Napi2b as the Target

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Honorarium
• Mersana
• AstraZeneca
• Genentech
• Tesaro/ GlaxoSmithKline
• Bayer
• Deciphera
Targets

Antibody targets should have high expression levels on tumor and not on normal tissue

Antibody targets should be present on the cell surface so the ADC can find them

Antibody targets should be internalizing so that the ADC is transported into the cell

Like a Trojan Horse
NaPi2b: An Antigen Broadly Expressed in Multiple Tumor Types

NaPi2b (SLC34A2) is a sodium-dependent phosphate transporter expressed in a high percentage of tumors from patients with epithelial ovarian cancer and lung adenocarcinoma, as well as other tumor types.

Limited expression in normal tissues

Tumor expression
- Salivary duct carcinoma
- Papillary thyroid carcinoma
- Lung adenocarcinoma
- Cholangiocarcinoma
- Papillary renal cell cancer
- Epithelial ovarian cancer
- Endometrial carcinoma

H score = 265

H score = 293

https://www.proteinatlas.org/
RPh2 Lifastuzumab vs. PLD

HR for stratified PFS was 0.78
(95% CI 0.46-1.31; p=0.34)

Banerjee et al. Annals of Oncology 2018
# RPh2 Lifastuzumab vs. PLD Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th>Lifastuzumab</th>
<th>PLD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>34% (95% CI 22-49%)</td>
<td>15% (95% CI 7-28%)</td>
</tr>
<tr>
<td>Grade 3 AEs</td>
<td>46%</td>
<td>51%</td>
</tr>
<tr>
<td>SAEs</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Grade ≥ 2 neuropathy</td>
<td>11%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Banerjee et al. Annals of Oncology 2018
## Common Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Lifastuzumab (n = 46)</th>
<th>PLD (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3–5* n (%)</td>
<td>Overall n (%)</td>
</tr>
<tr>
<td>No. patients with any AE</td>
<td>21 (46)</td>
<td>46 (100)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (4)</td>
<td>20 (44)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>21 (46)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (9)</td>
<td>21 (46)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (2)</td>
<td>17 (37)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>16 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (4)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (13)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (7)</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Peripheral neuropathy SQM</td>
<td>1 (2)</td>
<td>10 (22)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\*Grade 5 AEs included only one in the PLD arm with the term ‘General Physical Health Deterioration’. Otherwise, no deaths were reported as due to an AE.

AEs more common with Lifa: Abdominal pain, diarrhea, neutropenia

AEs more common with PLD: constipation, PPE, stomatitis

Banerjee et al. *Annals of Oncology* 2018
Phase Ib Lifastuzumab plus carboplatin in platinum sensitive recurrent ovarian cancer

**Best Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients N=41</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td></td>
<td>6 (15)</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td>18 (44)</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>13 (32)</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td>2 (5)</td>
</tr>
<tr>
<td>UE</td>
<td></td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

**ORR 59%**

**Dose expansions**

- **Cohort 5**
  - Cycles 1-6: LIFA 2.4 mg/kg + Carbo + Bev
  - Cycles 7 until progression: LIFA + Bev (n=12)

- **Cohort 4**
  - Cycles 1-6: LIFA 2.4 mg/kg + Carbo
  - Cycles 7 until progression: LIFA only (n=13)

**LIFA**: Lifastuzumab Vedotin (DNIB0000A), an antibody drug conjugate of anti-NaPi2b monoclonal antibody (MNIB2126A) and an anti-mitotic agent (MMAE)

**Carbo**: carboplatin at dose AUC 6 mg/m² min

**Bev**: bevacizumab at 15 mg/kg

Moore et al. Gynecol Oncol 2020
XMT-1536 (upifitamab rilsodotin; UpRi): A potent NaPi2b Dolaflexin ADC with a high drug-to-antibody ratio and a controlled bystander effect

**Dolaflexin**
Improved therapeutic index vs other platforms
- Polymer scaffold
- High Drug to Antibody Ratio (DAR) ~10-12
- Excellent drug like properties

**DolaLock Payload**
Efficacy without severe neutropenia, neuropathy, or ocular toxicity
- Novel auristatin
- Controlled bystander effect
- Selectively toxic to rapidly dividing cells
- Not a PgP substrate
- Induces immunogenic cell death
Auristatin DolaLock Payload provides Unique Pharmacology – a Controlled Bystander Effect

Bystander Killing
freely cell permeable

Metabolic Conversion in Tumor Cell

No Bystander Killing
Not cell permeable; not a Pgp substrate

ADCs with its cytotoxic drug conjugates are administered systemically to patients.

The ADC recognizes and binds to the tumor antigen leading to internalization and release of the payload.

The initially released payload is capable of crossing cell membranes and entering adjacent cells to exert a bystander effect.

The DolaLock payload is metabolized to a form that remains highly potent but loses the ability to cross the cell membrane locking it in the tumor and controlling the bystander effect.

= Tumor Antigen

= Initially Released Payload

= Metabolized Payload
Design for the Ovarian Cancer Cohort of the XMT-1536 (UpRi) Phase 1 Expansion Study

Patient population: High grade serous ovarian cancer (including fallopian tube and primary peritoneal cancer) progressing after standard treatments

- Measurable disease per RECIST v1.1
- ECOG Performance Status 0 or 1

Dosing: IV every 4 weeks until disease progression or unacceptable toxicity

- 36 mg/m2 cohort initiated in August 2019 and enrollment closed
- 43 mg/m2 cohort initiated in December 2019 and ongoing; current dose evaluated in EXP

Primary Objectives:
- Evaluate safety and tolerability of MTD
- Assess preliminary efficacy (ORR, DCR)

Secondary Objectives:
- Association of tumor NaPi2b expression and objective tumor response using an immunohistochemistry (IHC) assay with a broad dynamic range to distinguish tumors with higher and lower NaPi2b expression (as previously reported1,2,3)
- Further assessment of preliminary anti-neoplastic activity (DOR)

Assessments:
- Tumor imaging (MRI or CT): baseline and every 2nd cycle; response assessed per RECIST v1.1

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Ovarian Cancer Cohort
- 1-3 prior lines in platinum resistant
- 4 prior lines regardless of platinum status
- High grade serous histology
- Archived tumor and fresh biopsy (if medically feasible) for NaPi2b
- Exclusion: primary platinum-resistant defined as lack of response or disease progression within 3 mos after completing front-line platinum containing

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- Tumor imaging (MRI or CT): baseline and every 2nd cycle; response assessed per RECIST v1.1

Abbreviations: mos = months; EXP = expansion; RECIST = Response Evaluation Criteria in Solid Tumors; ECOG = Eastern Cooperative Oncology Group; MTD = maximum tolerated dose; ORR = objective response rate; DCR = disease control rate; DOR = duration of response

1 Tolcher TW et al. J Clin Oncol 37, 2019 (suppl; abstr 3010)
2 Richardson DL et al. Presented at SGO Annual Meeting 2020; LBA8
3 Hamilton E et al. Presented during the 2020 European Society of Medical Oncology (ESMO) Virtual Congress
### Patient Demographics and Disease Characteristics

Data cut off: 03 December 2020

<table>
<thead>
<tr>
<th>Ovarian Cancer Expansion Patients (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age; years</strong></td>
</tr>
<tr>
<td><strong>ECOG Performance Status; n (%)</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td><strong>Primary Tumor Typea; n (%)</strong></td>
</tr>
<tr>
<td>Ovarian</td>
</tr>
<tr>
<td>Fallopian Tube</td>
</tr>
<tr>
<td>Primary Peritoneal</td>
</tr>
<tr>
<td><strong>Prior Lines of Therapy; n (%)</strong></td>
</tr>
<tr>
<td>1-3</td>
</tr>
<tr>
<td>4+ab</td>
</tr>
<tr>
<td><strong>Prior Therapy; n (%)</strong></td>
</tr>
<tr>
<td>Bevacizumab</td>
</tr>
<tr>
<td>PARP inhibitor</td>
</tr>
<tr>
<td><strong>Platinum-free Intervalc; n (%)</strong></td>
</tr>
<tr>
<td>0-3 mos</td>
</tr>
<tr>
<td>&gt;3-6 mos</td>
</tr>
<tr>
<td>&gt;6 mosd</td>
</tr>
<tr>
<td>Unknowne</td>
</tr>
<tr>
<td><strong>BRCA1/2 Mutation; n (%)</strong></td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unknownf</td>
</tr>
<tr>
<td><strong>NaPi2b H-scoreg; n (%)</strong></td>
</tr>
<tr>
<td>Determined</td>
</tr>
<tr>
<td>Higher</td>
</tr>
<tr>
<td>Lower</td>
</tr>
<tr>
<td>Not Yet Determined (ND)</td>
</tr>
</tbody>
</table>

a Includes 1 Endometroid, 1 Low Grade, 1 Serous / Endometroid, and 1 Carcinosarcoma histology.
b Three patients enrolled with 5 prior lines of systemic therapy.
c Platinum-free interval defined as the time between the last cycle of most recent platinum-containing regimen and evidence of disease progression; determined from treatment dates and/or clinic notes.
d All patients are platinum-sensitive and had received 4 or 5 lines of prior therapy.
e Treatment dates missing/not provided; unable to determine.
f BRCA1/2 mutation status not available/not reported.
g Higher NaPi2b Expression: as defined in dose escalation as ≥110; Lower NaPi2b Expression: as defined in dose escalation as <110; ND = NaPi2b Expression not yet determined or tissue not available.
Consistent Tolerability Profile Without Severe Neutropenia, Peripheral Neuropathy, or Ocular Toxicity

Data as of December 3, 2020

Abbreviations: SAEs = serious adverse events; TRAE = treatment related adverse event
Continued Robust Activity Observed in Heavily-Pretreated Ovarian Cancer

### Best Response in Evaluable Patients with Ovarian Cancer (n = 47)

<table>
<thead>
<tr>
<th></th>
<th>All (n = 47)</th>
<th>Higher NaPi2b(^o) (n = 31)</th>
<th>Lower NaPi2b(^oo) (n = 13)</th>
<th>NaPi2b Not Yet Determined (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR; n(%)</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR; n(%)</td>
<td>11 (23)</td>
<td>8 (26)</td>
<td>2 (15)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>SD; n(%)</td>
<td>19 (40)</td>
<td>13 (42)</td>
<td>5 (38)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>PD; n(%)</td>
<td>15 (32)</td>
<td>8 (26)</td>
<td>6 (46)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>ORR; n (%)</td>
<td>13 (28)</td>
<td>10 (32)</td>
<td>2 (15)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>DCR; n (%)</td>
<td>32 (68)</td>
<td>23 (74)</td>
<td>7 (54)</td>
<td>2 (67)</td>
</tr>
</tbody>
</table>

All Responses are Confirmed

\(^{25}\) patients were not evaluable for RECIST response: 10 patients discontinued prior to first scans: 1 clinical progression; 1 related SAE (G5 pneumonitis); 3 unrelated SAEs; 5 withdrew consent; 15 patients did not yet have RECIST assessment as of the data cut

\(^o\) Higher NaPi2b Expression: defined in dose escalation as at / above lowest H-score at which response observed (≥110)

\(^oo\) Lower NaPi2b Expression: defined in dose escalation as below the lowest H-score at which response observed (<110)
Deep Responses Observed in Heavily-Pretreated Ovarian Cancer

30/45 (67%) had reductions in target tumor lesions

Maximum % Change from Baseline in Target Lesions in Patients with Ovarian Cancer (n = 45*)

* 2 patients not included in waterfall plot as tumor measurement data missing in the database as of data cut; both patients had BOR of PD due to new lesions

** Unconfirmed response, BOR per RECIST v1.1 is SD

*** CR of target lesions and non-CR/non-PD of non-target lesions, BOR per RECIST v1.1 is PR

H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = NaPi2b Expression not yet determined or tissue not available
Responses with XMT-1536 (UpRi) Occur Early and Appear to Deepen Over Time

Tumor response observed within 2 cycles in 69% (9 of 13) of Responders

Change from Baseline in Target Lesions in Patients with Ovarian Cancer (n = 45)

H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = NaPi2b Expression not yet determined or tissue not available
Clear Trend to Longer Time on Study with Higher NaPi2b Expression

Time on XMT-1536 Study in Patients with Ovarian Cancer (n = 72)

Abbreviations: CR = complete response; PR = partial response; H = Higher NaPi2b Expression; L = Lower NaPi2b Expression; ND = NaPi2b Expression not yet determined or tissue not available
Median Duration of Response Estimated to be ~5 Months in Patients with Higher NaPi2b Expression

Durability of Response in Patients with Ovarian Cancer and Higher NaPi2b (n = 10)

- Median Duration of Response: ~5 months

- 2 patients with Lower NaPi2b with DOR of 16.1 and 17.1 weeks, respectively
- 1 patient with NaPi2b ND with DOR 16.1 weeks
Complete Response in a Patient with Ovarian Cancer

- 70-yr-old woman with platinum-resistant high-grade serous OC previously treated with carboplatin/paclitaxel; carboplatin/gemcitabine; bevacizumab; niraparib; investigational anti-PD1

- Treated with 36 mg/m² q4w (with dose reduction to 30 mg/m² at Cycle 2); first PR observed after approx. 7 weeks of treatment with XMT-1536 (end of Cycle 2) which was confirmed with the following scan (end of Cycle 4); best overall response of CR
  - Patient remains disease free with DOR of ~10 months

![Baseline Oct 2019](image1)

![Confirmed PR Feb 2020 – Post](image2)

![Confirmed CR* April 2020](image3)

*CR confirmed at unscheduled scan 4 weeks after first observation of CR

![CA125](image4)

![Histology](image5)
Single-Arm UPLIFT Cohort – an amendment to the ongoing Ph1b study

UPLIFT will be operationalized as an amendment as opposed to initiating a new study

Objective

- Determine safety and MTD: 43 mg/m²
- Proof of concept achieved June 2020
- Expansion cohort serves as training set for NaPi2b biomarker
- Demonstrate clinically meaningful outcome
- Validate NaPi2b Biomarker

First in Human to Pivotal Cohort in One Study

Dose Escalation Cohort
(Enrollment Complete in March 2020)

Ovarian Cancer Expansion Cohort
(Enrollment August 2019 – Q1 2021)

UPLIFT: Single-Arm US Registration Strategy in Platinum Resistant Ovarian Cancer
(Planning Patient Dosing in Q1 2021)
UPLIFT: Single-Arm US Registration Strategy in Platinum Resistant Ovarian Cancer

UPLIFT Design

Platinum-Resistant High-Grade Serous Ovarian Cancer

- N=~100 Higher NaPi2b, up to ~180 Overall
  - 1-4 prior lines
- Prior bevacizumab not required for patients with 3 – 4 prior lines
- No exclusion for baseline peripheral neuropathy
- Enrolling regardless of NaPi2b expression

Primary Endpoint:
Confirmed ORR in higher NaPi2b

Key Secondary Endpoint:
Confirmed ORR in overall population

Other Secondary Endpoints: Duration of Response; Safety

Dose: 43 mg/m² IV q28d
Global: US, Europe, Australia, Canada

Planning to Initiate Patient Dosing in Q1 2021