Molecular Therapeutics for Ovarian Cancer: Targeting the Tumor Microenvironment

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Dept. Gynecologic Oncology & Reproductive Medicine
M.D. Anderson Cancer Center, Houston
## Disclosures

<table>
<thead>
<tr>
<th>Research Grants</th>
<th>Abbvie, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Esperance, Genentech/Roche, Janssen Biotech Inc, Merck, V-Foundation, Gateway Foundation</th>
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<tr>
<td>Advisory Committee</td>
<td>Abbvie, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Roche/Genentech, Esperance, Janssen Biotech Inc, Merck</td>
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</tbody>
</table>
The Tumor Microenvironment (TME) in Oncogenesis
TME: Angiogenesis as a Target

- Pericyte
- Tumor Endothelium
- Tumor Cell
- Stroma and Immune Cells
## TME: Angiogenesis as a Target

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Setting</th>
<th>HR-PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 218</td>
<td>Bevacizumab</td>
<td>Front-line/Maintenance</td>
<td>0.72 (0.63-0.82)</td>
</tr>
<tr>
<td>ICON7</td>
<td>Bevacizumab</td>
<td>Front-line/Maintenance</td>
<td>0.81 (0.70-0.94)</td>
</tr>
<tr>
<td>AGO-OVAR12</td>
<td>Nintedanib</td>
<td>Front-line/Maintenance</td>
<td>0.84 (0.72-0.98)</td>
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<tr>
<td>AGO-OVAR16</td>
<td>Pazopanib</td>
<td>Primary Maintenance</td>
<td>0.77 (0.64-0.91)</td>
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<tr>
<td>AURELIA</td>
<td>Bevacizumab</td>
<td>Recurrence, Platinum-resistant, 1-2 priors</td>
<td>0.48 (0.38-0.60)</td>
</tr>
<tr>
<td>TRINOVA-1</td>
<td>Trebananib</td>
<td>Recurrence, Platinum-resistant/sensitive, 1-3 priors</td>
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<tr>
<td>OCEANS</td>
<td>Bevacizumab</td>
<td>Recurrent, Platinum-sensitive, 1 prior</td>
<td>0.53 (0.41-0.70)</td>
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<tr>
<td>ICON6</td>
<td>Cediranib</td>
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<tr>
<td>GOG0213</td>
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<td>0.76 (0.55-1.05)</td>
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<td>0.82 (0.68-0.99)</td>
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Angiogenesis Therapy: The “Banana Effect”
Angiogenesis “Escape”

Bottsford-Miller, Coleman and Sood, J Clin Oncol 2012
Adaptive resistance to anti-VEGF drugs

Bevacizumab + paclitaxel started
Adaptive resistance to anti-VEGF drugs

Bevacizumab + paclitaxel started

Disease Progression
Phenotypic Diversity Of Macrophage Populations

Fig. 2. CSF1R/CD163+ macrophages increased in anti-angiogenic resistant ovarian cancer patients, but not in the sensitive patients.

Dalton, Coleman, Sood, Clin Cancer Res 2017
Targeting Immune Microenvironment

**VEGF-Resistance Model**

**Macrophage Trafficking**

**Macrophage VEGFR Expression**

Addition of CSF1-R inhibitor to adaptive resistant tumors treated with Pac/Bev

*Dalton, Clin Cancer Res 2017*
• Loss of VEGFR-1, 3 expression
• CSF-1R expressing macrophages
• Emactuzumab is a CSF-1R inhibitor
“Next-Gen” Angiogenesis Therapy

- Reverse epigenetic regulatory and response transcriptions factors (EZH2, VASH1, Dll4/Notch, etc)
- Alter EMT and MET processes
- Alternative growth signaling (FAK, Paxillin, Ephrins)
- Abrogate immune response (TAM’s, CAF, PD-1/PD-L1, etc)

Lu, Cancer Cell 2010
EZH2 Targeting: Tazametostat

VEGF → VEGFR-2 → Transcription Factors

Angiogenesis

EZH2

EZH2 Targeting: Tazametostat

Tazametostat

VASH1
PARP as a Therapeutic Target
DNA Damage Response: PARP

Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant, Niklas Schultz, Huw D. Thomas, Kayan M. Parker, Dan Flower, Elena Lopez, Suzanne Kyle, Mark Meuth, Nicola J. Curtin & Thomas Hellday

Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy

Hannah Farmer, Nuala McCabe, Christopher J. Lord, Andrew N. J. Tutt, Damian A. Johnson, Tobias B. Richardson, Manuela Santarosa, Krystyna J. Dillon, Ian Hickson, Charlotte Knights, Niall M. B. Martin, Stephen P. Jackson, Graeme C. M. Smith & Alan Ashworth

1 Cancer Research UK Gene Function and Regulation Group and 2 The Breakthrough Breast Cancer Research Centre Institute of Cancer Research, Fulham Road, London SW3 6JB, UK
3 Guy’s Hospital, St Thomas’ Street, London SE1 9RT, UK
4 KuDOS Pharmaceuticals Ltd, Cambridge Science Park, Cambridge CB4 0WG, UK
5 Wellcome Trust and Cancer Research UK, Gurdon Institute of Cancer and Developmental Biology, and Department of Zoology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QH, UK

Nature 2005
Olaparib: Objective Response - BRCA-mt

Matulonis U... Coleman RL. Ann Oncol 2016
# PARPi Phase III Maintenance Trials – Ovary

<table>
<thead>
<tr>
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<th>Rucaparib</th>
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<th>HR</th>
<th>P</th>
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<tr>
<td><em>tBRCA</em></td>
<td>16.8</td>
<td>5.4</td>
<td><strong>0.23</strong></td>
<td>P&lt;0.0001</td>
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<td><em>tBRCA + HRD</em></td>
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<td>P&lt;0.0001</td>
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<tr>
<td><strong>ITT</strong></td>
<td>10.8</td>
<td>5.4</td>
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<td><strong>PFS (BICR – Primary)</strong></td>
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<tr>
<td><em>tBRCA</em></td>
<td>21.0</td>
<td>5.5</td>
<td><strong>0.26</strong></td>
<td>P&lt;0.0001</td>
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<td><em>tBRCA + HRD</em></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>All non-gBRCA (<em>sBRCA+ HRD + HRC</em>)</td>
<td>9.3</td>
<td>3.9</td>
<td><strong>0.45</strong></td>
<td>P&lt;0.001</td>
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<tr>
<td><strong>ITT (FDA analysis)</strong></td>
<td>11.3</td>
<td>4.7</td>
<td><strong>0.42</strong></td>
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<td><strong>PFS (Inv Review - Primary)</strong></td>
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<td><em>gBRCA</em></td>
<td>19.1</td>
<td>5.5</td>
<td><strong>0.30</strong></td>
<td>P&lt;0.0001</td>
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Treatment Paradigm for Use of PARP Inhibitors

- Symptoms
- Diagnosis
- Evaluation
- Diagnosis: ? SLL
- Staging/debulking
- Chemo #1: Concomitant
- Maintenance
- Progression
- Secondary surgery?
- Supportive care
- Death
- Chemo #2: Concomitant
- Chemo #3: M
- Chemo #4+: M
- Supportive care

- Under investigation
- FDA approved
What’s Next?

• Enhancement therapy

• Resistance therapy

• Contextual synthetic lethality (inducing HRD in HR compliant tumors)
What’s Next?

- **Enhancement therapy**
  - Chemotherapy (DNA-damaging agents); GOG-3005
  - Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1)
  - Radiation therapy

- **Resistance therapy**
  - P53 targeted agents (AZD-1775, COTI-2, selinexor)
  - CDK inhibitors (ribociclib, palbociclib, roniciclib)
  - HDAC
  - HSP90
  - MEK

- **Contextual synthetic lethality (inducing HRD in HR compliant tumors)**
  - Hypoxia inducement (anti-angiogenesis, EZH2)
  - PI3K pathway inhibitors
  - ATR/ATM, CDK inhibitors
Targeting The Stroma (CAFs)
Targeting The Stroma (CAFs)

- Reactive stromal cells play an integral role in cancer cell survival
- An **adaptive response** to PARPi and anti-angiogenesis therapy
- Reliable therapeutic targets are few
- Glutamine pathway provides a unique energy source for CAFs

Yang, Cell Met 2016
Targeting The Stroma (CAFs)

- Synthetic lethal targeting glutamine synthetase in CAFs and glutaminase in cancer cells
- Selective inhibitors (CB-839, IACS-6274) are in phase I/II trials
- Synergy with chemotherapy may be due to reduced interstitial pressure and reprogramming immune surveillance

Yang, Cell Met 2016
Re-educating the Tumor Microenvironment

Tumor vasculature
- Bevacizumab (anti-VEGF-A)
- S-265610 (anti-CXCR2)
- Sunitinib (RTK inhibitor)
- VEGF-Trap (decoy receptor)

Immune activation
- Ipilimumab (anti-CTLA-4)
- Nivolumab (anti-PD1R)
- Lambrolizumab (anti-PD-L1)

Repolarization and re-education
- BLZ945 (anti-CSF-1R)
- CD40 mAb

Altered immune cell recruitment, expansion and depletion
- PLX3397 (anti-CSF-1R and anti-KIT)
- AMD3100 (anti-CXCR4)
- S-265610 (anti-CXCR2)
- GW2580 (anti-CSF-1R)
- Trabectedin (chemotherapy)

Metastasis and/or outgrowth
- MLN1202 (anti-CCR2)
Metastatic Organ “Tropism”

Mechanism of dissemination:
- Direct extension
- Ascites
- Vasculature
Metastatic Organ Tropism

Pradeep, Cancer Cell 2014
Metastatic Organ Tropism

Pradeep, Cancer Cell 2014
Metastatic Organ Tropism

Similar Effect Seen with MM-121
- Anti-ErbB3 antibody

Pradeep, Cancer Cell 2014
ErbB3-Targeting: Seribantumab

**ITT**

- **P** (n = 83)
  - Median time, months: 3.68
  - HR: 1.03
  - 95% CI: 0.74 to 1.43
  - Log rank P: .864

- **S + P** (n = 140)

**Biomarker Positive**

- **P** (n = 19)
  - Median time, months: 3.5
  - HR: 3.7
  - 95% CI: 0.18 to 0.76
  - Log rank P: .007

- **S + P** (n = 38)

Liu, J Clin Oncol 2016
Re-educating the Tumor Microenvironment
Immunotherapy

Tumor

Ipilimumab*

Tremelimumab

CTLA-4

PD-1/PD-L1

Priming phase

Effector phase

Nivolumab*

Pembrolizumab*

Atezolizumab*

Avelumab

Durvalumab

## Immune Checkpoint Inhibitors in Ovarian Cancer: Overview

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Pembrolizumab&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Avelumab&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Atezolizumab&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Durvalumab&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>20</td>
<td>26</td>
<td>124</td>
<td>12</td>
<td>20*</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td>≥4 in 55% of cases</td>
<td>≥5 in 38.5%</td>
<td>≥3 in 65.3%</td>
<td>≥6 in 58%</td>
<td>4* Median</td>
</tr>
<tr>
<td><strong>PD-L1+ prevalence</strong></td>
<td>80% (IC 2/3)</td>
<td>100% (≥1% TC)</td>
<td>77% (≥1% TC)</td>
<td>83% (IC 2/3)</td>
<td>73% (&gt;5% TC)</td>
</tr>
<tr>
<td><strong>ORR (95% CI)</strong></td>
<td>15%</td>
<td>11.5%</td>
<td>9.7%</td>
<td>25%</td>
<td>Not reported</td>
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<tr>
<td><strong>mPFS, months</strong></td>
<td>3.5</td>
<td>Not reached</td>
<td>2.6</td>
<td>2.9</td>
<td>Not reported</td>
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<td><strong>mOS, months</strong></td>
<td>20</td>
<td>Not reached</td>
<td>10.8</td>
<td>11.3 (IC2); 17.4 (IC3)</td>
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</table>

* Includes ovarian cancer (n = 15), triple-negative breast cancer (n = 2), cervical cancer (n = 2), and uterine leiomyosarcoma patients (n = 1)

CI, confidence interval; IC, immune cell; ORR, overall response rate; mOS, median overall survival; mPFS, median progression-free survival; TC, tumor cell; TRAE, treatment-related adverse event, Tx, treatment

Neoantigen Repertoire by Tumor Primary

Alexandrov Nature 2013
Neoantigen Repertoire by Tumor Primary

Alexandrov Nature 2013
FDA Regulatory Actions: Pembrolizumab GYN

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

For Immediate Release

May 23, 2017

Release

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort of KEYNOTE 158 (NCT02628067), a multicenter, non-randomized, open-label, multi-cohort trial. Patients were treated with pembrolizumab intravenously at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression. Among the 98 patients, approval was based on 77 (79%) patients who had
Enhancement Strategies: IO+PARPi

**TOPACIO**
- **Phase 1**
  - Dose 1: Niraparib 200 mg + Pembrolizumab 200 mg
  - Dose 2: Niraparib 300 mg + Pembrolizumab 200 mg
  - Endpoint assessment
  - Primary Endpoint: Evaluate DLT and establish RP2D

**Phase 2**
- Niraparib 200 mg + Pembrolizumab 200 mg IV (RP2D)
- Endpoint assessment
- Primary Endpoint: ORR by RECIST

---

**MEDIOLA**
- PSR OC 2L+ gBRCAm PARPi and IO naïve
- Durvalumab 1.5 g IV q4w
- Olaparib 300 mg po bid
- Target DCR at 12 weeks: 90%* → N=31

**Primary endpoints:**
- DCR at 12 weeks
- Safety

**Secondary endpoints:**
- DCR at 28 weeks
- ORR
- DoR
- PFS
- OS
- PD-L1 expression

**Exploratory endpoints:**
- TILs

---

*Target based on olaparib monotherapy efficacy

**Tumor assessments**
- 8 weeks

**Optional biopsies**
- 8 weeks

---

- Target DCR at 12 weeks: 90%* → N=31

---

*Target based on olaparib monotherapy efficacy
ATHENA

- Statistical Design (PFS) ($a = 0.0166$)
  - A vs B
  - A vs D
  - B vs D
- Step down procedure
  - tBRCA, if positive
  - tBRCA + LOH-H, if positive
  - ITT

SCREENING
- Newly diagnosed, histologically confirmed, advanced Stage III/IV high-grade EOC, FTC, or PPC
- Have shown response to first-line platinum doublet
- Completed cytoreductive surgery (either prior to chemotherapy or during neoadjuvant chemotherapy)
- ECOC performance score ≤ 1
- Excludes any prior treatment for ovarian cancer, other than first-line platinum regimen, including maintenance treatment

RANDOMIZATION 4:4:1:1
- stratified by:
- HRR status by NGS mutation analysis:
  - tBRCA
  - Non-tBRCA LOH^{high}
  - Non-tBRCA LOH^{low}
  - Non-tBRCA known
- Response to first-line platinum:
  - No residual disease
  - Residual disease
- Timing of Surgery:
  - Primary surgery
  - Surgery after neoadjuvant treatment

BLINDED TREATMENT PHASE
- IV dose administered Day 1 each cycle; oral dose continuous BID
- Disease assessment by RECIST v1.1 every 12 weeks with CT/MRI scans per BCR charter.
- PRO on Day 1 of each cycle. Safety assessments each visit.
- Continue blinded treatment until 24 months, disease progression, or unacceptable toxicity, whichever happens first.
- Regular IDMC reviews.

POST-TREATMENT PHASE
- Treatment discontinuation visit, if applicable. Safety follow-up 28 and 100 days after last dose.
- Safety assessments, PRO, disease assessments.
- Monitor for disease assessments/surveillance, subsequent treatment, and secondary malignancy.
- Every 12 weeks for 3 yrs; every 24 weeks thereafter until death, loss to follow-up, withdrawal of consent, or study closure.
ATHENA

- Statistical Design (PFS) (a= 0.0166)
  - A vs B
  - A vs D
  - B vs D
- Step down procedure
  - tBRCA, if positive
  - tBRCA + LOH-H, if positive
  - ITT
Cytoplasmic and Nuclear Exosomes
Hanahan, Cell (2011)
The Challenge...

- Tumor microenvironment is a dynamic and adaptive functional structure providing regulatory support for tumor survival, growth, spread and the EMT-MET process.

- Each element, tumor, vasculature, lymphatics, stroma, immune cells, nerves, exosomes, etc., provides treatment opportunity.

- Functional non-invasive and invasive real-time surveillance strategies are necessary to optimize treatment.

- Clinical trials designed for adaptive response need to keep pace with emerging information of tumor biology.