The Evolution of Ovarian Cancer

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Evolution of Biomarkers

Ovarian Cancer Biomarkers

Detection & Diagnostic
Prognostic
Predictive
Therapeutic

Blood
Tumor
Ascites

HGSOC
CA125
HE4
BRCA1/2
HRD
VEGF
ARID1A
FOLR1/FRα
Her2
TROP2
CDH6
MAGE-A4
B7-H4

PTEN/PIK3CA/AKT1
BRAF/KRAS/NRAS
ER+
ERBB2

LGSOC
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Conjugate</th>
<th>Indication</th>
<th>Target</th>
<th>Phase</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirvetuximab soravtansine</td>
<td>Maytansinoid (DM4)</td>
<td>Ovary</td>
<td>Folate Receptor α</td>
<td>3: Gloriosa 3: MIRASOL 2: SORAYA 2: PICCOLO</td>
<td>NCT05445778 NCT04209855 NCT04296890 NCT05041257</td>
</tr>
<tr>
<td>STRO-002 Luveltamab tazevibulin</td>
<td>SC209 (tubulin targeting)</td>
<td>Ovary</td>
<td>Folate Receptor α</td>
<td>1</td>
<td>NCT03748186 NCT05200364</td>
</tr>
<tr>
<td>MORAb-202</td>
<td>Eribulin</td>
<td>Ovary</td>
<td>Folate Receptor α</td>
<td>2</td>
<td>NCT05613088</td>
</tr>
<tr>
<td>Sacituzumab Govitecan (IMMU-132)</td>
<td>SN-38 (metabolite of topo 1 inhibitor)</td>
<td>Ovary</td>
<td>TROP2</td>
<td>2</td>
<td>NCT006028932</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine</td>
<td>DM1</td>
<td>Solid tumor (endo &amp; ovary)</td>
<td>HER2</td>
<td>2</td>
<td>NCT044439110</td>
</tr>
<tr>
<td>Trastuzumab deruxtecan</td>
<td>Deruxtecan</td>
<td>Solid tumor (endo, ovary, cervix)</td>
<td>HER2</td>
<td>2</td>
<td>NCT04482309</td>
</tr>
<tr>
<td>Raludotatug deruxtecan (DS6000a)</td>
<td>Deruxtecan</td>
<td>Solid tumor (ovary)</td>
<td>CDH6</td>
<td>1</td>
<td>NCT04707248</td>
</tr>
<tr>
<td>XB002</td>
<td>Auristatin</td>
<td>Solid tumor (endo, ovary, cervix)</td>
<td>TF</td>
<td>1</td>
<td>NCT04925284</td>
</tr>
<tr>
<td>XMT-1660</td>
<td>Auristatin F-Hydroxypropylamide</td>
<td>Solid tumor (endo, ovary)</td>
<td>B7-H4</td>
<td>1</td>
<td>NCT05377996</td>
</tr>
<tr>
<td>SGN-B7H4V</td>
<td>Monomethyl Auristatin E</td>
<td>Solid tumor (endo, ovary)</td>
<td>B7-H4</td>
<td>1</td>
<td>NCT05194072</td>
</tr>
<tr>
<td>AZD8205</td>
<td>Topoisomerase I inhibitor</td>
<td>Solid tumor (endo, ovary)</td>
<td>B7-H4</td>
<td>1</td>
<td>NCT05123482</td>
</tr>
</tbody>
</table>
GOG Ovarian Enrolling Portfolio

Symptoms

Chemo #1

Maintenance

Chemo #2  M  Chemo #3  M  Chemo #4+

PSOC

GOG-3068  HOTT

GOG-3066  DENALI

GOG-3067  GLORIOSA

GOG-3063  ARTISTRY-7

GOG-3067  MAMMOTH

GOG-3072  ZN-c3-002

GOG-3076  OnPrime

GOG-3044  PROFECTA-II

GOG-3073  ROSELLA

GOG-3081  PRESERVE-04

GOG-3087  NXP800-101

PROC

RARE

GOG-3097  RAMP-301

GOG-3051  BOUQUET

GOG-3084  SURPASS-3

GOG-3086  REFRaME-01
FRα Scoring

**PS2+ Scoring**
Determined by staining intensity and percentage of tumor cells staining at 0, 1+, 2+, or 3+

- **PS2+ Scoring**
  - Positive: ≥ 50% tumor cells with ≥ 2+ FRα membrane staining.

**10X Scoring**
Simplified scoring method based on % cells with membrane staining by ≤10X magnification, without regard to intensity

- **10X Scoring**
  - Positive: ≥ 50% of tumor cells with FRα membrane staining visible at 10X microscope objective.

**TPS Scoring**
A scoring paradigm based on the % of cells with any intensity expression.

- **TPS Scoring**
  - Simple and straight forward interpretation. Does not require differentiation between staining intensity. TPS >25% was selected for further analysis in STRO-002 studies.

Mirvetuximab FDA approved treatment for platinum-resistant ovarian cancer patients whose tumors express ≥75% viable cells show 2+ and/or 3+ staining.

Moore KN et al. ESMO. 2019; Oaknin A et al. ASCO 2023; www.fda.gov
Trials in Focus: Targeting FRα

REFRaME-01

- Recurrent disease
- Platinum resistant
- 1-3 prior regimens or platinum-sensitive
- 2-3 prior regimens
- Fresh or archival tissue required
- No mandate for FoRα expression
- At least 1 target lesion

Part 1

Luveltamab
4.3 mg/kg Q3W
n=23

Part 2

Luveltamab
5.2 mg/kg Q3W
n=21

ORR: N ~ 100

N ~ 440 pts

Primary endpoint: PFS by BICR
90% power to detect a HR of 0.7
Assumes a mPFS of 10 months on the control arm
Final PFS analysis @ 330 PFS events

GLORIOSA

Main Screening
Randomization and Study Treatment

ARM 1
Bevacizumab + MIRV Q3wks

ARM 2
Bevacizumab alone Q3wks

CR/PR or SD
Stratificationa & Randomizationb

a High-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers
b Stratification factors: prior PARP inhibitor, Yes vs No. CR or PR or SD, prior bevacizumab, Yes vs No.
c Enrollment into Trial for Randomization will require documented radiographic, confirmed CR, PR or SD
d Maintenance treatment must begin 12 weeks or less from last dose of triplet therapy and win 30 days of randomization. Treatment continued until progressive disease, unacceptable toxicity, withdrawal of consent, death, or Sponsor terminates the study

cOMP1
High FRα
2L Platinum-based doublet + Bev2

Oaknin et al. ASCO 2023 Abstract 5508
# Targeting HER2 in Ovarian Cancers

## Ovarian cancer
- Amplification: 14%.
- Highest in mucinous carcinomas (25%); mixed-type carcinomas (11.9%), clear cell carcinomas (4%), serous papillary carcinomas (3%), and endometrioid carcinomas (2.1%)
- HER2 expression was associated with worse PFS and OS
- In GOG160, a phase II trial evaluating trastuzumab in patients with recurrent or refractory ovarian cancer had ORR of 7.3 % in patients with HER2 overexpression (n=41)

<table>
<thead>
<tr>
<th>HER2</th>
<th>Breast (ASCO/CAP 2007)</th>
<th>Breast (ASCO/CAP 2013; 2018*)</th>
<th>Gastric (ASCO/CAP 2016)</th>
<th>Colorectal (HERACLES trial)</th>
<th>UPSC (Fader et al.) Endometrial</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 3+</td>
<td>&gt;30% strong, uniform, complete</td>
<td>&gt;10% circumferential, strong, complete</td>
<td>&gt;10%, strong complete or basolateral/lateral</td>
<td>&gt;50% strong, complete or basolateral/lateral</td>
<td>&gt;30% strong complete or basolateral/lateral</td>
</tr>
<tr>
<td>FISH amplification</td>
<td>HER2/CEPT17 ratio &gt;2.2 Patients with HER2/CEPT17 ratio 2-2.2 eligible</td>
<td>HER2/CEPT17 ratio ≥2.0 OR ratio &lt;2.0 and HER2 signal &gt;6.0/nucleus <em>(if IHC 2+ or 3+)</em></td>
<td>HER2/CEPT17 ratio &gt;2.0 OR ratio &lt;2.0 and HER2 signal &gt;6.0/nucleus</td>
<td>HER2/CEPT17 ratio &gt;2.0 in &gt;50% of cells</td>
<td>HER2/CEPT17 ratio ≥2.0</td>
</tr>
</tbody>
</table>

Trastuzumab deruxtecan (T-DXd), HER2-targeted ADC under clinical investigation for patients with HER2-expressing tumors including OC.

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; ERBB2, erb-b2 receptor tyrosine kinase 2; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; OC, ovarian cancer; q3w, every 3 weeks.


### Objective Response Rate by HER2 status

<table>
<thead>
<tr>
<th></th>
<th>Confirmed ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>50.0</td>
</tr>
<tr>
<td>IHC 3+</td>
<td>75.0</td>
</tr>
<tr>
<td>IHC 2+</td>
<td>40.0</td>
</tr>
<tr>
<td>IHC 3+</td>
<td>57.5</td>
</tr>
<tr>
<td>IHC 2+</td>
<td>47.1</td>
</tr>
<tr>
<td>IHC 3+</td>
<td>45.0</td>
</tr>
<tr>
<td>IHC 2+</td>
<td>36.8</td>
</tr>
</tbody>
</table>

**Ovarian**

- HER2 3+: 7/11 (63.6%)
- HER2 2+: 7/19 (36.8%)
- HER2 1+: 4/10 (40%)

<table>
<thead>
<tr>
<th></th>
<th>Median DOR, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>11.8 (9.8–NE)</td>
</tr>
<tr>
<td>IHC 3+</td>
<td>22.1 (9.3–NE)</td>
</tr>
<tr>
<td>IHC 2+</td>
<td>9.8 (4.2–12.6)</td>
</tr>
</tbody>
</table>

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=8], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=68) or IHC 2+ (n=34) status.  

Select novel emerging investigational agents in recurrent OC

**Immunotherapy**
- Nemvaleukin alfa
- Olvimulogene nanivacirepvec
- Gemogenovatucel-T (Vigil)
- Immune checkpoint inhibitors combinations (eg, pembro + pac + bev)
- Oncolytic viruses
- Cellular therapy

**Targeting cell cycle regulation and DNA repair**
- PI3K inhibitors (eg, alpelisib)
- CHK1 inhibitor (eg, afuresertib)
- WEE1 inhibitor (eg, adavosertib, ZN-c3)

**ADCs (target)**
- DS-6000a (CDH6)
- Farletuzumab ecteribulin (FRα)
- Luvellamab tazevibulin (FRα)
- Tisotumab vedotin (tissue factor)
- XMT-1660 (B7-H4)

**Other**
- Batiraxcept
- Relacorilant

**Unmet needs in recurrent OC**
- Identification of new molecular targets and corresponding therapies to improve outcomes for more patients
- Identify new therapeutic options for patients with HRP cancers
- New treatment options for patients who progress after PARP inhibitor treatment
- New treatment options for patients with recurrent platinum-resistant disease

ADC, antibody-drug conjugate; bev, bevacizumab; BRCA, BRCA DNA repair associated gene; CDH6, cadherin 6; CHK1, checkpoint kinase 1; EOC, epithelial ovarian cancer; FRα, folate receptor alpha; HRP, homologous recombination proficient; NaPi2b, sodium-dependent phosphate transport protein 2B; pac, paclitaxel; pembro, pembrolizumab; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-3 kinase.

# Trials in Focus

<table>
<thead>
<tr>
<th>Study</th>
<th>Biomarker</th>
<th>Endpoints</th>
<th>Strategy/opportunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG-3066 Zentalis</td>
<td>None (previous CCNE1 amp)</td>
<td>ORR, DOR</td>
<td>Trial in PROC, not restricted amendment being operationalized</td>
</tr>
<tr>
<td>GOG-3076 Genelux</td>
<td>None</td>
<td>PFS</td>
<td>Induction IP administration of oncolytic virus; platinum-doublet/bev retreatment in PROC</td>
</tr>
<tr>
<td>GOG-3087 Nuvectis</td>
<td>ARID1A</td>
<td>ORR, DOR</td>
<td>Targeting clear cell, endometrioid</td>
</tr>
<tr>
<td>GOG-3084 Adaptimmune</td>
<td>HLA 2:01, MAGE-A4</td>
<td>ORR, DOR</td>
<td>Screening can take place during other therapy; ± nivolumab</td>
</tr>
</tbody>
</table>
**Trials in Focus: Rare Tumors**

**GOG-3097/ENGOT-ov81/RAMP 301**

- **Key Inclusion Criteria**
  - Confirmed LGSOC diagnosis
  - Recurrent disease after prior platinum therapy
  - Documented KRAS mutation status
  - Measurable disease per RECIST v1.1
  - Prior MEKi allowed
  - Prior Bev allowed

- **Avutometinib + Defactinib**
  - N = 135
  - 3.2 mg PO BIW
  - 3 weeks on, 1 week off

- **Investigator’s Choice**
  - N = 135
  - Prespecified Tumor Material
  - Palmar-Plantar Erythrodysesthesia
  - Fatigue
  - Leukopenia
  - Anemia

- **Primary Endpoint**
  - PFS via RECIST v1.1 per BICR

- **Secondary Endpoints**
  - OS
  - PFS via RECIST v1.1 per INV Assessment
  - ORR
  - DoR
  - Safety
  - Pharmacokinetics
  - PROs

- **May crossover upon BICR confirmed PD**

- **Stratification Factors**
  - KRAS mutation status: wt vs mt

- **Prescreening**
  - Biomarker testing (F1CDx and ER IHC) and pathology

- **Trials at a Glance**
  - 1:1 Randomization N = 270

**ESMO 2023: Cobimetinib: ORR: 16% in ITT – 33% in LGSOC – to expand**

- **Primary efficacy endpoint:**
  - *Measurable persistent or recurrent platinum-resistant rare eOC (LGSOC): clear-cell, mucinous, undifferentiated or grade 1/2 endometrioid carcinoma, carcinosarcoma, malignant Brenner tumour or mesonephric-like adenocarcinoma*)
  - 1–4 prior lines of non-hormonal systemic therapy
  - ECOG PS 0 or 1
  - Tumour sample available

- **Non-matched**
  - **n=20 per arm, with potential to expand to n=50**

- **BOUQUET – GOG-3051**

- **Primary Endpoint**
  - investigator-assessed cORR per RECIST v1.1

- **Non-matched**
  - BRAF/KRAS/NRAS-activating mutation and/or PIK3CA- or AKT1-activating mutation

- **Prescreening**
  - Biomarker testing (F1CDx and ER IHC) and pathology

- **General and arm-specific screening**
  - PTEN LOF alteration and/or PIK3CA- or AKT1-activating mutation
  - ER+
  - PIK3CA-activating mutation
  - Non-matched
  - Inavolisib + palbociclib
  - Inavolisib + olaparib
  - Inavolisib + giredestrant
  - Inavolisib + bevacizumab
  - Atezolizumab + bevacizumab
  - Atezolizumab + bevacizumab and cyclophosphamide

**Coming Soon**

ASCO 2023 Abstract 5508, 5515, ESGO 2023
Conclusions

• Clinical trial pipeline is robust and evolving especially with biomarker development providing prognostic and predictive inference to trial development and participation

• Opportunities to leverage expression and sequencing data in the GOG Partners portfolio are robust

• Screen frequently; expression portfolio may change with time and age of sample