Antibody Drug Conjugates: Promise Beyond Breast Cancer

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Sarah Cannon Research Institute
Antibody Drug Conjugates: A Paradigm Shift

Are they:

• the future of personalized precision chemotherapy?
• the way to actually deliver targeted therapy?
• the path for combination treatment (antibody/ADCC & chemotherapy)?
Antibody drug conjugates (ADC)

More than 15 companies are developing 30+ ADCs in a variety of hematologic malignancies and solid tumors.

<table>
<thead>
<tr>
<th>Hematologic Malignancies</th>
<th>Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>Breast</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia (ALL)</td>
<td>Lung (NSCLC/SCLC)</td>
</tr>
<tr>
<td>Acute myelogenous leukemia (AML)</td>
<td>Prostate</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia (CLL)</td>
<td>Glioblastoma (GBM)</td>
</tr>
<tr>
<td>Multiple myeloma (MM)</td>
<td>Ovarian</td>
</tr>
<tr>
<td></td>
<td>Colorectal carcinoma (CRC)</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma (RCC)</td>
</tr>
</tbody>
</table>
ADC Components

1. Antibody
2. Linker
3. Drug

1. A highly selective monoclonal antibody for a tumor-associated antigen that has restricted expression on normal cells
2. A potent cytotoxic agent designed to induce target cell death when internalized in the cell and released
3. A linker that is stable in circulation, but releases the cytotoxic agent in target cells (controlled by altering stability and degree of hindrance around disulfide bond)
## Cytotoxic Mechanisms of Action

<table>
<thead>
<tr>
<th>Cytotoxic Drug (warhead)</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auristatins</td>
<td>Tubulin polymerase inhibitor</td>
</tr>
<tr>
<td>Maytansines</td>
<td>Tubulin depolymerisation</td>
</tr>
<tr>
<td>Calicheamicins</td>
<td>DNA cleavage</td>
</tr>
<tr>
<td>Duocarymycins</td>
<td>DNA minor groove alkylation agent</td>
</tr>
<tr>
<td>PBD dimers</td>
<td>DNA minor groove cross-linker</td>
</tr>
<tr>
<td>α-Amanitin</td>
<td>RNA polymerase II inhibitor</td>
</tr>
</tbody>
</table>
ADC Mechanism of Action

1. ADC in circulation
2. ADC binds to receptor
3. ADC-receptor complex is internalized
4. Cytotoxic agent is released in lysosomes
5. Microtubule disruption
6. Apoptosis (cell death)

Liu, et al. AACR 2013
That’s Simple – But What Could Go Wrong?

• **Efficacy**
  – Inadequate binding to the target cell
  – Inadequate internalization
  – Inadequate drug concentrations released into the target cell
  – Target cell not sensitive to drug

• **Toxicity**
  – Suboptimal monoclonal antibody specificity
  – Drug is toxic even when linked to antibody
  – Drug releases in circulation
  – Drug leaches out of target cell
T-DM1 (Kadcyla) ado-trastuzumab emtansine

- **Target expression:** HER2
- **Monoclonal antibody:** Trastuzumab
- **Cytotoxic agent:** DM1
- **Highly potent cytotoxic agent**
- **Linker:** MCC
- **Systemically stable**

**T-DM1 is a novel ADC**

Average drug: antibody ratio ≈ 3.5:1
**EMILIA Study Design**

- **HER2+ (central) LABC or MBC (N=980)**
  - Prior taxane and trastuzumab
  - Progression on metastatic tx or within 6 mos of adjuvant tx

- **T-DM1**
  - 3.6 mg/kg q3w IV

- **Capecitabine**
  - 1000 mg/m² orally bid, days 1–14, q3w
  - + Lapatinib
  - 1250 mg/day orally qd

- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease

- **Primary end points:** PFS by independent review, OS, and safety

- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Progression-Free Survival by Independent (IRC) and Investigator (INV) Review

IRC

Cap + Lap HR=0.650 (95% CI, 0.55, 0.77)  
Unstratified HR by independent review=0.66 (P<0.0001).

INV

Cap + Lap HR=0.658 (95% CI, 0.56, 0.77)  
Unstratified HR by independent review=0.66 (P<0.0001).

Second Interim Analysis of Overall Survival

Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease

ORR

Difference: 12.7\% (95\% CI, 6.0, 19.4)

\( P=0.0002 \)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (95% CI)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>30.8% (28.2, 33.3)</td>
<td>120/389</td>
</tr>
<tr>
<td>T-DM1</td>
<td>43.6% (40.6, 46.6)</td>
<td>173/397</td>
</tr>
</tbody>
</table>

DOR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median, mos (95% CI)</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>6.5 (5.5, 7.2)</td>
<td>120/105</td>
</tr>
<tr>
<td>T-DM1</td>
<td>12.6 (8.4, 20.8)</td>
<td>173/159</td>
</tr>
</tbody>
</table>

Blackwell, et al. ASCO 2012
## Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades, %</th>
<th>Grade ≥3, %</th>
<th>All Grades, %</th>
<th>Grade ≥3, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>79.7</td>
<td>20.7</td>
<td>23.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>58.0</td>
<td>16.4</td>
<td>1.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29.3</td>
<td>4.5</td>
<td>19.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8.6</td>
<td>4.1</td>
<td>8.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.9</td>
<td>3.5</td>
<td>35.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.1</td>
<td>2.3</td>
<td>6.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>9.4</td>
<td>0.8</td>
<td>22.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.6</td>
<td>4.3</td>
<td>5.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.5</td>
<td>0.2</td>
<td>28.0</td>
<td>12.9</td>
</tr>
</tbody>
</table>

1st Line mBC Phase III MARIANNE Study: BO22589/TDM4788g

**Patients stratified by:**
- World region
- Neo/Adjuvant therapy (Y/N)
- Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

**Arm A**
- Trastuzumab + taxane (until PD) n=364

**Arm B**
- T-DM1 + pertuzumab (until PD) n=364

**Arm C**
- T-DM1 + pertuzumab placebo (until PD) n=364

**FPI July 6 2010**

**Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer**

**Primary endpoints:** PFS as assessed by IRF; Safety

**Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers

**Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm**

**Interim futility analysis:** Option to drop experimental arm
## Selected Antibody Drug Conjugates in Development – Hematologic Malignancies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Biomarker</th>
<th>Tumor</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>Pfizer</td>
<td>CD22</td>
<td>NHL, ALL</td>
<td>III</td>
</tr>
<tr>
<td>RG-7596</td>
<td>Genentech</td>
<td>CD79b</td>
<td>DLBCL, NHL</td>
<td>II</td>
</tr>
<tr>
<td>RG-7593 (pinatuzumab vedotin)</td>
<td>Genentech</td>
<td>CD22</td>
<td>DLBCL, NHL</td>
<td>II</td>
</tr>
<tr>
<td>SAR-3419</td>
<td>Sanofi</td>
<td>CD19</td>
<td>DLBCL, ALL</td>
<td>II</td>
</tr>
<tr>
<td>Milatuzumab doxorubicin</td>
<td>Immunomedics</td>
<td>CD74</td>
<td>CLL, MM, NHL</td>
<td>I, II</td>
</tr>
<tr>
<td>IMGN-529</td>
<td>Immunogen</td>
<td>CD37</td>
<td>B-cell lymphoma, CLL, NHL</td>
<td>I</td>
</tr>
<tr>
<td>SGN-CD19A</td>
<td>Seattle Genetics</td>
<td>CD19</td>
<td>ALL, NHL</td>
<td>I</td>
</tr>
<tr>
<td>SGN-75 (Vorsetuzumab mafodotin)</td>
<td>Seattle Genetics</td>
<td>CD70</td>
<td>NHL</td>
<td>I</td>
</tr>
<tr>
<td>SGN-CD33A</td>
<td>Seattle Genetics</td>
<td>CD33</td>
<td>AML</td>
<td>I</td>
</tr>
<tr>
<td>DFRF4539A</td>
<td>Genentech</td>
<td>Myeloma Antigen</td>
<td>Multiple Myeloma</td>
<td>I</td>
</tr>
</tbody>
</table>
# Selected Antibody Drug Conjugates in Development – Solid Tumors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Biomarker</th>
<th>Tumor</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDX-011 (glembatumumab vedotin)</td>
<td>Celldex</td>
<td>Glycoprotein NMB (GNMB)</td>
<td>Breast, Melanoma</td>
<td>I, II, III</td>
</tr>
<tr>
<td>PSMA-ADC</td>
<td>Progenics</td>
<td>PSMA</td>
<td>Prostate</td>
<td>II</td>
</tr>
<tr>
<td>ABT-414</td>
<td>AbbVie</td>
<td>EGFR</td>
<td>GBM, NSCLC</td>
<td>I, II</td>
</tr>
<tr>
<td>IMGN901 (Lorvotuzumab mertansine)</td>
<td>Immunogen</td>
<td>CD56</td>
<td>SCLC, MM, Ovarian, MCC</td>
<td>I, II</td>
</tr>
<tr>
<td>IMGN853</td>
<td>Immunogen</td>
<td>Folate receptor α</td>
<td>Ovarian, NSCLC</td>
<td>I</td>
</tr>
<tr>
<td>IMGN289</td>
<td>Immunogen</td>
<td>EGFR</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>ASG-5ME</td>
<td>Agensys</td>
<td>SLC44A4 (AGS-5)</td>
<td>Pancreatic, Stomach</td>
<td>I</td>
</tr>
<tr>
<td>ASG-22CE</td>
<td>Astellas</td>
<td>Nectin 4</td>
<td>Urothelial cancer</td>
<td>I</td>
</tr>
<tr>
<td>AGS-16C3F</td>
<td>Astellas</td>
<td>ENPP3</td>
<td>RCC</td>
<td>I</td>
</tr>
<tr>
<td>AMG-172</td>
<td>Amgen</td>
<td>CD27L</td>
<td>RCC</td>
<td>I</td>
</tr>
<tr>
<td>AMG-595</td>
<td>Amgen</td>
<td>EGFRvIII</td>
<td>Glioma</td>
<td>I</td>
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<tr>
<td>BAY 94-9343</td>
<td>Bayer</td>
<td>Mesothelin</td>
<td>Mesothelioma, Ovarian</td>
<td>I</td>
</tr>
</tbody>
</table>
## Selected Antibody Drug Conjugates in Development – Solid Tumors

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<thead>
<tr>
<th>Drug</th>
<th>Company</th>
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<th>Tumor</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMUC5754A</td>
<td>Roche/Genentech</td>
<td>MUC16</td>
<td>Ovarian</td>
<td>I</td>
</tr>
<tr>
<td>Anti-NaPi2b-vc-E</td>
<td>Roche/Genentech</td>
<td>NaPi2b</td>
<td>Lung, Ovarian</td>
<td>I</td>
</tr>
<tr>
<td>RG-7636</td>
<td>Genentech</td>
<td>Endothelin receptor ETB</td>
<td>Melanoma</td>
<td>I</td>
</tr>
<tr>
<td>RG-7450</td>
<td>Genentech</td>
<td>STEAP1</td>
<td>Prostate</td>
<td>I</td>
</tr>
<tr>
<td>DEDN6526A</td>
<td>Genentech</td>
<td>Endothelin-B receptor</td>
<td>Melanoma</td>
<td>I</td>
</tr>
<tr>
<td>IMMU-132</td>
<td>Immunomedics</td>
<td>TACSTD2 (TROP2/EGP1)</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>Labetuzumab-SN-38</td>
<td>Immunomedics</td>
<td>CEA (CD66e)</td>
<td>CRC</td>
<td>I</td>
</tr>
<tr>
<td>PF-06647263</td>
<td>Pfizer</td>
<td>Not Disclosed</td>
<td>Solid tumors (TNBC), Ovarian</td>
<td>I</td>
</tr>
<tr>
<td>SAR-566658</td>
<td>Sanofi</td>
<td>Mucin 1</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>SGN-LIV1A</td>
<td>Seattle Genetics</td>
<td>LIV-1A</td>
<td>Breast</td>
<td>I</td>
</tr>
<tr>
<td>SC16LD6.5</td>
<td>StemCentRx</td>
<td>SCLC surface protein</td>
<td>SCLC</td>
<td>I</td>
</tr>
<tr>
<td>MLN-0264</td>
<td>Takeda</td>
<td>Guanylyl cyclase C</td>
<td>GI</td>
<td>I</td>
</tr>
</tbody>
</table>
Targeting MUC16 with the Antibody-Drug Conjugate DMUC5754A in Patients with Platinum-Resistant Ovarian Cancer: A Phase I Study of Safety and Pharmacokinetics


1Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
2University of Oklahoma Health Sciences Center, Oklahoma City, OK
3Harvard Medical School, Boston, MA
4Genentech, Inc., South San Francisco, CA
5Sarah Cannon Research Institute, Nashville, TN

AACR, April 6-10, 2013, Washington, DC
MUC16 Background

- MUC16 is a large transmembrane protein that belongs to the mucin protein family
- Highly expressed in ~80% of epithelial ovarian cancers and ~50% of pancreatic cancers
- Putative role in tumorigenesis
  - Immune evasion (via NK cell suppression)
  - Facilitate metastasis through cell-cell interactions via mesothelin
- CA125, the extracellular portion of MUC16 cleaved and released into circulation, is a well-established ovarian cancer disease biomarker

Liu, et al. AACR 2013
Anti-MUC16 Antibody-Drug Conjugate (ADC): DMUC5754A

- Anti-MUC16 monoclonal antibody conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker
- Antibody binds to mucin repeats present in both membrane-bound MUC16 and circulating CA125
- MUC16 is a possible diagnostic biomarker

Liu, et al. AACR 2013
<table>
<thead>
<tr>
<th>Exposure, cycles</th>
<th>0.3 mg/kg (n=3)</th>
<th>0.6 mg/kg (n=3)</th>
<th>1.2 mg/kg (n=3)</th>
<th>1.8 mg/kg (n=3)</th>
<th>2.4 mg/kg (n=29)</th>
<th>3.2 mg/kg (n=3)</th>
<th>All Patients (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (SD)</td>
<td>2 (0) 2–2</td>
<td>3 (2) 2–6</td>
<td>3 (1) 2–4</td>
<td>12 (10) 2–22</td>
<td>6 (4) 1–16</td>
<td>6 (7) 1–14</td>
<td>6 (5) 1–22</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose Limiting Toxicities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Treatment-Related Dose Modifications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose reduction, N (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>2</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Drug permanently discontinued, N (%)</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

- Protocol-defined DLTs occurred at 3.2 mg/kg and were grade 4 neutropenia and grade 4 uric acid increase
- 2.4 mg/kg q3wk determined to be the Maximum Tolerated Dose
Peripheral Neuropathy (DMUC5754A Related)

- Peripheral neuropathy is a known risk for the vc-MMAE antibody drug conjugate platform
- Appears to be related to cumulative exposure and dose level
- Generally reversible with dose delays and dose reductions
- All patients have had prior treatment with taxane

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=29 patients at 2.4 mg/kg)</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>12</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>-</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Liu, et al. AACR 2013
### DMUC5754A Activity: Radiologic Responses

#### Patients Treated at 2.4 mg/kg

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dx Unselected</th>
<th>IHC 0</th>
<th>IHC 1+</th>
<th>IHC 2+</th>
<th>IHC 3+</th>
<th>IHC N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level 2.4 mg/kg (n=29)</td>
<td>5/29 (17%)</td>
<td>0/5 (0%)</td>
<td>0/0 (0%)</td>
<td>1/5 (20%)</td>
<td>4/17 (24%)</td>
<td>0/2 (0%)</td>
</tr>
</tbody>
</table>

Liu, et al. AACR 2013
First-in-human Phase I dose-escalation study of a novel anti-mesothelin antibody drug conjugate, BAY 94-9343, in patients with advanced solid tumors

J Bendell,1 G Blumenschein,2 R Zinner,2 D Hong,2 S Jones,1 J Infante,1 H Burris,1 P Rajagopalan,3 M Kornacker,4 D Henderson,4 A Kelly,3 R Hassan5

1Sarah Cannon Research Institute, Nashville, TN; 2MD Anderson Cancer Center, Houston, TX; 3Bayer HealthCare Pharmaceuticals, Montville, NJ; 4Bayer Pharma AG, Berlin, Germany; 5National Cancer Institute, NIH, Bethesda, MD

AACR, April 6-10, 2013, Washington, DC
BAY 94-9343 Mesothelin Antibody-Drug Conjugate

- Mesothelin, an internalizing antigen, is overexpressed by mesotheliomas (95% [77% to 100%])*, pancreatic (63% [63% to 100%])* and ovarian adenocarcinomas (81% [55% to 100%])*.

*Bayer data [range of values reported in literature]; ADC, antibody drug conjugate

Bendell, et al. AACR 2013
BAY 94-9343 DLT and Adverse Events

- **DLTs**
  - 5.5 mg/kg: Gr. 3 hyponatremia (n=1)
  - 6.5 mg/kg: Gr. 3 AST elevation (n=1)

- **Non-tolerable AEs reported in Cycle 2 at 7.5 mg/kg:**
  - Gr. 4 ocular / corneal toxicity (microcystic changes and corneal epithelial deposits), Gr. 4 amylase and lipase elevation and Gr. 3 peripheral neuropathy.
  - Gr. 2 ocular / corneal toxicity and Gr. 2 peripheral neuropathy.

- **MTD determined to be 6.5 mg/kg, based on significant AEs at 7.5 mg/kg**

*Bendell, et al. AACR 2013*
**IMGN853**

- **Target:** folate receptor α (FRα)
  - Markedly up-regulated in cancer
  - Distinct from homeostatic folate transporters (folate carriers, FRβ)

- **Components**
  - FRα-binding antibody selected for ability to deliver maytansinoid payload
  - Linker/DM4 cell-killing agent pairing selected for best efficacy
  - Linker engineered to resist cellular export pumps to counter multi-drug resistance (MDR)
IMGN853: Key Types of FRα Over-Expressing Cancers

**Ovarian Cancer**
- Serous: 70% (77%)
- Endometrioid: 51% (74%)

**NSCLC**
- AdenoCA: 59% (70%)
- BAL: 71% (71%)

**Endometrial Cancer**
- Serous: N/A (50-69%)*
- Endometrioid: 40% (69%)

**Renal Cell**
- Clear cell: 26% (85%)

*Scorer, et al; Novacastra Journal of Histopathology 3:8-12, 2010
IMGN853 Phase I FIM Results

• IMGN853 is well tolerated at doses up to 5.0 mg/kg; safety assessment continues with enrollment of additional patients
• Encouraging preliminary activity observed at 5.0 mg/kg (2 unconfirmed PRs) and 3.3 mg/kg (confirmed CA125 response/SD for 6 cycles)
• Half life has been determined to be approximately 4 days
• IMGN853 will be evaluated at MTD to further assess safety, PK, PD and efficacy in 3 expansion cohorts of 14 patients each: (1) platinum-resistant EOC, (2) relapsed/refractory EOC and (3) relapsed/refractory NSCLC

Kurkjian, et al. ASCO 2013
NaPi2b Background

Function of NaPi2b
- Normally expressed on brush border membrane of the small intestine and apical membrane of lung pneumocytes
- Controls transcellular absorption of inorganic phosphate

Clinical correlates
- Mutations in NaPi2b have been associated with clinical syndromes of alveolar and testicular microlithiasis

Cell surface target ideal for ADCs
- Highly expressed in non-mucinous ovarian cancer, non-squamous non-small cell lung cancer and papillary thyroid cancer
Anti-NaPi2b Antibody-Drug Conjugate (ADC): DNIB0600A

- DNIB0600A is a monoclonal antibody conjugated to the cytotoxic agent monomethyl auristatin E (MMAE) via a protease-cleavable peptide linker (vc-MMAE platform, Seattle Genetics)
Companion Diagnostic Prototype IHC Assay Being Developed for NaPi2b

**Ovarian Cancer**
- IHC: 0
- IHC: 2+
- IHC: 3+

**Lung Cancer**
- IHC: 0
- IHC: 2+
- IHC: 3+

### Prevalence Estimates

<table>
<thead>
<tr>
<th>Ovarian*</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>1+</td>
<td>4</td>
</tr>
<tr>
<td>2+</td>
<td>47</td>
</tr>
<tr>
<td>3+</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung*</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>1+</td>
<td>1</td>
</tr>
<tr>
<td>2+</td>
<td>14</td>
</tr>
<tr>
<td>3+</td>
<td>46</td>
</tr>
</tbody>
</table>

*Prevalence estimates based upon vendor procured cancer specimens (ovarian, n=154; lung, n=74)
Progression Free Survival: Ovarian Cancer

- 2.8 mg/kg
- 2.4 mg/kg
- 1.8 mg/kg

PR
On study

Progression-Free Survival (Days)
Patient with Ovarian Cancer Dosed at 2.4 mg/kg with a Partial Response

- 67 yo woman treated with carbo/paclitaxel, gem/bev, and liposomal dox
- Treated at 2.4 mg/kg q3w with a PR noted after 4 cycles of treatment
- Patient remains on study with dose reduction after Cycle 3, currently Cycle 9
DNIB0600A Activity
Maximum Declines in Measureable Disease

- Approximately 70% of NSCLC and 90% of OC patients expressed high levels (IHC 2+/3+) of NaPi2b
- Of the 60 patients with NaPi2b IHC Score of 2+ or 3+, treated at dose levels 1.8–2.8 mg/kg, 14 patients had a confirmed partial response (PR); 3 of 26 (12%) NSCLC and 11 of 22 (50%) OC patients, respectively
- Three additional NSCLC patients had unconfirmed PRs
- No patient was enrolled with NaPi2b IHC Score of 1+; no responses were reported among the 13 patients with NaPi2b IHC Score of 0 or unavailable, at any dose level
Lung Cancer Patient Vignette

73yo woman with poorly differentiated NSCLC. Prior treatment included carboplatin/pemetrexed/bevacizumab complicated by pancytopenia and acute renal failure. Erlotinib was used intermittently with intolerance due to rash, and discontinued due to symptomatic progression.

Screening NaPi2b IHC 3+. Patient treated a dose level of 1.8 mg/kg q3wks with confirmed PR
Lung Cancer Patient Vignette

62yo man with NSCLC (Alk neg; EGFR wt; KRAS wt) who progressed following treatment with carboplatin / paclitaxel / bevacizumab and docetaxel single agent.

Screening NaPi2b IHC score 2+. Patient treated at 2.4 mg/kg with confirmed PR.
DNIB0600A (Anti-NaPi2b ADC) Ongoing Trials

- Phase 1b study of the safety and pharmacology of DNIB0600A in combination with carboplatin (with or without bevacizumab) in patients with platinum-sensitive ovarian cancer

- Randomized phase II study of DNIB0600A compared to pegylated liposomal doxorubicin in patients with platinum resistant ovarian cancer
A First-in-Human Phase I Study of the Safety and Pharmacokinetic Activity of DEDN6526A, an anti-Endothelin B Receptor (anti-ET\textsubscript{B}R) Antibody-Drug Conjugate in Patients with Metastatic or Unresectable Melanoma

Jeffrey R. Infante,\textsuperscript{1} Shahneen K. Sandhu,\textsuperscript{2} Catriona M. McNeil,\textsuperscript{3} Omar Kabbarah,\textsuperscript{4} Chunze Li,\textsuperscript{4} Wei Zhong,\textsuperscript{4} Jyoti Asundi,\textsuperscript{4} Katie Wood,\textsuperscript{4} Yu-Waye Chu,\textsuperscript{4} and Omid Hamid\textsuperscript{5}

\textsuperscript{1}Sarah Cannon Research Institute/Tennessee Oncology, PPLC, Nashville, TN, USA  
\textsuperscript{2}Peter MacCallum Cancer Centre, Melbourne, Australia  
\textsuperscript{3}Royal Prince Alfred Hospital, Sydney, Australia  
\textsuperscript{4}Genentech, Inc., South San Francisco, CA, USA  
\textsuperscript{5}The Angeles Clinic and Research Institute, Los Angeles, California, USA

2014 AACR Annual Meeting, 7 April 2014  
Clinical Trials Symposium: LB Abstract #9115
Role of Endothelin B Receptor (ET$_B$R) in Melanoma

- ET$_B$R is a G-protein coupled receptor with activating ligands (endothelin-1, -2, and -3) that signal through RAF & MEK.

- During embryonic development ET$_B$R regulates migration and proliferation of melanocyte precursors from the neural crest.

- Possible role in melanoma development
  - ET$_B$R is associated with malignant transformation of melanocytes and with potentiation of metastatic spread.

- Overexpression of ET$_B$R is observed in >50% of melanomas and is much higher than in normal skin cells.

Anti-ET$_B$R Antibody-Drug Conjugate (ADC): DEDN6526A is Targeted Chemotherapy to Melanoma

- Anti-ET$_B$R ADC is a monoclonal antibody to ET$_B$R conjugated to the toxin monomethyl auristatin E (MMAE) via a peptide linker (licensed from Seattle Genetics).
**ET\textsubscript{B}R Expression can be Detected by an Immunohistochemistry (IHC) Assay**

- A prototype ET\textsubscript{B}R IHC assay is being developed as a potential companion diagnostic in melanoma.
- The assay is used on formalin fixed paraffin embedded (FFPE) melanoma.
- **IHC Score:**
  - 0: ≤ 10% of tumor cells exhibit membrane staining
  - 1+/2+/3+: the given staining pattern with the highest percentage

![IHC: 0](image1)
![IHC: 1+](image2)
![IHC: 2+](image3)
![IHC: 3+](image4)

**ET\textsubscript{B}R Staining Intensity**
## Patients with Multiple Prior Therapies Enrolled in Dose-Escalation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=28, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M stage</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>M1a</td>
<td>7 (25%)</td>
</tr>
<tr>
<td>M1b</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>M1c</td>
<td>17 (60%)</td>
</tr>
<tr>
<td>Number of prior regimens</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>1</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>2</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Types of prior therapy</td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>Investigational</td>
<td>9 (32%)</td>
</tr>
<tr>
<td>BRAF/MEK inhibitor</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Anti PD-1/PD-L1</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Other(^b)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

\(^b\)Other category for prior therapy includes treatment with Interleukin-2 and/or Interferon-Alpha

Analysis cut-off date of 28 February 2014
## Patient Characteristics: Dose Escalation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=28, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>65 (24–82)</td>
</tr>
<tr>
<td>Male</td>
<td>17 (61%)</td>
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<tr>
<td>Female</td>
<td>11 (39%)</td>
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<tr>
<td>ECOG status</td>
<td></td>
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<tr>
<td>0</td>
<td>18 (64%)</td>
</tr>
<tr>
<td>1</td>
<td>10 (36%)</td>
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<tr>
<td>BRAF status</td>
<td></td>
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<tr>
<td>Mutant</td>
<td>4 (11%)</td>
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<tr>
<td>Wild type</td>
<td>22 (71%)</td>
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<tr>
<td>Unknown(^a)</td>
<td>2 (18%)</td>
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<tr>
<td>LDH &gt; Upper Limit of Normal</td>
<td>16 (57%)</td>
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<tr>
<td>Subtype</td>
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</tr>
<tr>
<td>Cutaneous</td>
<td>17 (60%)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Ocular</td>
<td>8 (29%)</td>
</tr>
</tbody>
</table>

\(^a\)BRAF mutation status is unknown for 2 patients with ocular melanoma

Analysis cut-off date of 28 February 2014
DLTs Observed in Dose-Escalation Defined
2.4 mg/kg as the Potential Phase 2 Dose

Dose Escalation Cohorts

*DLT
2.8 mg/kg
n=6

2.4 mg/kg
n=7

*DLT
1.8 mg/kg
n=6

1.2 mg/kg
n=6

*DLT
0.6 mg/kg
n=3

0.3 mg/kg
n=3

Potential Recommended Phase 2 Dose (RP2D)

Expansion Cohort ~ 24 patients
2.4 mg/kg q3wk

Data analysis is ongoing

*Three protocol-defined DLTs:
- Grade 3 infusion related reaction (1.8 mg/kg)
- Grade 3 transaminitis (2.4 mg/kg)
- Grade 3 elevated ALT and AST + transient Grade 2 elevated bilirubin (2.8 mg/kg)
Early and Sustained Responses Observed in Patients Treated at Doses ≥ 1.8 mg/kg

N=16 patients

Analysis cut-off date of 28 February 2014
Confirmed Partial Response in Patient with Cutaneous Melanoma Dosed at 1.8 mg/kg

- 79 year old male with BRAF wild-type cutaneous melanoma who had progressed through two prior therapies, including most recently ipilimumab for 2 months, who enrolled on Study GO27935 and was dosed with DEDN6526A at 1.8 mg/kg.

- Patient had a confirmed partial response (↓ 42.5%) and was on study for 9 months.

Lesion is cystic, suggesting central necrosis.

Images courtesy of Dr. Jeff Infante, Sarah Cannon Research Institute, with review by Sandra Sanabria, Clinical Imaging, Genentech.
SC16LD6.5 (Stem CentRx)

- Antibody drug conjugate targeting protein expressed on the surface of most small cell lung cancers (SCLC)
- D6.5 is a potent DNA damaging agent that is cell cycle independent
- Phase I/II FIM trial ongoing in patients with recurrent SCLC
MLN0264 (Takeda Pharmaceuticals)

• Target: guanyl cyclase C (GCC)
  Cytotoxic: monomethyl auristatin E (MMAE)
  Linker: Seattle Genetics technology

• GCC expressed in CRC (95%), gastric (67%) and pancreatic cancer (≥ 50%)

• Phase I dose escalation study ongoing in GI malignancies

• Preclinical synergy documented with gemcitabine (Veiby et al. AACR-NCI-EORTC 2013); phase II trial in pancreatic cancer planned in 2014 with combination

• Participating sites: Moffitt, U of Colorado, Val d’Hebron, MGH
ASG-5ME (Seattle Genetics/Agensys)

- Target: SLC44A4 antigen
  Cytotoxic: monomethyl auristatin E (MMAE)
  Linker: Seattle Genetics technology

- SLC44A4 is an ion transporter expressed on >90% of pancreatic ductal adenocarcinomas (PDA)

- Ph I dose escalation study in patients with mPDA (1.2 mg/kg/wk)

- 1 partial response; 12 stable disease; 5 CA 19-9 reductions (N= 35)

- AE: fatigue, abdominal pain, vomiting, nausea, and neutropenia

- Additional trials enrolling gastric and prostate cancer patients

- Participating sites: TGen, UCSF, U Chicago, DFCI, Texas Oncology Baylor Sammons and Tyler, Seattle Cancer Care

Coveler, et al. GI ASCO 2013
Labetuzumab-SN-38 or IMMU130 (Immunomedics)

- Target: carcinoembryonic antigen, CEACAM5
- Cytotoxic: SN-38
- Linker: Immunomedics pH-sensitive linker

- Phase I dose escalation ongoing in metastatic CRC previously treated with prior irinotecan
- 1 DLT of gr 3 thrombocytopenia observed at 16 mg/kg q 2wks
- Dose escalation continues at MSKCC
- Additional phase I trial dosing D1, 8 every 21 days ongoing at Christiana, Indiana, Fox Chase, VICC
- Phase II CRC trial pending with q2 week dosing

Segal, et al. AACR 2013
IMMU 132 (Immunomedics)

- Target: Trop-2 (trophoblastic antigen-2, EGP-1, GA733-1)
  Cytotoxic: SN-38
  Linker: Immunomedics pH-sensitive linker

- Trop-2 is a pan-epithelial cancer antigen

- Ph I trial conducted in advanced epithelial tumors at Christiana, MD
  Orlando, Indiana, Weill Cornell, and Virginia Mason Seattle

- Recommended phase II dose 10 mg/kg, 1 & 8 every 21

- AE: neutropenia, anemia, N/V, diarrhea, fatigue

- Responses observed in CRC, TNBC, and SCLC including patients
  progressing on a prior topo-1 inhibitor; Ph II studies planned

Starodub, et al. AACR-NCI-EORTC 2013
Conclusions

• The approval of antibody drug conjugates for the treatment of Her2+ breast cancer and Hodgkins lymphoma has created great enthusiasm for the technology as a proven paradigm.

• Antibody drug conjugates against novel targets are in development for a large number of solid tumors and blood cancers.

• The possibilities for developing and utilizing these agents are limited only by the discovery of suitable targets, both highly expressed on and relatively specific to cancer cells.

• ADCs allow more precise delivery of chemotherapy to cancer cells, which should improve effectiveness relative to toxicity.