Antibody Drug Conjugates for Triple Negative Breast Cancer: Targeting Positive in the Negative

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Financial Disclosure

- Consultant/Advisory Board:
  - Novartis
  - Genentech
  - Pfizer
  - Spectrum pharma
Objectives

- Understand the concept of novel antibody drug conjugates
- Gain knowledge in the clinical development of novel antibody drug conjugates, particularly gp-NMB-specific glembatumumumab vedotin and anti-Trop-2 sacituzumumab govitecan, in triple negative breast cancer.
Acknowledgement:
Targeted Therapy in Breast Cancer

Elwood V. Jensen:
Discovered Estrogen Receptor in 1958

Craig V Jordan:
Targeted therapy against ER+ BC

Robert Weinberg:
? Discovered HER2 in 1982

Dennis Slamon:
Targeted therapy against HER+ BC
History of TNBC

• Defined by what it does not have
• Receptor based classification

• ? First used in October 2005

• Pubmed search (till Sept 2017):
  – 7,632 articles
  – 7632/4383 → >1 article/day…
2011: Underwent lumpectomy with radiotherapy for pT2N0 invasive breast cancer, ER-/PR-/HER2-
2012: Received AC-T chemotherapy
2015: Noticed increase in shortness of breath, which prompted restaging scans that revealed pulmonary and liver lesions. CT guided biopsy revealed breast adenocarcinoma, ER-/PR-/HER2-
2015: Started carboplatin (AUC = 6))
2015: Disease progression after 5 months

What therapy to chose next?
Chemotherapy for TNBC

- Capecitabine
- Vinorelbine
- Ixabepilone
- Gemcitabine
- Liposomal doxorubicin
- Albumin bound-paclitaxel
- Eribulin

Duration of response usually short, with rapid relapse
Toxicity major issue clinically
Patient Story: 43F

- 2011: Underwent lumpectomy with radiotherapy for pT2N0, invasive breast cancer, ER-/PR-/HER2-
- 2012: Received AC-T chemotherapy
- 2015: Pulmonary metastasis
- 2015: Started carboplatin (AUC = 6)
- 2015: Disease progression after 5 months
- 2016: Received capecitabine followed by eribulin

What therapy would you choose next?

Cheerful lady:
- Why is this called TNBC?
- Can we find something positive?
Patient Story: 43F

- 2016: Received capecitabine followed by eribulin

What therapy would you choose next?

Cheerful lady:
- Why is this called TNBC?
- Can we find something positive?

Tumor Genotyping:
- TP53 mutation...

What if there are no actionable genomic alterations?
Finding the Positive in Negative: Actionable Targets

• Targeting key intracellular signaling pathways:
  – Androgen receptor (AR)

• Targeting cell-surface markers for selective delivery of potent agents:
  – $g_pNMB$ ADC
  – Trop-2 ADC
(11th-12th Century BC):
After a fruitless 10-year siege, the Greeks constructed a huge wooden horse, and hid a select force of men inside. The Trojans pulled the horse into their city. That night the Greek force crept out of the horse and opened the gates for the rest of the Greek army. The Greeks entered and destroyed the city of Troy, ending the war.

Homer, *Odyssey* 8.492-495
Components of ADC

Antibody
- High affinity and specificity to tumor antigen
- Efficient internalization
- Reduced immunogenicity

Payload
- Highly potent
- Microtubule inhibitors
  - Auristatins
  - Maytansines
- DNA damaging agents
  - Calicheamicin
  - Duocarmycins
  - SN-38

Linker
- Stable in the blood stream
- Capable of releasing payload once internalized
- Cleavable linker
- Non-cleavable linker

Selective delivery of toxic payload

1. Binding of an ADC to antigen
2. Internalization to the early endosome
3. Degradation of ADCs in the lysosome
4. Release and action of payload
5. Apoptosis of the cancer cell

Another Mechanism of Action: Activation of ADCC?

Poster Child for ADC: T-DM1 for HER2+ MBC

Verma S et al. NEJM. 2012.
Finding the Positive in Negative: Actionable Targets

• Targeting key genomic drivers and intracellular signaling pathways:
  – *BRCA*
  – Androgen receptor (AR)

• Targeting markers for selective delivery of potent agents:
  – *gpNMB* ADC
  – Trop-2 ADC

ADC, antibody drug conjugate
Glembatumumab Vedotin: ADC Targeting \textit{gpNMB} in TNBC

\textit{valine-citrulline enzyme-cleavable linker}

CR011: fully-human IgG\textsubscript{2} targeting GPNMB  MMAE: dolastatin-like tubulin inhibitor
Glycoprotein NMB (gpNMB): Overexpressed in TNBC

- **gpNMB**: Glycoprotein NMB, a transmembrane protein, expressed at higher levels in several malignant human tissues than in normal tissue.
- Poor prognostic marker in breast and lung cancer

Glembatumumab Vedotin: ADC Targeting \textit{gpNMB} in TNBC

valine-citrulline enzyme-cleavable linker

CR011: fully-human IgG₂ targeting GPNMB  MMAE: dolastatin-like tubulin inhibitor

Glembatumumab vedotin binding to gpNMB  Internalization and linker cleavage  Free MMAE causes tubulin inhibition and cell death
gpNMB in breast cancer: Pre-clinical Findings
Glembatumumab vs chemotherapy: Phase-2 clinical trial in MBC

Assessed for eligibility (N = 348)

Randomly assigned (n = 124)

Glembatumumab vedotin (n = 83)

Received treatment (n = 81)

Discontinued treatment (n = 81)
Progression of disease (n = 53)
Symptomatic deterioration (n = 12)
Adverse event (n = 8)
Patient decision (n = 8)

Did not receive treatment (n = 2)

Completed study follow-up (n = 75†)
Death (n = 57)
Progression (n = 15)
New anticancer therapy (n = 3)
Discontinued study follow-up (n = 6)
Patient request (n = 4)
Lost to follow-up (n = 1)
Other (n = 1)

Investigator’s choice chemotherapy (n = 41)

Received treatment (n = 41)

Discontinued treatment (n = 41)
Progression of disease (n = 30)
Symptomatic deterioration (n = 4)
Adverse event (n = 2)
Patient decision (n = 4)
Investigator decision (n = 1)

Entered cross-over phase via cross-over phase (n = 15)

Discontinued treatment (n = 15)
Progression of disease (n = 9)
Symptomatic deterioration (n = 3)
Adverse event (n = 2)
Patient decision (n = 1)

Completed study follow-up (n = 14†)
Death (n = 10)
Progression (n = 2)
New anticancer therapy (n = 2)
Discontinued study follow-up (n = 1)
Patient request (n = 1)

Glembatumumab vedotin via cross-over phase

Excluded (n = 224)
Tumor tissue not tested/inadequate for testing (n = 20)
gpNMB-negative tumor (n = 5)
gpNMB-positive tumor (n = 199)
Did not meet other eligibility criteria (n = 80)
Clinical deterioration (n = 34)
Exclusionary medical condition (n = 25)
Exclusionary or inadequate prior treatment (n = 14)
Other/unknown (n = 7)
Refused to participate (n = 11)
Enrollment closed (n = 108)†

Analyzed

ITT population (n = 83)
PP population (n = 67)
Excluded from PP population (n = 16)

Did not initiate study treatment (n = 2)
Major protocol violation: screening tumor assessment performed >10 weeks prior to study entry (n = 1)
No evaluable post-treatment tumor assessment (n = 13)
Symptomatic deterioration (n = 7)
Patient request (n = 4)
Adverse event (n = 2)

Analyzed

ITT population (n = 41)
PP population (n = 36)
Excluded from PP population (n = 5)

No evaluable post-treatment tumor assessment (n = 5)
Symptomatic deterioration (n = 2)
Patient request (n = 1)
Adverse event (n = 2)

Analyzed

ITT population: Cross-over data excluded from ITT analysis (n = 0)
PP population (n = 13)
Excluded from PP population (n = 2)
No evaluable post-treatment tumor assessment (n = 2)
Symptomatic deterioration (n = 1)
Patient request (n = 1)
Response Rate Stratified by gpNMB in metastatic Breast Cancer

Glematumumab

Higher gpNMB expression associated with response to glematumumab, but not chemotherapy

Glembatumumab Vedotin: Survival Results Stratified by gpNMB

Glembatumumab associated with higher PFS, only in gpNMB+ TNBC

Glembatumumab Vedotin: Adverse Events

<table>
<thead>
<tr>
<th>Any treatment-related AE</th>
<th>GV (n = 96)*</th>
<th>IC (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 to 4</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>44</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>19</td>
<td>46</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Dehydration</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagram A**

- **Rash in cycle 1 (n = 37)**
  - Median (months): 3.4
- **No rash in cycle 1 (n = 46)**
  - Median (months): 1.5

HR, 0.51; 95% CI, 0.31 to 0.84; P = .008

Progression-Free Survival (%) vs Time (months)
Glembatumumab Vedotin: Phase III Clinical Trial (METRIC)

Metastatic Triple Negative Breast Cancer
(0-2 prior line) and gpNMB positive (N = 300)

Primary endpoint
PFS

Glembatumumab

Capecitabine

Issues:
- gpNMB cut-off
- Type of specimen
- Heterogeneity in TNBC

The METRIC Study in Triple Negative Breast Cancer

m&ric
A Clinical Trial of CDX-011 in Metastatic Triple-Negative Breast Cancer
Finding the Positive in Negative: Actionable Targets

- Targeting key genomic drivers and intracellular signaling pathways:
  - BRCA
  - Androgen receptor (AR)
- Targeting markers for selective delivery of potent agents:
  - gpNMB ADC
  - Trop-2 ADC
Sacituzumab Govitecan (IMMU132): ADC Targeting *trop-2* in TNBC
Trop-2 Antigen

- Trop-2/EGP-1 is a pan-epithelial cancer antigen
- Related to but distinct from EGP-2 (aka EpCAM).
- Trop2e is seen in all BC subtypes, including TNBC.
- Trop2e correlates with the expression of genes involved in cell epithelial transformation, adhesion, and proliferation

Vidula N et al. ASCO, 2017
Trop-2 is cleaved by proteolysis and signals through b-catenin

- Trop2 is cleaved through regulated intramembrane proteolysis into an intracellular and extracellular domain
- This cleavage is mediated by TACE and gamma secretase complex
- The intracellular fragment can enter the nucleus, where it binds to the b-catenin transcription factor, increasing the expression of cyclin D1 and c-myc
Trop-2 Expression in Diverse Cancers

Prostate cancer

Pancreatic cancer

TNBC

SCLC

All examples are from patients enrolled in IMMU-132-01 Clinical Trial
Sacituzumab Govitecan (IMMU-132) (First in Class ADC)

**Novel linker and ADC construct**

**CL2A linker**

- **Glucuronidation site** (10th position) is protected while bound to IgG
  - Much lower SN-38G concentrations in serum than with irinotecan
- Linker coupled to 20th position stabilizes lactone ring
  - pH dependent release
- **Site-specific coupling to interchain thiols (N = 8)**
  - Average of ~ 7.6 SN-38 molecules/IgG
  - High doses of SN-38 delivered
Sacituzumab Govitecan (IMMU-132): Mechanism of Action

**Novel linker and ADC construct**
- Glucuronidation site protected while bound to IgG
- Short PEG for solubility
- Maleimide group
- Thioether coupling to thiols on IgG
- pH-dependent cleavage site
- Lactone ring (intact while coupled to linker)

**Internalization into Trop-2-positive cells**

**Inhibit topo-1**

**Inhibit DNA replication and repair**

**Apoptosis**
### IMMU-132 Specificity: Detection of dsDNA Breaks

#### HCC1806 (Trop2<sup>pos</sup>)

- **Cell alone**
  - Median fluorescence intensity: 4.25

- **Cell + anti-rH2AX-AF488**
  - Median fluorescence intensity: 168

- **Cell + IMMU-132 + anti-rH2AX-AF488**
  - Median fluorescence intensity: 546

- **Cell + hA20-SN38 + anti-rH2AX-AF488**
  - Median fluorescence intensity: 167

#### HCC1395 (Trop2<sup>neg</sup>)

- **Cell alone**
  - Median fluorescence intensity: 5.54

- **Cell + anti-rH2AX-AF488**
  - Median fluorescence intensity: 122

- **Cell + IMMU-132 + anti-rH2AX-AF488**
  - Median fluorescence intensity: 123

### Notes:

1. IMMU-132 or irrelevant anti-CD20-SN-38 conjugate incubated for 1 h @ 4°C
2. Wash and replace media; incubate overnight 37°C
3. Anti-histone Mab to detect dsDNA breaks
4. Analyze by flow cytometry

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**HCC1395 Trop-2-Negative TNBC**

- No difference between no treatment, irrelevant or specific conjugate treatment

**HCC1806 Trop-2-Positive TNBC**

- IMMU-132 shows 3-fold increase in dsDNA break formation

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**dsDNA breaks are the result of the selective delivery of SN-38 to Trop-2 expressing cells by IMMU-132**

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IMMU-132 Improves SN-38 Delivery to Tumors

Tissues from nude mice bearing human tumor xenografts given IMMU-132 or irinotecan were analyzed for SN-38 and other constitutive products.

Concentrations of products over time (AUC) in mice bearing Capan-1 or NCI-N87 tumors administered irinotecan or IMMU-132

<table>
<thead>
<tr>
<th>Tissue</th>
<th>SN-38</th>
<th>SN-38G</th>
<th>Irinotecan</th>
<th>SN-38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capan-1</td>
<td>0.40</td>
<td>1.08</td>
<td>48.37</td>
<td>54.25</td>
</tr>
<tr>
<td>NCI-N87</td>
<td>2.11</td>
<td>0.31</td>
<td>45.69</td>
<td>43.88</td>
</tr>
</tbody>
</table>

### SN-38 deliver ratio
- IMMU-132/Irinotecan: 135.6
- IMMU-132/Irinotecan: 20.8

\(a\) AUC are expressed as (µg/g·h).

**IMMU-132 delivers as much as 136-fold more SN-38 to tumors than irinotecan**

mABs against Trop-2 in breast cancer

• Need both trop-2 antibody and SN-38 (ADC)
Clinical results in mTNBC
Relapsed/Refractory Metastatic TNBC (mTNBC): Background

• No single standard chemotherapy for relapsed/refractory mTNBC
• Duration of response usually short, with rapid relapse
• Visceral and brain metastases very common
• Median PFS 1.7-3.7 months (Capecitabine, Cisplatin or Carboplatin, Eribulin, Nab-Paclitaxel)
• Median survival 10-13 months from metastasis
## Sacituzumab (IMMU132) in TNBC: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>68 (99)</td>
</tr>
<tr>
<td>Male</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>56 (31-81)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57 (83)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>6 (9)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>23 (33)</td>
</tr>
<tr>
<td>1</td>
<td>46 (67)</td>
</tr>
<tr>
<td><strong>Stage at initial diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12 (17)</td>
</tr>
<tr>
<td>II</td>
<td>25 (36)</td>
</tr>
<tr>
<td>III</td>
<td>21 (30)</td>
</tr>
<tr>
<td>IV</td>
<td>10 (14)</td>
</tr>
<tr>
<td><strong>Median No. of prior therapies (range)</strong></td>
<td>5 (1-12)</td>
</tr>
<tr>
<td><strong>Prior chemotherapy drugs (&gt; 10%)</strong></td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>67 (97)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>63 (91)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>58 (84)</td>
</tr>
<tr>
<td>Platinum agents</td>
<td>48 (70)</td>
</tr>
<tr>
<td>Fluoropyrimidine agents</td>
<td>34 (49)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30 (43)</td>
</tr>
<tr>
<td>Eribulin</td>
<td>27 (39)</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>13 (19)</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>8 (12)</td>
</tr>
</tbody>
</table>

**Heavily pre-treated population**

Median # prior therapies = 5
Sacituzumab (IMMU132) in TNBC: Objective Response Rates

- Response rate = 30%
- Clinical benefit rate (CR+PR+SD at 6 months) = 46%

Bardia A, et al. JCO. 2017
Sacituzumab (IMMU132) in TNBC: Duration of Response

- Median onset of response = 1.9 months
- Median duration of response = 8.9 months

Bardia A, et al. JCO. 2017
Sacituzumab (IMMU132) in TNBC: Survival

Breakthrough Therapy status from FDA in metastatic TNBC in Feb 2016

Bardia A, et al. JCO. 2017
## Sacituzumab (IMMU132) in TNBC: Adverse Events

<table>
<thead>
<tr>
<th>Patients with events</th>
<th>All Grades</th>
<th>Grades ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>74%</td>
<td>7%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>68%</td>
<td>39%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>59%</td>
<td>13%</td>
</tr>
<tr>
<td>Anemia</td>
<td>55%</td>
<td>14%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51%</td>
<td>10%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51%</td>
<td>9%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>38%</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>28%</td>
<td>1%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>25%</td>
<td>16%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23%</td>
<td>9%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Back pain</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>22%</td>
<td>0%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16%</td>
<td>0%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Includes all events >15% (all grades) or >3% (grade ≥3)

- No patient discontinued therapy for treatment-related toxicity.
- No anti-IMMU 132 antibody response with repeated cycles.
TNBC - Skin Lesion Response

Baseline (March 2013) FU: 22 weeks (August 2013) After 12 treatments
Sacituzumab (IMMU132) in TNBC: Clinical Response post PD-1 Inh

- 4 prior therapy lines, including check-point inhibitor (PD-L1 inhibitor).
- Patient treated with IMMU-132 (41 doses) for **14.4 months** until progression.
- PR status achieved after 1.7 months, with **54% best tumor shrinkage response**.
- Duration of tumor response 12.7 months.

Baseline (29 Jan 2015)  
Best response assessment (19 May 2015)

Trop-2: 1+ to 2+; 70% positive
Patient story #2: 67F

- 2007: ER+ breast cancer and had a lumpectomy with XRT.
- 2013: Found to have metastatic disease, which switched to ER-. Enrolled in a clinical trial and discontinued due to progression
- Apr 2014: SRS for brain mets, and then started Eribulin
- Sept 2014: Disease progression on Eribulin
- Tumor Genotyping revealed:
  - TP53 mutation
  - CCND2 mutation (VUS)
  - CDK6 mutation (VUS)
  - Cyclin E amplification

Multiple actionable genomic alterations....
Patient story #2: 67F Enrolled in IMMU132 Trial

Pre-Treatment

Post-Treatment

Panel G: Trop-2 expression by immunohistology showing 2+ to 3+ staining in an archival specimen.

Bardia A, et al. JCO. 2017
Sacituzumab (IMMU132) in TNBC: Summary and Next Steps

- Sacituzumab govitecan was well-tolerated and induced early and durable responses in heavily-pretreated patients with metastatic TNBC, with median PFS around 6 months

- Trop-2 is potentially a novel therapeutic target for TNBC

- Breakthrough Therapy status from FDA in metastatic TNBC

- Phase III randomized, controlled trial (planned under a special protocol agreement with FDA)
Sacituzumab vs SOC Phase-3 Trial (ASCENT)

Stratification Factors
- Geographic Region
- # Prior Regimens
- Presence/absence of known brain mets

Issues:
- All comers
- Heterogeneity in TNBC

AGENTS
Sacituzumab govitecan (IMMU-132)
Physician’s Choice (Choice of 4 regimens)

Metastatic TNBC
≥ 2 prior txs*
N=328
Objective response = 15/49 = 31%
Clinical benefit ratio [CR+PR+(SD ≥4 mo)] = 63%*

How do we move the field further?

Internalization of mAb into Trop-2-positive cancers

Inhibit topo-1

Inhibit DNA replication and repair

HRD Score

Combination therapy
IMMU-132 plus PARPi: BRCA1/2-def and wild-type TNBC
T-DM1 renders HER2+ breast cancer highly susceptible to PD-1 Inh

Philipp Müller et al., Sci Transl Med 2015;7:315ra188
Sacituzumab Govitecan (IMMU-132) (First in Class ADC)

- Novel linker and ADC construct

**CL2A linker**

- Short PEG for solubility
- Thioether coupling to thiols on IgG
- Site-specific coupling to interchain thiols (N = 8)
  - Average of ~ 7.6 SN-38 molecules/IgG
  - High doses of SN-38 delivered
- Glucuronidation site (10th position) is protected while bound to IgG
  - Much lower SN-38G concentrations in serum than with irinotecan
- Linker coupled to 20th position stabilizes lactone ring
  - pH dependent release
PK, UGT1A1 Polymorphism, and Adverse Effects

UGT1A1 polymorphisms could impact Adverse Events
Sacituzumab Govitecan (IMMU-132) (First in Class ADC)

- **Novel linker and ADC construct**

- **CL2A linker**
  - Short PEG for solubility

- **Glucuronidation site**
  - Glucuronidation site (10th position) is protected while bound to IgG
  - Much lower SN-38G concentrations in serum than with irinotecan

- **SN-38**
  - Lactone ring (intact while coupled to linker)
  - pH-dependent cleavage site
  - pH-dependent release

- **Site-specific coupling to interchain thiols (N = 8)**
  - Average of ~ 7.6 SN-38 molecules/IgG
  - High doses of SN-38 delivered

- **Linker coupled to 20th position stabilizes lactone ring**
Patients with the 158 F/F genotype received less benefit from the addition of trastuzumab.
ADCC may play a substantial component in the efficacy of trastuzumab.

Gavin P, et al. JAMA. 2017
Precision Oncology: Sacituzuamub for TNBC

Host Factors (UGT1A1)

Pre-Clinical Studies

Response/Resistance

Sacituzuamub

Complete Response

Tumor Biology (HRD)

PARP

Immune Component (ADCC)

PD-1

Pharmacogenomics

Complex Interaction

Precision Oncology
Biomarkers Based Hypothesis: Neoadjuvant Trial

- Improves rate of breast-conservation therapy
- Allows assessment of tumor response to therapy
- Facilitates identification of predictive biomarkers
- Provides an efficient trial design for assessment of efficacy of novel therapies utilizing pCR (pathological complete remission) as a surrogate marker for survival, particularly TNBC

Bardia A et al. CCR. 2013.
Targeting key genomic drivers and intracellular signaling pathways:
- **BRCA**
- Androgen receptor (AR)

Targeting markers for selective delivery of potent agents:
- **gpNMB ADC**
- **Trop-2 ADC**
## Finding the Positive in Negative: Actionable Targets

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TNBC Terminology: Lets think about this…

- If ADCs against gpNMB+ TNBC pan out, would we then call it QNBC
- What if another actionable alteration linked with targeted therapy pans out: PNBC…What if then another actionable alteration linked with targeted therapy pans out: SNBC….then…
  - SNBC, ONBC, NNBC, DNBC…

- I do not have answers…One could consider either:
  - Objective definition based on tumor biology
  - Functional definition based on patient input and keeping in view the emerging actionable targets

- In not so distance future we might need to take a step back and re-think the TNBC terminology…
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**Gratitude to patients:**

*Thank you!*
Thank you for your attention