<th>Treatment</th>
<th>Percent Survival</th>
<th>Days Post Tumor Inoculation</th>
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<tbody>
<tr>
<td>Saline, n=30</td>
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<tr>
<td>Varilumab, n=30</td>
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<tr>
<td>Anti-PD-L1, n=30</td>
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<tr>
<td>Varilumab + anti-PD-L1, n=30</td>
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- *P* = 0.0001 vs. saline
- *P* < 0.0001 vs. all groups

BCL1 model: K-M survival hCD27-Tg BALB/c mice (n=10) administered 1x10^7 BCL1 cells i.v. on day 0. Varilumab (200 ug) or saline was administered i.p. on days 4, 6, 8, 10 and 12 and anti-PD-L1 (100 ug) was administered i.p. on days 4, 6 and 8. Mice were followed for survival.
Varlilumab Clinical Studies

Multiple Indications (including RCC)

- Phase 1/2 study collaboration with BMS—varlilumab and nivolumab (PD-1 immune checkpoint inhibitor) in up to 225 patients
- Preliminary data on 35 patients in Phase 1 presented at AACR 2016
  - CRC (n=20), ovarian (n=8), metastatic melanoma (n=4) and HNSCC (n=3); 69% of patients had 3+ prior therapies
  - No MTD reached; minimal additive toxicity from varlilumab with no evidence of increased autoimmunity/inappropriate immune activation
  - Combo therapy led to marked changes in the tumor microenvironment
    - Increased infiltrating CD8+ T cells and increased PD-L1 expression, which have been shown to correlate with a greater magnitude of treatment effect from checkpoint inhibitors in other clinical studies
    - Additional favorable immune biomarkers noted—increase in inflammatory chemokines and decrease in T regulatory cells

Sanborn AACR 2016.
Varilulumbab Clinical Studies

Multiple Indications (including RCC)

- Preliminary data on 35 patients in Phase 1 presented at AACR 2016
  - In a subset of patients (n=17) on study who had both pre- and post-tumor biopsies available, preliminary evidence suggest a correlation between biomarker data (including changes in TILs) and stable disease or better in seven of these patients.

Sanborn AACR 2016.
Varilumab Clinical Studies

Multiple Indications (including RCC)

• Phase 2 opened to enrollment in Q2 2016
  – Enrolling patients with advanced (recurrent, locally advanced, or metastatic) disease
    – CRC (n=18), ovarian cancer (n=18), glioblastoma (n=20), head and neck squamous cell carcinoma (n=48) and RCC (n=75)

  – For RCC and SCCHN
    – Nivolumab dosing 240 mg IV every 2 weeks in combination with
    – Varilumab at one of three dose levels (0.3 mg/kg q4 wks, 3 mg/kg q2 wks, and 3 mg/kg q12 wks)

  – Key Inclusion/Exclusion Criteria for RCC
    – Have histologically confirmed diagnosis of predominant clear cell renal cell carcinoma
    – Must have received 1 or 2 prior anti-angiogenic therapies
    – No more than 5 total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy
    – Disease progression during or after the last treatment regimen and within 6 months before study entry
    – No prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy
    – No prior anti-CTLA-4 or anti-CD27 antibody within 3 mos of study start
    – No history of brain metastasis
Varlilumab Clinical Studies

Renal Cell Carcinoma

• Phase 1/2 study collaboration with Roche—varlilumab and atezolizumab (anti-PDL1)
  – Phase 1 portion in multiple solid tumors (primarily renal cell carcinoma and bladder)- Enrollment Complete
  – Phase 2 planned in renal cell carcinoma
    – Approximately 60 RCC patients in second-line or subsequent therapy

• Phase 1/2 study of varlilumab and sunitinib
  – Phase 1 open to enrollment in metastatic clear cell renal cell carcinoma
    – Approximately 60 patients total in entire study (phase 1 and 2 combined)
CDX-014: An Anti-TIM-1 ADC
T-Cell Immunoglobulin and Mucin Domain 1 (TIM-1) as a Target Also Known as KIM-1 (Kidney Injury Molecule-1)

- TIM-1 is a novel renal cell and ovarian cancer target that has restricted expression in healthy tissues
- Known expression:
  - Kidney proximal tubular epithelial cells (apical surface)
  - Up-regulation in kidney injury
  - Renal cell carcinoma: clear cell and papillary histology
  - Endometrial (5/18 tissues) and ovarian (15/16) clear cell carcinomas

![Papillary RCC](image1.png)
![Papillary RCC](image2.png)
![Clear Cell RCC](image3.png)
![Chromophobe RCC](image4.png)
CDX-014: ADC Directed to a Novel Renal Cell Carcinoma and Ovarian Target

• CDX-014 is an antibody-drug conjugate (ADC): fully human anti-TIM-1 IgG1 antibody covalently linked to a potent cytotoxin, monomethyl auristatin E (MMAE)
  – Exhibits potent in vitro cytotoxic activity against TIM-1 expressing cell lines and in vivo anti-tumor activity in xenograft models

![Ovarian cancer model](image)

• Phase 1/2 study in advanced renal cell carcinoma (clear cell and papillary) initiated July 2016
  – Phase 1 dose escalation study to assess safety and MTD
  – Followed by Phase 2 expansion cohort to assess ORR at MTD

Thank you

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