ADC Opportunities in Ovarian Cancer
Isabelle Ray-Coquard, MD, PhD
ADCs are engineered to limit systemic toxicity and improve the therapeutic index of cytotoxic agents

ADCs are a class of targeted therapies that are designed to selectively deliver cytotoxic drugs to cancer cells\(^1\)

- **Systemic chemotherapies** (eg, taxanes)\(^2\)
- Cytotoxic agents that target rapidly dividing cancerous and healthy cells
- Severe side effects limit administrable dose
- **Narrow therapeutic window** resulting from a small therapeutic index

ADCs are engineered to limit systemic toxicity and improve the therapeutic index of cytotoxic agents

ADCs (eg, Mirvetuximab soravtansine)\(^1,2\)

- Designed to reduce off-target toxicities of potent cytotoxic payloads
- Broader therapeutic window by limiting exposure of healthy tissue to cytotoxic drugs

ADCs induce cancer cell death via chemical or enzyme-mediated release of payload in lysosomes

**Mechanism of action**¹⁻³

1. Antibody binds to the target antigen at the surface of the cancer cell
2. ADC–antigen complex is internalized by receptor-mediated endocytosis
3. An early endosome is formed whereby cargo is sent through 2 pathways:
   - Recycling, which results in trafficking back to the plasma membrane, or
   - Endolysosomal degradation
4. The payload is released by degradation of the linker in the endolysosomal compartment
5. Drug payload enters the cytoplasm
6. Drug payload acts on microtubules or DNA, resulting in apoptosis

---

ADC, antibody-drug conjugate; DNA, deoxyribonucleic acid.

The linker is designed to ensure that the ADC is highly stable in circulation, yet efficiently releases the payload in the tumor cells. Stable linkers in ADCs maintain antibody concentration in circulation, preventing premature cytotoxic drug release and reducing off-target effects.

**Cleavable linker**
- Uses the inherent properties of tumor cells to selectively release cytotoxic payload (protease-sensitive, pH-sensitive, glutathione-sensitive)
- Potential for premature payload release (pH-sensitive linkers)
- Examples: gemtuzumab ozogamicin, brentuximab vedotin

**Noncleavable linker**
- No obvious drug release mechanism, relies on the complete lysosomal proteolytic degradation of the antibody
- More stable in circulation
- Limited diffusion to neighboring cancer (or healthy) cells
- Example: trastuzumab emtansine

**Linker must be stable in serum and extracellular environment, and cleavable once in the tumor cells.** Stable linkers in ADCs maintain antibody concentration in circulation, preventing premature cytotoxic drug release and reducing off-target effects.
Payload is the effector component of the ADC

Two classes of antitumor drugs are commonly used as payloads in ADCs

<table>
<thead>
<tr>
<th>Class</th>
<th>Considerations</th>
<th>Targets rapidly proliferating cells</th>
<th>Potent agents that may target DNA independent of cell cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microtubule inhibitors</td>
<td>• Auristatins (eg, MMAE, MMAF)</td>
<td></td>
<td>• Calicheamicin</td>
</tr>
<tr>
<td></td>
<td>• Eribulin</td>
<td></td>
<td>• Duocarmycin</td>
</tr>
<tr>
<td></td>
<td>• Hemilasterlin</td>
<td></td>
<td>• Pyrrolobenzodiazepine</td>
</tr>
<tr>
<td>DNA-damaging agents</td>
<td>• Maytansinoids (eg, DM1, DM4)</td>
<td></td>
<td>• Topoisomerase inhibitor</td>
</tr>
<tr>
<td></td>
<td>• Tubulysin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Examples                     | • Mirvetuximab soravtansine                                                  |                                    | • Sacituzumab govitecan                                    |
|                              | • Tisotumab vedotin                                                           |                                    | • Trastuzumab deruxtecan                                   |

Bystander effect is an important characteristic, especially in tumors with heterogeneous antigen expression

1. Membrane-permeable payloads diffuse from target cell into neighboring cells, leading to cell death
2. Under amenable extracellular conditions, payload may be released into the extracellular space

Bystander effect can be an advantage in heterogeneous tumors if the neighbor cell is a tumor cell; however, if payloads diffuse into healthy tissue or bloodstream, this can lead to off-target toxicity

Currently approved ADC payloads


In addition to cytotoxic drugs, immune-stimulating ADCs with toll-like receptor (TLR) and stimulator of interferon gene (STING) agonists are in early phases of clinical investigation.  

ADC, antibody-drug conjugate; bcxXL: B-cell lymphoma – extra long; CPT-11, irinotecan; DM1, mertansine; DM4, ravelansine; DNA, deoxyribonucleic acid; DXD, deruxtecan; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin; PBD, pyrrolobenzodiazepine; PNU, effective metabolite of the anthracycline nemorubicin; SN-38, active metabolite of irinotecan; STING, stimulus of interferon genes; TLR, toll-like receptor.
Summary of currently approved ADCs for cancer treatment in the United States

7 Belantamab mafodotin was approved in 2020 for the treatment of relapsed or refractory multiple myeloma; however, withdrawal of this indication was initiated in November 2022 at the request of the US Food and Drug Administration.3,6

2 ADCs approved for gynecologic cancers2:
- Mirvetuximab soravtansine (FRα+ ovarian)
- Tisotumab vedotin (Cervical [tissue factor])

Approval list as of October 2023

**Select ADCs under clinical development in gynecologic oncology**

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>DAR</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>B7-H4</td>
<td>XMT-1660&lt;sup&gt;1&lt;/sup&gt;</td>
<td>6</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>SGN-B7H4V&lt;sup&gt;2&lt;/sup&gt;-4</td>
<td>4</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>AZD8205&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>8</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td>CDH6</td>
<td>DS-6000a&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>~8</td>
<td>Ovarian</td>
</tr>
<tr>
<td>FRα</td>
<td>Luveltamab tazevibulin (STRO-002)&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>4</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>Farletuzumab cetrebibulin (MORAb-202)&lt;sup&gt;11,12&lt;/sup&gt;</td>
<td>4</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td>HER2</td>
<td>SYD985&lt;sup&gt;13,14&lt;/sup&gt;</td>
<td>2.7</td>
<td>Ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>T-DXd&lt;sup&gt;15,16&lt;/sup&gt;</td>
<td>7–8</td>
<td>Cervical, ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>DB-1303/BNT323&lt;sup&gt;17,18&lt;/sup&gt;</td>
<td>~8</td>
<td>Endometrial</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>BMS-986148&lt;sup&gt;19,20&lt;/sup&gt;</td>
<td>3</td>
<td>Ovarian</td>
</tr>
<tr>
<td>Tissue factor</td>
<td>XB002&lt;sup&gt;21,22&lt;/sup&gt;</td>
<td>4</td>
<td>Cervical, ovarian</td>
</tr>
<tr>
<td>TROP2</td>
<td>Sacituzumab govitecan&lt;sup&gt;23, 24&lt;/sup&gt;</td>
<td>7.5</td>
<td>Cervical, ovarian, endometrial</td>
</tr>
<tr>
<td></td>
<td>DB-1305&lt;sup&gt;25, 26&lt;/sup&gt;</td>
<td>~4</td>
<td>Ovarian, endometrial</td>
</tr>
</tbody>
</table>

**Notes:**
Mirvetuximab soravtansine (Elahere), the first FRα-targeted ADC approved for treatment of PROC

**Accelerated approval granted in November 2022 based on data from pivotal SORAYA trial**

**SORAYA (NCT04296890)** was a global, single-arm pivotal study evaluating mirvetuximab soravtansine in adult patients with FRα-positive platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer

**Key eligibility criteria**
- Platinum-resistant ovarian cancer
- Prior bevacizumab required, prior PARPi allowed
- 1–3 prior lines of therapy
- Patients with BRCA mutations allowed
- FRα-positive (≥75% of cells staining positive with ≥2+ staining intensity)

**MIRV is an ADC comprising an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload**

**Primary endpoint**
- ORR per Investigator

**Secondary endpoints**
- DOR, PFS, OS, CA-125 response by GCIG criteria, safety

---

Summary of mirvetuximab soravtansine efficacy and safety

**SORAYA key efficacy endpoints**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All Grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
<th>All Grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>3 (&lt;1)</td>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>64 (14)</td>
<td>4 (&lt;1)</td>
<td>14 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>36 (8)</td>
<td>4 (&lt;1)</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>4 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>2 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>21 (5)</td>
<td>0</td>
<td>5 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>43 (9)</td>
<td>4 (&lt;1)</td>
<td>8 (8)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>43 (9)</td>
<td>1 (&lt;1)</td>
<td>10 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (8)</td>
<td>2 (&lt;1)</td>
<td>14 (13)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*a*Data shown from SORAYA safety population are derived from a separate data cutoff of April 29, 2022. DOR: duration of response; mDOR, median duration of response; ORR, objective response rate; TRAE, treatment-related adverse event.

MIRASOL (GOG-3045/ENGOT-ov55): phase 3 mirvetuximab soravtansine vs IC chemotherapy in FRα-high PROC\textsuperscript{1,a}

Confirmatory trial designed to generate the randomized data to support full approval\textsuperscript{2}

**Key inclusion criteria:**
- Platinum-resistant disease (PFI ≤6 mo)
- FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells
- High-grade serous histology
- 1\textdegree platinum-refractory disease excluded (primary PFI <3 mo)
- 1–3 prior lines of therapy
- Prior BEV and PARPi allowed
- Patients with BRCA mutations allowed

**Endpoints**
- Primary: PFS by investigator (BICR sensitivity analysis)
- Key secondary: ORR by inv, OS, PROs (EORTC-OV28)\textsuperscript{a}, CA-125\textsuperscript{b}

\textsuperscript{1}PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (EORTC-OV28) study instrument. \textsuperscript{a}Gynecological Cancer InterGroup (GCIG) criteria.

AIBW, adjusted ideal body weight; BEV: bevacizumab; BICR, blinded independent central review; BRCA, breast cancer gene; CA-125, cancer antigen 125; DOR, duration of response; FRα, folate receptor alpha; IC, investigator’s choice; IHC, immunohistochemistry; inv, investigator; IV, intravenous; MIRV, mirvetuximab soravtansine; mo, months; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; q3w, every 3 weeks; q4w, every 4 weeks; R, randomization.

Primary endpoint: PFS by investigator

Data cutoff: March 6, 2023

IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; mPFS, median progression-free survival.


<table>
<thead>
<tr>
<th></th>
<th>MIRV (n=227)</th>
<th>IC Chemo (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS (95% CI)</td>
<td>5.62 (4.34, 5.95)</td>
<td>3.98 (2.86, 4.47)</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>176 (77.5)</td>
<td>166 (73.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.52, 0.81)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. Participants at Risk

<table>
<thead>
<tr>
<th></th>
<th>MIRV</th>
<th>IC Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRV</td>
<td>227</td>
<td>151</td>
</tr>
<tr>
<td>IC Chemo</td>
<td>226</td>
<td>98</td>
</tr>
</tbody>
</table>
Key secondary endpoint: OS

Overall survival was statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313.

CI, confidence interval; HR, hazard ratio; IC Chemo, investigator’s choice chemotherapy; MIRV, mirvetuximab soravtansine; mOS, median overall survival.

Data cutoff: March 6, 2023; median follow-up time: 13.11 months.

*Overall survival was statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313.

<table>
<thead>
<tr>
<th></th>
<th>MIRV (n=227)</th>
<th>IC Chemo (n=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (95% CI)</td>
<td>16.46 (14.46, 24.57)</td>
<td>12.75 (10.91, 14.36)</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>90 (39.6)</td>
<td>114 (50.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.67 (0.50, 0.89)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0046</td>
<td></td>
</tr>
</tbody>
</table>
Maximum percentage change in target lesion size from baseline by investigator (N=453)

80% with tumor reduction

42% ORR (confirmed)

55% with tumor reduction

16% ORR (confirmed)

Data cutoff: March 6, 2023

IC chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; ORR, objective response rate.

Gorp TV et al. Poster presented at ESGO 2023; Abstract 1015.
Exploratory endpoints: Activity of MIRV post PARPi treatment

<table>
<thead>
<tr>
<th>No. Participants at Risk</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARPi treated</strong></td>
<td></td>
</tr>
<tr>
<td>MIRV</td>
<td>IC Chemo</td>
</tr>
<tr>
<td>124</td>
<td>127</td>
</tr>
<tr>
<td>88</td>
<td>52</td>
</tr>
<tr>
<td>54</td>
<td>25</td>
</tr>
<tr>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>MIRV (n=124)</th>
<th>IC Chemo (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS (95% CI)</td>
<td>5.85 (4.57, 7.06)</td>
<td>3.91 (2.60, 4.37)</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>91 (73.4)</td>
<td>90 (70.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.58 (0.43, 0.78)</td>
<td></td>
</tr>
<tr>
<td>Nominal P-value</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th></th>
<th>MIRV (n=124)</th>
<th>IC Chemo (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (95% CI)</td>
<td>19.88 (15.61, NR)</td>
<td>11.37 (9.89, 13.77)</td>
</tr>
<tr>
<td>Events, n (%)</td>
<td>42 (33.9)</td>
<td>67 (52.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.48 (0.33, 0.71)</td>
<td></td>
</tr>
<tr>
<td>Nominal P-value</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff: March 6, 2023.
CI, confidence interval; HR, hazard ratio; IC Chemo, investigator’s choice chemotherapy; MIRV, mirvetuximab soravtansine; PFS, median progression-free survival; OS, median overall survival; NR, not reached; PARPi, poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors.
### Safety summary observed with mirvetuximab soravtansine

Data cutoff: March 6, 2023.
The safety population comprises all patients who received at least 1 dose of MIRV or IC chemo.
IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; SAE, serious adverse events; TEAE, treatment-emergent adverse events; Topo, topotecan.
Gorp TV et al. Poster presented at ESGO 2023; Abstract 1015.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MIRV (n=218)</th>
<th>IC Chemo (n=207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE, n (%)</td>
<td>210 (96)</td>
<td>194 (94)</td>
</tr>
<tr>
<td>Grade 3+ TEAEs, n (%)</td>
<td>91 (42)</td>
<td>112 (54)</td>
</tr>
<tr>
<td>SAEs, n</td>
<td>52 (24)</td>
<td>68 (33)</td>
</tr>
<tr>
<td>Deaths on study drug or within 30 days of last dose, n (%)</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Dose reductions due to TEAEs, n (%)</td>
<td>74 (34)</td>
<td>50 (24)</td>
</tr>
<tr>
<td>Dose delays due to TEAEs, n (%)</td>
<td>117 (54)</td>
<td>111 (54)</td>
</tr>
<tr>
<td>Discontinuations due to TEAEs, n (%)</td>
<td>20 (9)</td>
<td>33 (16)</td>
</tr>
</tbody>
</table>
Mirvetuximab soravtansine + bevacizumab in patients with PROC in the phase 1b/2 FORWARD II study

Study designed to evaluate the efficacy and safety of MIRV + bevacizumab in recurrent FRα-expressing epithelial ovarian cancer

Patient population:1,2

- FRα expression was assessed using immunohistochemistry PS2+ scoring, scored as the percent of viable tumor cells staining with ≥2+ intensity
  - FRα Low: ≥25% to 49%
  - FRα Medium: 50% to 74%
  - FRα High: ≥75%
- Platinum status was stratified by PFI as PFI >6 months or PFI ≤6 months
- Bev treatment status was defined as Bev-naïve or Bev-treated (defined as having received Bev in any line of therapy)

Treatment schedule: MIRV 6 mg/kg, adjusted ideal body weight + bev 15 mg/kg IV on day 1 of a 3-week cycle

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>62 (39–81 years)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>60 (64)</td>
</tr>
<tr>
<td>1</td>
<td>34 (36)</td>
</tr>
<tr>
<td>FRα expression, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥75%</td>
<td>44 (47)</td>
</tr>
<tr>
<td>50–74%</td>
<td>39 (42)</td>
</tr>
<tr>
<td>25–49%</td>
<td>11 (12)</td>
</tr>
<tr>
<td>No. of prior systemic therapies, n (%)</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>45 (48)</td>
</tr>
<tr>
<td>≥3</td>
<td>49 (52)</td>
</tr>
<tr>
<td>Prior exposure, %</td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>91 (97)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>55 (59)</td>
</tr>
<tr>
<td>PARPi</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Epithelial ovarian cancer</td>
<td>72 (77)</td>
</tr>
<tr>
<td>Fallopian tube cancer</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Primary peritoneal cancer</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

- 52% had ≥3 prior LOT
- 59% had received prior bev

1. O’Malley et al. Poster presented at IGCS 2022; Abstract 496
Phase 1b/2 FORWARD II PROC: overall response rate

**ORR\(^a\) in the overall population and by FR\(\alpha\) expression level subgroups**

### Overall Population
- Total population: 126
  - PR, 38%
  - CR, 8%
  - DOR: 44% (95% CI: 35.6–63.6)

### FR\(\alpha\) Expression\(^b\)
- High: 62
  - CR, 8%
  - PR, 44%
  - DOR: 52% (95% CI: 38.6–64.5)
- Medium: 51
  - CR, 0%
  - PR, 39%
  - DOR: 39% (95% CI: 28.6–53.9)
- Low: 13
  - CR, 31%
  - PR, 8%
  - DOR: 31% (95% CI: 9.1–61.4)

---

**ORR\(^a\) in subgroups by bev treatment status, platinum-free interval, and prior lines of therapy**

### ORR\(^a\) in the overall population and by FR\(\alpha\) expression level subgroups

- **Total population** (N=126)
  - CR, 10%
  - PR, 38%
  - DOR: 44% (95% CI: 35.6–53.6)

### Prior Exposure to BEV
- **BEV-naive** (N=60)
  - CR, 6%
  - PR, 38%
  - DOR: 44%
- **BEV-treated** (N=66)
  - CR, 10%
  - PR, 48%
  - DOR: 58% (95% CI: 44.9–70.9)

### Platinum-Free Interval
- > 6 mo (N=31)
  - CR, 3%
  - PR, 38%
  - DOR: 32% (95% CI: 20.9–44.4)
- ≤ 6 mo (N=94)
  - CR, 5%
  - PR, 38%
  - DOR: 44% (95% CI: 33.4–54.2)

### No. Prior Lines of Therapy
- 1 (N=27)
  - CR, 7%
  - PR, 36%
  - DOR: 63% (95% CI: 42.4–80.6)
- 2-3 (N=70)
  - CR, 7%
  - PR, 34%
  - DOR: 41% (95% CI: 26.8–52.8)
- 4+ (N=29)
  - CR, 3%
  - PR, 31%
  - DOR: 34% (95% CI: 17.9–54.3)

---

\(^a\)DOR (a secondary endpoint) was defined as the time from the date of first response (complete or partial response) to the date of PD or death from any cause, whichever occurred first. \(^b\)Low, 25% to 49%; medium, 50% to 74%; high ≥ 75% of tumor cells with ≥2+ staining intensity.

Bev, bevacizumab; CI, confidence interval; CR, complete response; DOR, duration of response; FR\(\alpha\), folate receptor alpha; NE, not estimable; ORR, objective response rate; PD, progressive disease; PROC, platinum-resistant ovarian cancer; PR, partial response.

O'Malley et al. Poster presentation at IGCS 2022; Abstract 496.
Phase 1b/2 FORWARD II PROC: safety summary

Most TRAEs were low grade; GI, ocular, and fatigue were the most common

48% of patients experienced grade ≥3 events; the most common was hypertension (16%)

Due to treatment-emergent AEs, 30% discontinued MIRV and 37% discontinued bev

- 4 patients (3%) discontinued MIRV due to blurred vision

Patients received a median of 8 cycles of MIRV + bev (range 1–35 cycles)

There was 1 death, which was deemed related to a study treatment (intestinal perforation possibly related to bev)

Data cutoff: June 21, 2021.

TRAE, adverse event; MIRV, mirvetuximab soravtansine; PROC, platinum-resistant ovarian cancer; TRAE, treatment-related adverse event.

1. O’Malley et al. Poster presented at IGCS 2022; Abstract 496.
**Other promising FRα ADCs: Luveltamab tazevibulin (Luvelta, STRO-002) FRα-targeted ADC**

**Luvelta**

- Luveltamab (STRO-002) is a homogenous ADC targeting FRα
- Cathepsin B linker, which is a stable protease-cleavable linker
- Hemiasterlin-derivative cytotoxic payload
- DAR=4

**Efficacy**

Phase 1 dose-expansion study (NCT03748186)

<table>
<thead>
<tr>
<th>ADC</th>
<th>ORR</th>
<th>TPS</th>
<th>Subset of FRα &gt; 25% by TPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3 mg/kg Q3W n=23</td>
<td>31.7%</td>
<td>Yes</td>
<td>37.5%</td>
</tr>
<tr>
<td>5.2 mg/kg Q3W n=21</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Safety**

Phase 1 dose-expansion study

**TRAEs leading to dose reduction in 61.4%**
- Neutropenia in 17 patients (39%)
  - Primarily G3/4 uncomplicated (abnormal lab value only)
  - Febrile neutropenia in 2 patients (4.5%)
  - Resolved without growth factor support in most patients
- Median duration of G3+ AEs, 8 days
- Arthralgia in 8 patients (18%)
- Peripheral neuropathy in 3 patients (6.8%)
- Most G1/2

**TEAEs leading to dose discontinuation in 3 patients (6.8%)**
- G3 fatigue
- G2 neuropathy
- G5 Sepsis

---

*Luveltamab tazevibulin (Luvelta, STRO-002) homogenous ADC targeting FRα. Cathepsin B linker, a stable protease-cleavable linker.*

**Currently moving to late phase trial**
Other promising FRα ADCs: Farletuzumab ecteribulin (MORAb-202) FRα-targeted ADC

MORAb-202 is an ADC consisting of:
- Antibody: farletuzumab
- Linker: cathepsin B cleavable linker
- Payload: eribulin, microtubule inhibitor
- DAR=4

**Efficacy**

Phase 1 dose-expansion study (NCT03386942)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1: MORAb-202 0.9 mg/kg (n=24)</th>
<th>Cohort 2: MORAb-202 1.2 mg/kg (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n (%)</td>
<td>1 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>5 (20.8)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>10 (41.7)</td>
<td>9 (42.9)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>8 (33.3)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>ORR, n (5, 95% CI)*</td>
<td>6 (25.0), (9.8–46.7)</td>
<td>11 (52.4), (29.8–74.3)</td>
</tr>
<tr>
<td>DCR, n (5, 95% CI)*</td>
<td>16 (66.7), (44.7–84)</td>
<td>20 (96.2), (76.2–99.9)</td>
</tr>
<tr>
<td>mPFS, mo (95% CI)*</td>
<td>6.7 (1.5–12)</td>
<td>8.2 (4.2–10.4)</td>
</tr>
<tr>
<td>mOS, mo (95% CI)*</td>
<td>10.5 (6.4–15.1)</td>
<td>NE (12.5–NE)</td>
</tr>
</tbody>
</table>

Data cutoff date: October 31, 2021.

**Safety**

Phase 1 dose-expansion study

- The most common TEAE was interstitial lung disease (ILD)/pneumonitis at both dose levels
  - Cohort 1: 37.5%
    - (n=9; 8 with Gr 1; 1 with Gr 2)
  - Cohort 2: 66.7%
    - (n=14; 6 with Gr 1; 7 with Gr 2, 1 with Gr 3)
- Other common TEAEs of any grade, in Cohorts 1 and 2, respectively, were:
  - Nausea (25.0%; 33.3%)
  - Pyrexia (33.3%; 42.9%)
  - Malaise (16.7%; 28.6%)
  - Headache (12.5%; 47.6%)

---

*CI calculations: ORR, DCR–Clopper-Pearson’s exact method; PFS, OS–Kaplan-Meier estimate and Greenwood formula. ADC, antibody-drug conjugate; CI, confidence interval; CR, complete response; DAR, drug-to-antibody ratio; DCR, disease control rate; FRα, folate receptor alpha; Gr, grade; HGS, high-grade serous; ILD, interstitial lung disease; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

Other promising FRα ADCs: PRO1184 & IMGN1511 in phase 1/2 Studies

PRO1184 (NCT05579366)\(^1,2\) – Phase 1/2

IMGN 151 (NCT04209855)\(^3,4\) – Phase 1/2

- B5327A: asymmetric biparatopic anti-FRα antibody comprised of IMGS83 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-L-G: new more potent maytansine-derived payload/linker

**PRO1184 Structure**

![PRO1184 Structure Diagram](image)

**IMGN 151 (NCT04209855)**

![IMGN 151 (NCT04209855) Diagram](image)

**Part A: Dose escalation and dose level expansion**

- Potential tumor types:
  - EOC
  - anti-neutrophilic cancer
  - breast cancer (HER2, HER2-)
  - mesotheliomas

**Part B: FRα-positive tumor specific dose-expansions**

- **Tumor Type 1**
  - mPFS: 6.75 mg/kg

- **Tumor Type 2**
  - mPFS: 50 mg/kg

- **Tumor Type 3**
  - mPFS: 100 mg/kg

- **Tumor Type 4**
  - mPFS: 150 mg/kg

**DM21-L-G**

- Medium FRα (H-score 120)
- Low FRα (H-score 48)

**Expansions**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Expansion Phase</th>
<th>Endometrial Cancer (n=12 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort A</td>
<td>Endometrial Cancer</td>
<td>Imiglmab 150 mg/kg</td>
</tr>
<tr>
<td>Cohort B</td>
<td>PROC</td>
<td>Imiglmab 150 mg/kg</td>
</tr>
</tbody>
</table>

**Patient Selection**

- Full Expansion
- Cohort B: enrollment of 12 patients (at least 2 patients with endometrial cancer and proficient polyplidome)

**Shared with permission**
Raludotatug deruxtecan (DS-6000a), CDH6-directed ADC\textsuperscript{1,2}

**Efficacy**
- **Confirmed ORR:** 53%; unconfirmed ORR: 57% in the 4.8–8.0 mg/kg OVC cohort
- **DCR:** 98%

**Safety**

<table>
<thead>
<tr>
<th>Most common (≥10%) TEAEs</th>
<th>All grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>35 (58.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (45.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (33.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (28.3)</td>
<td>11 (18.3)</td>
</tr>
<tr>
<td>Decreased neutrophil count</td>
<td>15 (25.0)</td>
<td>7 (11.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (26.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15 (25.0)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>10 (16.7)</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7 (11.7)</td>
<td>0</td>
</tr>
<tr>
<td>Malaise</td>
<td>6 (10.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

**DS-6001\textsuperscript{1,2}**
- A humanized anti-CDH6 IgG1 monoclonal antibody
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker
- DAR ~8

**NCT04707248:** Recruiting
- Estimated enrollment: 140 participants
- Estimated primary completion date: October 31, 2024

---


---

**Data cutoff:** July 14, 2023

**Abbreviations:**
- ADC, antibody-drug conjugate
- CDH6, cadherin-6
- DAR, drug-to-antibody ratio
- DCR, disease control rate
- DOR, duration of response
- f/u, follow-up
- IgG1, immunoglobulin G1
- NE, not estimable
- OVC, serous ovarian cancer
- PFS, progression-free survival
- PR, partial response
- PROC, platinum-resistant ovarian cancer
- RCC, renal cell carcinoma
- TEAE, treatment-emergent adverse event

**Table:**
- Best % change from baseline in sum of diameters of target lesions

**Chart:**
- Starting dose level

---

**Legend:**
- Humanized anti-CDH6 IgG1 mAb
- Deruxtecan
- Cleavable tetrapeptide-based linker
- Topoisomerase I inhibitor payload (Exatecan)

---

**Note:**
- DOR: Median f/u for DOR: 5.8 months (range: 1.4–16.8).
- PFS: Median f/u for PFS: 5.6 months (range: 0.03–25.1).
Trastuzumab deruxtecan (T-DXd), HER2-targeted ADC under clinical investigation for patients with HER2-expressing tumors including OC

DESTINY-PanTumor02 (NCT04482309), phase 2, T-DXd in select advanced HER2-expressing tumors (including GYN tumors)\(^1,2\)

Trastuzumab deruxtecan (T-DXd)\(^1\)

- ADC targeting ERBB2 (HER2)
- Conjugated to a topoisomerase inhibitor
- DAR=8

Study design and population

Patient population (N=299)
- Locally advanced, inoperable, or metastatic disease
- Measurable disease
- Prior HER2-targeting therapy allowed

<table>
<thead>
<tr>
<th>Cohort</th>
<th>T-DXd 3.4 mg/kg q3w (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.3 (4.1, 22.1)</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>63.6</td>
</tr>
<tr>
<td>4</td>
<td>36.8</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Cohort 1: biliary tract cancer
Cohort 2: bladder cancer
Cohort 3: cervical cancer
Cohort 4: endometrial cancer
Cohort 5: ovarian cancer
Cohort 6: pancreatic cancer
Cohort 7: rare tumors* (GYN tumors)

NCT04482309: Active, not recruiting
- Actual enrollment: 468 participants
- Estimated primary completion date: March 2027

Objective response and duration of response in ovarian cancer cohort

ADC, antibody-drug conjugate; cORR, confirmed overall response rate; DAR, drug-to-antibody ratio; DOR, duration of response; ERBB2, erb-b2 receptor tyrosine kinase 2; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OC, ovarian cancer; q3w, every 3 weeks.