Advances in Ovarian Cancer

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Conflicts of Interest

• None
Goals

• Discuss spectrum of ovarian cancer care
  • Prevention → treatment
• Brief review of current treatment paradigms

• Topics with recently updated data
  • Focus:
    • Genomics
    • Targeted therapies
    • Consensus guideline updates
Gynecologic Cancers: Ovary

**Estimated New Cases**
- Uterine: ~52,000
- Cervix: ~12,000
- Others: ~6,000
- Ovary: ~24,000

Total = ~84,000

**Estimated Cancer Deaths**
- Uterine: ~10,000
- Cervix: ~4,000
- Others: ~2,000
- Ovary: ~16,000

Total = ~30,000
2012 Age-standardized rates (World) incident cases, females, all vs Ovarian cancers
Ovarian cancer subtypes

- Serous: A disease of genomic instability
- Mucinous: A disease of aberrant Ras pathway signaling
- Endometrioid: A disease of aberrant PTEN, PI-3K, AKT signaling
- Clear Cell: A disease of ARID1A
Consensus guidelines in ovarian cancer

• National Comprehensive Cancer Network (NCCN)
  • https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

• Society of Gynecologic Oncology (SGO)
  • https://www.sgo.org/clinical-practice/guidelines/

• American Society of Clinical Oncology
  • http://www.asco.org/practice-guidelines/quality-guidelines/guidelines
## Prevention?

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Contributory?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Yes. 😏 😋</td>
</tr>
<tr>
<td>Obesity</td>
<td>Likely</td>
</tr>
<tr>
<td>Hormone replacement therapy (HRT)</td>
<td>Maybe</td>
</tr>
<tr>
<td>Infertility</td>
<td>Complicated</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>Likely</td>
</tr>
<tr>
<td>Talc</td>
<td>Controversial</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Contributory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heritable gene mutations</td>
<td>15-25% YES</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Decrease risk</td>
</tr>
<tr>
<td>Diet and nutrition</td>
<td>Matters – how much unclear</td>
</tr>
<tr>
<td>Exercise and physical activity</td>
<td>Matters – how much unclear</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Yes – mucinous cancers</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Maybe</td>
</tr>
</tbody>
</table>
Screening / Early detection goals

• Cure more patients
• Enable those patients who will not achieve a cure to live longer

• Challenges (Ovarian cancer):
  • Relatively uncommon (1:70 lifetime risk – fewer events)
  • No clearly definable pre-invasive phase
  • Few if any early clinical symptoms
  • Expensive to study (follow-up)

• Important study endpoints: overall survival (OS), sens/spec, NNT (# of patients who undergo surgery to find (1) ovarian cancer
Screening / Early detection summary

• Annual Ca-125: NO
• Annual pelvic ultrasound: NO
• Annual Ca-125 and pelvic ultrasound: NO
• Annual pelvic exam: …. Controversial sure why not?
• ROCA: not yet
  • Randomized groups: xxx vs xxx vs xxx
  • No OS improvement (201x)
Ovarian cancer screening trials (average risk)

- Prostate, Lung, Breast and Ovarian Cancer (PLCO) trial
  - 78,216 women patients between 1993 and 2001
  - Randomization: annual Ca-125 + pelvic ultrasound vs usual care
  - No OS improvement… (2011)

- UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
  - 202,000 patients between 2001 and 2015
  - Randomization: usual care vs MMS vs UMS
  - No OS improvement… (2015)

- Stage I/II diagnoses: 40% among screened vs 26% non-screened patients
UKCTOCS Multi-Modal Screening (MMS)

Annual Ca-125/ROCA

- NORMAL or “LOW”
  - LR

Repeat CA-125/ROCA

- INTERMEDIATE
  - 12 wks
  - HR or IR x 3

- HIGH

TVUS

- Abnormal
  - Clinical assessment
    - +/-
  - Normal TVUS

SURGERY
Definitions

• **Primary treatment**
  • Some combination of: surgery + chemotherapy
  • Expectation: remission (~70+%)  

• **Recurrent treatment**: *1st question* → how long one remains in remission
  • Platinum sensitive
  • Platinum resistant
  • Platinum refractory

• *Changing treatment paradigms with genomic / precision oncology*
Initial management

• Surgery + chemo

• Chemo + surgery + chemo

• Both are essential in advanced stage disease
ASCO + SGO guidelines (Aug 2016)

• All new patients should be evaluated by a gynecologic oncologist prior to initiation of medical therapy
  • Surgical evaluation: R0 resectable?

• If cannot be optimally resected → chemotherapy (3 cycles) followed by interval surgery and an additional 3 cycles
Quality of surgery matters

• “Optimal vs Sub-optimal”
  • Goal: “R0” resection = no visible disease at completion
  
  • Optimal = largest remaining diameter < 1 cm
  
  • Sub-optimal = > 1 cm residual disease
Survival by surgical outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Residual disease</th>
<th>No.</th>
<th>Median survival (mo)</th>
<th>5-yr survival (%)</th>
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<tbody>
<tr>
<td>Hoskins</td>
<td>1994</td>
<td>No gross</td>
<td>41</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤1 cm</td>
<td>62</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 cm</td>
<td>12</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2 cm</td>
<td>65</td>
<td></td>
<td>&lt;20</td>
</tr>
<tr>
<td>Chi</td>
<td>2006</td>
<td>No gross</td>
<td>67</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤0.5 cm</td>
<td>70</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6-1 cm</td>
<td>99</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 cm</td>
<td>53</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2 cm</td>
<td>176</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>du Bois</td>
<td>2010</td>
<td>No gross</td>
<td>1,046</td>
<td>99.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≤1 cm</td>
<td>975</td>
<td>36.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;1 cm</td>
<td>1,105</td>
<td>29.6</td>
<td></td>
</tr>
</tbody>
</table>

J Gynecol Oncol. 2010 Jun;21(2):75-80.  
https://doi.org/10.3802/jgo.2010.21.2.75
Primary adjuvant treatment

• Backbone: “Platinum + taxane”
  • Carboplatin or cisplatin + paclitaxel or docetaxel
  • Intravenous (IV) only vs IV + intraperitoneal (IP)
  
+  

• Bevacizumab (complicated)
• Numerous other candidate drugs… (clinical trials)
Clinical Trials

- Patients on clinical trials do **as well or better** than patients not enrolled on clinical trials (trials *in general* – including early phase)

- Clinical trials are the primary tool for advancing the treatment of ovarian cancer

- Current crisis: Trial availability and enrollment has precipitously declined since 2011
Not Fake News: Crisis in available clinical trials for women with gynecologic cancers

Hyperthermic Intraperitoneal Extracorporeal Chemotherapy (HIPEC)

• Old concept (1980s)
• Standard therapy for select gastrointestinal cancers
• Numerous small ovarian trials
  • No clear survival advantage
  • Improved IV IV/IP (non-HIPEC) drug options
  • TOXIC!!

• Since: improved technique, expertise, standardization, drug choice…
Phase 3 Trial of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Ovarian Cancer

W.J. van Driel¹,², K. Sikorska¹, J.H. Schagen van Leeuwen³, H.W. Schreuder⁴, R.H. Hermans⁵, I.H. de Hingh⁵,⁶, J. van der Velden⁷, H.J. Arts⁸, L. Massuger⁹, A.G. Aalbers¹,⁶, V.J. Verwaal¹⁰, K.K. van de Vijver¹, N.K. Aarsonson¹, G.S. Sonke¹,²

¹Netherlands Cancer Institute, Amsterdam; ²Dutch Gynecological Oncology Group; ³Sint Antonius Hospital, Nieuwegein; ⁴University Medical Center Utrecht; ⁵Catharina Hospital, Eindhoven; ⁶The Dutch Peritoneal Oncology Group; ⁷Amsterdam Medical Center; ⁸University Medical Center Groningen; ⁹Radboud University Medical Centre, Nijmegen; ¹⁰Aarhus University Hospital

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Study Design OVHIPEC

- Epithelial ovarian cancer
- FIGO stage III
- 3 cycles neoadjuvant carboplatin/paclitaxel
- N=245

Randomization (1:1)
Stratified by the number of involved peritoneal regions, hospital and prior surgery

Interval CRS + HIPEC
n=122

Interval CRS only
n=123

Primary endpoint
- RFS (locally assessed by RECIST 1.1 and GCIG criteria)

Secondary endpoints
- Overall survival
- Quality of life
- Safety

- All patients planned to received three additional cycles of carboplatin/paclitaxel after surgery
- Follow-up visits were performed every 12 weeks for 24 months, then every 26 weeks thereafter
- Tumor assessments with CT scans were performed 26, 52, and 104 weeks after the last chemotherapy
- Final analysis planned after 192 RFS events
  - 80% power to detect a 33% risk reduction (hazard ratio 0.67) with two-sided α=5%

RFS, recurrence-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; OVHIPEC is registered at ClinicalTrials.gov (NCT00428257)
Recurrence-free Survival

- CRS + HIPEC
- CRS only

Overall Survival

- CRS + HIPEC
- CRS only

### Recurrence-free Survival (RFS)

<table>
<thead>
<tr>
<th></th>
<th>CRS+HIPEC</th>
<th>CRS only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median RFS, months</td>
<td>14.2</td>
<td>10.7</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.68 (0.51–0.89)</td>
<td></td>
</tr>
</tbody>
</table>

### Overall Survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>CRS+HIPEC</th>
<th>CRS only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>45.7</td>
<td>33.9</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.67 (0.48–0.94)</td>
<td></td>
</tr>
</tbody>
</table>
Completion of primary therapy

• Okay – now what?
  • Complete Remission
    • Normal Ca-125, exam, film
  • Partial response
    • Improvement but disease still apparent
  • Progressive disease
    • Cancer worsens during primary treatment

• Maintenance therapy??
  • Must effectively fight cancer and be less toxic
FDA approved maintenance therapies

• *Primary treatment*
  
  • None (U.S.); Olaparib in Europe
    • Long list of potentials have been evaluated
  
  • Off label?: bevacizumab, pazopanib, PARP?
    • Controversial...

• Multiple clinical trials with drugs vying for this space
Front Line Maintenance Clinical Trials: PARPi switch maint

SOLO-1 (Olaparib)

- St III-IV Ov
- BRCA mutation
- HG serous or endometrioid
- PR/CR & ≥ 6 cycles

Olaparib (PO) 300 mg tablet BID

Primary endpoint:
- PFS
Secondary:
- OS
- PFS2
- QoL

Placebo

PRIMA (Niraparib)

Niraparib maintenance in First-line therapy
High Risk patients: Stage IV; residual Stage III

- Continuous cycles

ClinicalTrials.gov Identifier: NCT01844986
Front Line Maintenance Clinical Trials: PARPi continuous + maint

GOG 3005 (Veliparib)

- Paclitaxel (standard or dose-dense) Carboplatin AUC 6 (IV)*
- Placebo PO BID
- Veliparib 100 mg PO BID

PAOLA-1 (Olaparib)

Combining olaparib with bevacizumab

- Paclitaxel (standard or dose-dense) Carboplatin AUC 6 (IV)*
- Veliparib 400 mg PO BID

Collaborative development with AbbVie (M13-694) including international participation, seeking EMA and FDA regulatory approval.

Open: JUL 2015 (856 as of 07FEB2017)
Closed:
Target Accrual: ~1100 pts (264 BRCA1/2 +)

Coleman R, for GOG ClinicalTrials.gov Identi
ClinicalTrials.gov Identifier: NCT02477644
NCT02470585
FDA approved maintenance therapies

• *Relapsed treatment*
  
  • Nirapirib (March 2017)
    
    • Maintenance treatment following a partial or complete response to most recent platinum therapy
      
      • No biomarker test required
New FDA approvals for recurrent disease

• Bevacizumab (Dec 2016) expanded indication
  • Platinum *sensitive* recurrence in combination with chemotherapy
    • Gemcitabine + Carboplatin
    • Paclitaxel + Carboplatin
  • Followed by bevacizumab maintenance
New FDA approvals for recurrent disease

- Rucaparib (Dec 2016)
  - BRCA mutated (germline or somatic) ovarian cancer treatment
    - 2 or more prior therapies
    - FoundationFocus CDxBRCA test simultaneously approved for assessment of BRCA status (tumor/tissue test)

- *Olaparib (Dec 2014)
  - BRCA mutated (germline) ovarian cancer treatment
    - 3 or more prior therapies
    - BRAC Analysis CDX for BRCA status
ARIEL2: Phase 2 Trial of Rucaparib in Prospectively Defined Molecular Subgroups

Key Eligibility
- High-grade serous or endometrioid ovarian cancer
- ≥1 prior platinum chemotherapy
- Platinum-sensitive, relapsed, measurable disease
- Adequate tumor tissue (screening biopsy and archival)
- No prior PARPi

Primary Endpoint
- PFS (RECIST) in
  - BRCA\textsuperscript{mut}
  - BRCA-like (excludes BRCA\textsuperscript{mut})
  - Biomarker negative

Secondary Endpoints
- ORR (RECIST and CA-125)
- Safety
- Pharmacokinetics

N = 180
Cap on known germline BRCA\textsuperscript{mut}

ARIEL2 (Rucaparib): PFS (2016)


<table>
<thead>
<tr>
<th>Subgroup Comparison</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA\text{mut} vs</td>
<td>0.25</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BRCA\text{wt/LOH}^\text{low}</td>
<td>(0.15-0.42)</td>
<td></td>
</tr>
<tr>
<td>BRCA\text{wt/LOH}^\text{high} vs</td>
<td>0.51</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>BRCA\text{wt/LOH}^\text{low}</td>
<td>(0.34-0.74)</td>
<td></td>
</tr>
</tbody>
</table>

Median, mo (95% CI)
- BRCA\text{mut} vs BRCA\text{wt/LOH}^\text{low}: 12.8 (9.0-14.7)
- BRCA\text{wt/LOH}^\text{high} vs BRCA\text{wt/LOH}^\text{low}: 7.2 (5.5-9.6)
- BRCA\text{wt/LOH}^\text{low}: 5.0 (3.6-5.4)

Available Time, mo
- BRCA\text{mut}: 40 40 39 39 36 36 34 33 32 27 25 22 20 19 16 12 9 7 5 5 5 2 2 2 0
- BRCA\text{wt/LOH}^\text{high}: 69 65 54 50 43 42 36 31 27 23 21 20 18 17 14 10 5 4 3 1 1
- BRCA\text{wt/LOH}^\text{low}: 83 81 60 54 42 37 23 22 15 14 12 10 6 4 3 2 1 0
Rucaparib Activity (2016) in BRCA\textsuperscript{mut} and BRCA\textsuperscript{wt}

- **BRCA\textsuperscript{mut} patients (n = 40)**
  - 69% ORR (RECIST)
  - 82% ORR (RECIST and CA-125)
  - 83% of patients continuing on treatment (+)

- **BRCA\textsuperscript{like} signature (n = 82)**
  - 30% ORR (RECIST)
  - 45% ORR (RECIST and CA-125)
  - 52% of patients continuing on treatment (+)

- **BRCA\textsuperscript{wt} patients without BRCA\textsuperscript{like} signature (n = 70)**
  - 13% ORR (RECIST)
  - 21% ORR (RECIST and CA-125)
  - 38% of patients continuing on treatment (+)

*BRCA-like = LOH\textsuperscript{high} by NGS analysis.*

Immunotherapy

• Broad term – includes numerous different strategies

  • Adoptive T cell transfer
    • Chimeric Antigen Receptor T cell therapy (CAR-T)

  • Bispecific monoclonal antibodies

  • Checkpoint inhibition
    • PD-1
    • CTLA-4
Immunotherapy basic mechanism

- Key concepts:
  - Multiple arms make up immune system, most broadly: innate and adaptive
  - Balance between T cell activation and regulation
Checkpoint inhibitor targets
Pembrolizumab in Patients with PD-L1-positive Advanced Ovarian Cancer: Updated Analysis of KEYNOTE-028

Andrea Varga,¹ Sarina Piha-Paul,² Patrick A. Ott,³ Janice M. Mehnert,⁴ Dominique Berton-Rigaud,⁵ Anne Morosky,⁶ Guo Qing Zhao,⁶,⁷ Reshma Rangwala,⁶ Daniela Matei⁸

¹Institut Gustave Roussy, Villejuif, France; ²The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ³Dana-Farber Cancer Institute, Boston, MA, USA; ⁴Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; ⁵ICO Centre René Gauducheau, Saint-Herblain, France; ⁶Merck & Co., Inc., Kenilworth, NJ, USA; ⁷MRL, MSD China, Beijing, China; ⁸Northwestern University Feinberg School of Medicine, Chicago, IL, USA

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KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1–positive Advanced Solid Tumors

**Patients**
- Advanced ovarian epithelial, fallopian tube, or primary peritoneal carcinoma
- Failure of or inability to receive standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion
- PD-L1 positivity

**Pembrolizumab 10 mg/kg IV Q2W**

**Response Assessment***
- Complete response, partial response, or stable disease
- Confirmed progressive disease† or unacceptable toxicity
- Treat for 24 months or until progression† or intolerable toxicity
- Discontinue pembrolizumab

*Response assessment: Every 8 weeks for the first 6 months; every 12 weeks thereafter
Primary end points: ORR per RECIST v1.1 and safety
Secondary end points: PFS, OS, duration of response

†Clinically stable patients were allowed to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Patients who experienced progression after discontinuing pembrolizumab were eligible for up to 1 year of additional treatment if no other anticancer therapy was received.

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ECOG = Eastern Cooperative Oncology Group; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status

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## Best Overall Response (RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>3</td>
<td>11.5</td>
<td>2.4, 30.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>1</td>
<td>3.8</td>
<td>0.1, 19.6</td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
<td>7.7</td>
<td>0.9, 25.1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7</td>
<td>26.9</td>
<td>11.6, 47.8</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16</td>
<td>61.5</td>
<td>40.6, 79.8</td>
</tr>
</tbody>
</table>
Longitudinal Change in Tumor Size from Baseline (RECIST v1.1, Investigator Review)
How does this compare with other I/O data in EOC?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>N</th>
<th>Response</th>
<th>Stable Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>20</td>
<td>10% CR, 5% PR</td>
<td>30%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1</td>
<td>26</td>
<td>4% CR, 8% PR</td>
<td>27%</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>124</td>
<td>10% PR</td>
<td>44%</td>
</tr>
<tr>
<td>Durvalumab + Olaparib</td>
<td>PD-L1 + PARP</td>
<td>10</td>
<td>10% PR</td>
<td>70%</td>
</tr>
<tr>
<td>Duralumab + Cediranib</td>
<td>PD-L1 + VEGFR</td>
<td>4</td>
<td>25% PR</td>
<td>50%</td>
</tr>
</tbody>
</table>

Hamanishi et al. J Clin Onc 2015, 33; Varga et al. ASCO 2017; Disis et al J Clinic Oncol 34 (suppl): 2016; Lee et al J Clin Onc 34 suppl): 2016  Table as presented by Paul Sabbatini at ASCO 2017
Responses to checkpoint inhibitors in ovarian cancer

<table>
<thead>
<tr>
<th>Immunotherapy agent(s)</th>
<th>Trial number</th>
<th>Disease status</th>
<th>Phase</th>
<th>N</th>
<th>Results (N; duration)</th>
<th>G3/4 adverse events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td></td>
<td>recurrent EOC, previously treated with GVAX vaccine</td>
<td>I</td>
<td>9</td>
<td>PR (1; 35+ mos.), SD (3; 1 for 6+ mos.)</td>
<td>diarrhea</td>
<td>Hodi et al. [50]</td>
</tr>
<tr>
<td>BMS-936559 (anti-PD-L1)</td>
<td>NCT00729664</td>
<td>recurrent EOC</td>
<td>I</td>
<td>17</td>
<td>6% PR (1; 1.3+ mos.), 18% SD (3; 6+ mos.)</td>
<td>infusion-related reaction, adrenal insufficiency</td>
<td>Brahmer et al. [80]</td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td>platinum resistant EOC</td>
<td>II</td>
<td>20</td>
<td>10% CR (2; 11+ mos.), 5% PD (1; 11+ mos.), 30% SD (6; 1 for 11+ mos.)</td>
<td>lymphocytopenia, hyposalbuminemia, elevated ALT, rash, fever, anemia</td>
<td>Hamanishi et al. [25]</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT02054806</td>
<td>recurrent EOC, PD-L1 positive</td>
<td>Ib</td>
<td>26</td>
<td>4% CR (1; 6+ mos.), 8% PR (2; 6+ mos.), 23% SD (8; 2 for 6+ mos.)</td>
<td>transaminitis</td>
<td>Varga et al. [26]</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>NCT01611558</td>
<td>recurrent EOC</td>
<td>II</td>
<td>40</td>
<td>10% BR (4; NA)</td>
<td>NA</td>
<td>clinicaltrials.gov [27]</td>
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<tr>
<td>Avelumab</td>
<td>NCT01772004</td>
<td>recurrent EOC</td>
<td>Ib</td>
<td>124</td>
<td>10% PR (12; 4 for 6+ mos.), 44% SD (55; NA)</td>
<td>rash, edema, elevated amylase/lipase, arthritis, colitis, hyperglycemia/DM</td>
<td>Disis et al. [28]</td>
</tr>
<tr>
<td>Durvalumab + Olaparib</td>
<td>NCT02484404†</td>
<td>recurrent EOC</td>
<td>I/II</td>
<td>10</td>
<td>PR (1; 11+ mos.), SD (7; 4+ mos.)</td>
<td>Lymphopenia, anemia</td>
<td>Lee et al. [29]</td>
</tr>
<tr>
<td>Durvalumab + Cediranib</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>PR (1; 7 mos.), SD (2; 1 for 6 mos.)</td>
<td>Lymphopenia, anemia, nausea, diarrhea, hypertension, PE, pulmonary hypertension, fatigue, headache</td>
<td></td>
</tr>
</tbody>
</table>
Future directions

• Promising advances in early detection

• Surgery affirmed as an essential pillar of primary therapy

• Defective DNA repair is achilles heel of ovarian cancer
  • Drugs that exploit this will become increasingly important

• Targeted therapies including coimations emerging
  • Includes anti-angiogenesis, PARP-I and immunotherapy agents