Emerging opportunities in platinum-resistant recurrent ovarian cancer

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UC San Diego

November 11, 2022
New & Emerging Data...
Mirvetuximab + Bevacizumab

**Patient population (N=126):**
Patients with FRα-positive epithelial ovarian, primary peritoneal, or fallopian tube cancer

- FRα expression (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 platinum-free interval as PFI > 6 months or PFI ≤ 6 months
- BEV treatment defined as BEV-naïve or BEV-treated (BEV in any line of therapy)

**Treatment schedule**
MIRV 6 mg/kg, adjusted ideal body weight + BEV 15 mg/kg intravenously on day 1 of a 3-week cycle

**Endpoints:**
Primary: Confirmed ORR by RECIST v1.1
Secondary: DOR, PFS, Safety

**Expansion**
BEV-naïve (N=21)
BEV-pretreated (N=34)
Platinum-agnostic (N=60)

**Escalation**
MIRV 5 mg/kg + BEV 15 mg/kg (N=3)
MIRV 6 mg/kg + BEV 15 mg/kg (N=11)

**46% had ≥3 prior lines of therapy**
**52% had received prior BEV**
**75% had a most recent PFI of ≤6 months**
**40% had low or medium FRα expression** (25%–74% of tumor cells with ≥2+ intensity FRα staining)

O’Malley et al. IGCS 2022
Mirvetuximab + Bevacizumab (ORR and DOR)

**Objective response rate (ORR)**

- **Overall Population**
  - **Total population** (N=126)
  - **High** (n=62)
  - **Medium** (n=51)
  - **Low** (n=13)

  - **FRα Expression**
    - **High**
      - CR, 8%
      - PR, 44%
    - **Medium**
      - CR, 0%
      - PR, 39%
    - **Low**
      - CR, 23%
      - PR, 8%

  - **ORR**
    - **Overall Population**
      - **FRα Expression**
        - **High**
          - 52% (95% CI, 35.6–64.5)
        - **Medium**
          - 39% (95% CI, 25.8–53.9)
        - **Low**
          - 31% (95% CI, 9.1–61.4)

  - **Overall Population**
    - **FRα Expression**
      - **High**
        - 44% (95% CI, 35.6–53.6)
      - **Medium**
        - 39% (95% CI, 25.8–53.9)
      - **Low**
        - 52% (95% CI, 38.6–64.5)

**Duration of response (DOR)**

- **Overall Population**
  - **FRα Expression**
    - **High**
      - 11.8 months (95% CI, 8.3–13.7)
    - **Medium**
      - 11.8 months (95% CI, 8.6–13.7)
    - **Low**
      - 8.3 months (95% CI, 3.9–NE)

- **Overall Population**
  - **FRα Expression**
    - **High**
      - 18.5 months (95% CI, NE–NE)

- **Median duration of response, mo**

  - **Overall Population**
    - **FRα Expression**
      - **High**
        - 11.8 months (95% CI, 8.3–13.7)
      - **Medium**
        - 11.8 months (95% CI, 8.6–13.7)
      - **Low**
        - 8.3 months (95% CI, 3.9–NE)

**Side Effects**

- 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%).

O'Malley et al. IGCS 2022

- 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).

- One patient had a death that was deemed related to a study treatment (intestinal perforation possibly related to BEV).
Forward-1 PRO: Phase 3, open-label, randomized (2:1) trial (N=366), in patients with FR-alpha + PROC

- Patients completed PRO assessments during screening, on day 1 of cycle 1, every 9 weeks thereafter until disease progression, and at the end of treatment visit

<table>
<thead>
<tr>
<th>PRO assessment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 (C30)</td>
<td>A 30-item questionnaire designed to assess the QoL in patients with cancer by measuring functional domains, symptoms, and global QoL/health status</td>
</tr>
<tr>
<td>EORTC QLQ-OV28 (OV28)</td>
<td>A 28-item ovarian cancer supplemental module developed to augment the C30 with 3 multi-item functional scales and 5 multi-item symptom scales</td>
</tr>
<tr>
<td>FOSI</td>
<td>An 8-item measure of symptom response to treatment for ovarian cancer</td>
</tr>
</tbody>
</table>

- Categorical change analyses of FOSI scores demonstrated that by cycle 7:
  - 88.9% of ITT population patients on IC chemo had declined vs 70.3% with MIRV
  - 88.1% of FRα-high population patients on IC chemo had declined vs 65.0% with MIRV

**Figure 1. Improvement in the OV28 Abdominal/GI Symptom Subscale by Treatment Group at Week 8/9**

<table>
<thead>
<tr>
<th>Frequency of patients with ≥15-point improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population (n=115/142)</td>
<td>P=0.0162*</td>
</tr>
<tr>
<td>IC chemo (n=7/50)</td>
<td>14.0%</td>
</tr>
<tr>
<td>MIRV (n=24/88)</td>
<td>31.7%</td>
</tr>
<tr>
<td>FRα-high population (n=44/99)</td>
<td>P=0.1426*</td>
</tr>
<tr>
<td>IC chemo</td>
<td>13.3%</td>
</tr>
<tr>
<td>MIRV</td>
<td>27.3%</td>
</tr>
</tbody>
</table>

*Improvement was defined as ≥15-point increase from baseline. Any change ≥15 points was categorized as unimproved.
*P value from chi-square test or Fisher exact test if necessary.

**Figure 2b. FRα-High Population: TSW on the OV28 Abdominal/GI Symptom Subscale**

- Positive PRO findings, further support MIRV as a potential novel treatment strategy in the PROC space

Moore et al. ESMO 2022
ARIEL-4

Trial eligibility and design

Patients with:
- Relapsed, high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer
- ≥2 prior chemotherapy regimens, including ≥1 platinum-based regimen
- Deleterious germline or somatic BRCA mutation
- No prior PARP inhibitor or single-agent paclitaxel treatment

PFI from last platinum
- 1 month
- 6 months
- 12 months

Platinum status:
- Resistant
- Partially sensitive
- Fully sensitive

Treatment
- Rucaparib 600 mg twice daily
- or
- Platinum-based chemotherapy
  - Weekly paclitaxel 60-80 mg/m²
  - Single-agent platinum or platinum-doublet

Radiologically confirmed disease progression, unacceptable toxicity, death or termination of study

Follow-up
- 28 days after last treatment dose, then long-term follow-up every 12 weeks

Optional crossover
- Patients in the chemotherapy group could crossover to rucaparib upon PD

Investigator-assessed PFS: Efficacy population

- Median, mo 95% CI
  - Rucaparib (n=220): 7.4, 7.3–9.1
  - Chemotherapy (n=105): 5.7, 5.5–7.3
- HR, 0.64
- 95% CI, 0.49–0.84
- P=0.001

Efficacy endpoints
- Prespecified secondary endpoint: OS in the ITT population
- Exploratory endpoints: OS in platinum-status subgroups; PFS2 in the ITT population and in platinum-status subgroups

Oza et al. ESMO 2022
ARIEL-4: OS data

OS: ITT Population

- 45% of fully platinum sensitive patients receiving Rucaparib DID NOT report receiving a subsequent anti-cancer txt
- 38% of partially platinum sensitive...
- 43% of platinum resistant...

If you exclude cross over from chemotxt to Rucaparib, the Rucaparib arm had a median OS of 19.4 mo compared to 9.1 mo for chemotherapy (HR 0.432; 95% CI 0.276-0.659). 90% received rucaparib after randomization or crossover

Oza et al. ESMO 2022
Corcept Phase 2

Relacorilant + Nab-paclitaxel Phase 2 Study Design

- Cortisol contributes to Chemotherapy resistance by suppressing apoptotic pathways
- GR is abundantly expressed in ovarian malignancies, and high expression is associated with poor outcomes
- GR modulation with relacorilant inhibits antia apoptotic affects and enhances activity of cytotoxic chemoTx

Biologic Rational

Colombo et al. ASCO 2022
Corcept Phase 2

Intermittent Relacorilant + Nab-Paclitaxel
Improved OS

**Overall survival (%)**

**Number at risk (events/cumulative events)**

<table>
<thead>
<tr>
<th></th>
<th>CONTINUOUS</th>
<th>RELACORILANT</th>
<th>CONTINUOUS</th>
<th>RELACORILANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTINUOUS</td>
<td>59 (0/0)</td>
<td>52 (0/0)</td>
<td>48 (9/13)</td>
<td>50 (0/0)</td>
</tr>
<tr>
<td>RELACORILANT</td>
<td>60 (0/0)</td>
<td>55 (1/0)</td>
<td>67 (5/15)</td>
<td>57 (1/0)</td>
</tr>
</tbody>
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**Number at risk (events/cumulative events)**

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<th>RELACORILANT</th>
</tr>
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<tbody>
<tr>
<td>CONTINUOUS</td>
<td>58 (0/0)</td>
<td>53 (5/5)</td>
<td>28 (5/29)</td>
<td>28 (5/29)</td>
</tr>
<tr>
<td>RELACORILANT</td>
<td>60 (0/0)</td>
<td>58 (8/3)</td>
<td>30 (7/22)</td>
<td>30 (7/22)</td>
</tr>
</tbody>
</table>

**Events, no. (%):**

<table>
<thead>
<tr>
<th></th>
<th>INTERMITTENT</th>
<th>CONTINUOUS</th>
<th>COMPARATOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=60</td>
<td>37 (61.7%)</td>
<td>42 (72.4%)</td>
<td>49 (81.7%)</td>
</tr>
</tbody>
</table>

**Median OS, mo (95% CI):**

<table>
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<th>CONTINUOUS</th>
<th>COMPARATOR</th>
</tr>
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<tbody>
<tr>
<td>N=58</td>
<td>13.9 (11.1, 18.4)</td>
<td>11.3 (7.5, 16.4)</td>
<td>12.2 (7.7, 15.3)</td>
</tr>
</tbody>
</table>

**HR vs Comparator:**

<table>
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<tr>
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<th>INTERMITTENT</th>
<th>CONTINUOUS</th>
<th>COMPARATOR</th>
</tr>
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<tbody>
<tr>
<td>N=60</td>
<td>0.67 (0.43, 1.03)</td>
<td>0.85 (0.56, 1.29)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**P-value=0.066 vs. nab-paclitaxel alone**

**Median follow-up time: 22.5 months**

**Data cutoff: March 7, 2022**

In the **INTERMITTENT** arm, 27% of patients were still alive at 24 months compared to 14% in the **COMPARATOR** arm.

Trend toward improved OS consistent at primary and final analyses.

Colombo et al. ASCO 2022
**Corcept Phase 2**

**Intermittent Relacorilant + Nab-Paclitaxel**

**Improved OS**

<table>
<thead>
<tr>
<th></th>
<th>INTERMITTENT* N=53</th>
<th>CONTINUOUS N=55</th>
<th>COMPARATOR N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>33 (62.3%)</td>
<td>40 (72.7%)</td>
<td>48 (81.4%)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>13.9 (11.1, 18.4)</td>
<td>12.3 (7.6, 16.4)</td>
<td>12.2 (7.7, 15.3)</td>
</tr>
<tr>
<td>HR vs Comparator</td>
<td>0.63 (0.39, 0.99)</td>
<td>0.84 (0.54, 1.29)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*P-value=0.045 vs. nab-paclitaxel alone

**Subgroup:** excluding patients with primary platinum-refractory disease

Data cutoff: March 7, 2022

**Number at risk (events/cumulative events)**

- **CONTINUOUS:** 65 (0/0), 60 (5/5), 42 (7/12), 32 (10/22), 27 (5/27), 20 (5/32), 15 (5/37), 12 (0/37), 5 (2/38), 1 (1/40), 0 (0/40)
- **INTERMITTENT:** 53 (0/0), 45 (4/4), 41 (4/8), 33 (5/13), 27 (8/19), 21 (8/25), 17 (4/29), 10 (3/32), 5 (1/53), 1 (0/53), 1 (0/53), 0 (0/53)
- **COMPARATOR:** 59 (0/0), 56 (3/3), 44 (12/15), 30 (8/23), 28 (6/29), 22 (6/35), 14 (8/43), 8 (2/45), 3 (2/47), 1 (1/49), 0 (0/48)

CONTINUOUS, once-daily relacorilant + nab-paclitaxel; INTERMITTENT, intermittent relacorilant + nab-paclitaxel; COMPARATOR, nab-paclitaxel monotherapy
Surpass (Adaptimmune): Preliminary Clinical Outcomes of ADP-A2M4CD8, a Next-Generation Autologous T-Cell Receptor T-Cell Therapy, in Patients With Advanced Epithelial Ovarian Cancer

**Objectives**

**Primary:** Safety and tolerability

**Secondary:** Antitumor activity

**Exploratory:** Persistence, phenotype, function; tumor and serum factors that may influence response or resistance

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**SURPASS trial design**

- **Surpass (Adaptimmune):** Preliminary Clinical Outcomes of ADP-A2M4CD8, a Next-Generation Autologous T-Cell Receptor T-Cell Therapy, in Patients With Advanced Epithelial Ovarian Cancer

- **Objectives**

  - **Primary:** Safety and tolerability
  - **Secondary:** Antitumor activity
  - **Exploratory:** Persistence, phenotype, function; tumor and serum factors that may influence response or resistance

- **Design:**
  - CD4+ T-cells with CD8α co-receptor have enhanced killing capacity
  - Tumor cell death

- **Monotherapy:**
  - N=30 planned

- **Combination therapy in a cohort of selected patients:**
  - N=30 planned

- **Trial assessments**
  - Baseline tumor measurements
  - Days −7 to −4
  - Day 1
  - Week 4
  - End of interventional phase

- **Long-term follow-up:**
  - Years 1–15

- **HLA and MAGE-A4**
  - HLA screening followed by MAGE-A4 immunohistochemistry testing

- **Eligibility assessment, leukapheresis, and manufacturing of ADP-A2M4CD8**

- **ADP-A2M4CD8 infusion**

- **Nivolumab every 4 weeks**

- **Lymphodepletion**

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**Notes:**

- Patient is hospitalized for T-cell infusion and discharged at the discretion of the Investigator

**Moore et al. ESGO 2022**

**NCT04044859**
Surpass (Adaptimmune): Preliminary Clinical Outcomes of ADP-A2M4CD8, a Next-Generation Autologous T-Cell Receptor T-Cell Therapy, in Patients With Advanced Epithelial Ovarian Cancer

Eligibility in ovarian cancer based on HLA and MAGE-A4 inclusion criteria (NCT02636855)
• HLA eligible: 49%
• MAGE-A4 positive: 24%

Baseline patient and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>59 (40, 75)</td>
</tr>
<tr>
<td>H-score, median (range)</td>
<td>237.5 (95, 300)</td>
</tr>
<tr>
<td>Transduced T-cells x 10^9, median (range)</td>
<td>3.17 (1.14, 9.95)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>1</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>No. of prior lines of therapy, median (range)</td>
<td>4 (2, 8)</td>
</tr>
</tbody>
</table>

Overall response rate
• 36% (5 of 14 patients)*

Disease control rate
• 79% (11 of 14 patients)

*1 patient was not evaluable (died prior to their first scan)

Duration of response (range)
• 9+ to 30 weeks

Serious adverse events and those related to T-cell infusion in ≥5% of patients

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>N=44, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAE</td>
</tr>
<tr>
<td>Any SAE</td>
<td>27 (61.4)</td>
</tr>
<tr>
<td>CRS</td>
<td>14 (31.8)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>ICANS</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (6.8)</td>
</tr>
</tbody>
</table>

There were 2 related Grade 5 (fatal) SAEs: CRS and Pancytopernia

Maximum percentage change from baseline in target lesion SD through PD (inclusive) or prior to surgical resection

Overall response rate
• 36% (5 of 14 patients)
Discussion
GOG-P Trials in the PROC Space...
PROC Space: Mirasol (GOG-3045)

GOG-3045 / ENGOT -Ov55
PHASE 3 RANDOMIZED TRIAL
FOR MIRVETUXIMAB IN FR α-HIGH
PATIENTS WITH PLATINUM -
RESISTANT OVARIAN CANCER

TARGET TIMELINES

ENROLLING GLOBALLY

TOP - LINE DATA
Q3 2022

sBLA 2023

PI: Kathleen Moore, MD
ClinicalTrials.gov Identifier: NCT04209855

GOG Foundation

*Eligibility criterion different than SORAYA; potential sBLA approval in 2023
sBLA: Supplemental Biologics License Application; IC: investigator’s choice; PLD: pegylated liposomal doxorubicin; OS: overall survival; PRO: patient-reported outcomes

**Patient Population:** HGSOC\(^a\) progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
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<tbody>
<tr>
<td>• Platinum-resistant ovarian cancer (PROC)</td>
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<tr>
<td>• 1–4 prior lines of therapy</td>
<td></td>
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<tr>
<td>• Grade ≤2 peripheral neuropathy</td>
<td></td>
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<tr>
<td>• Archival or fresh tissue required for biomarker evaluation</td>
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</tbody>
</table>

<table>
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<tr>
<th>Key Exclusion Criteria</th>
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<tr>
<td>• 1–2 prior lines bevacizumab-naive</td>
<td></td>
</tr>
<tr>
<td>• Primary platinum-refractory disease</td>
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</tbody>
</table>

**UpRi 36 mg/m\(^2\) up to max 80 mg; IV Q4W**

**Global**

US, Europe, Australia, Canada

**Primary Endpoint**
- Confirmed ORR in NaPi2b-high (N = ~100)

**Secondary Endpoint**
- Confirmed ORR in overall population (N = up to ~180 including 100 NaPi2b-high)

**Other Secondary Endpoints**
- DoR
- Safety

Prospectively-defined retrospective analysis to validate NaPi2b biomarker cutoff

**NCT03319628 (FPD April 2021) – Study has completed accrual**

\(^a\) HGSOC including fallopian tube and primary peritoneal cancer.

DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; PROC, platinum-resistant ovarian cancer; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.
PROC Space: PROFECTA-II (GOG-3044) Open Label Randomized Phase II trial of Afuresertib plus Palcitaxel versus Paclitaxel

- Afuresertib MOA: Pan AKT inhibitor
  - Inhibits Akt 1/2/3
- Hypothesized to restore chemosensitivity
- PROC is a rational therapeutic population
- Can be combined with a chemoTx backbone (Phase 1B data)

N=141; Primary Endpoint PFS

Accrual is currently on hold.

PI: Tom Herzog, MD; NCT04374630
PROC Space: Phase III ROSELLA (GOG3073): Relacorilant + Nab-Paclitaxel vs. Nab-Paclitaxel

- Open-label, randomized study of relacorilant, a selective glucocorticoid receptor modulator

28-day cycles

Relacorilant 150 mg PO QD
Nab-Paclitaxel 80 mg/m² IV; D1,8,15
(n = 180)

Nab-Paclitaxel 80 mg/m² IV; D1,8,15
(n = 180)

Women with grade 3 serous, epithelial ovarian, primary peritoneal, or fallopian tube carcinoma; ECOG PS 0-1; 1-3 lines of prior treatment; platinum resistant but not refractory
(Estimated N = 360)

- Primary endpoint: PFS (BICR)
- Secondary endpoints: OS, PFS (investigator), ORR, DoR, CBR, CA-125

Until PD, unacceptable AEs, or patient withdrawal