Targeted Agents and Chemotherapy in Gynecologic Malignancies in 2018

Gerardo Colon-Otero, M.D.
Professor of Medicine, Mayo Clinic College of Medicine
Dean, Mayo Clinic School of Medicine, Florida Campus
Disclosures

• Research support from Novartis to Mayo Clinic for Investigator Initiated Trials.
GOALS


• Incorporate that data into the standard care of gynecologic cancers.
Gynecologic cancers 2018

- Ovarian cancer
  - 22,240 new cases
  - 14,070 deaths

- Endometrial cancer
  - 63,230 new cases
  - 11,350 deaths

- Cervical, vaginal, vulvar cancers
  - 24,800 new cases
  - 6,700 deaths

Total Gyn cancers
- 110,000 new cases
- 32,000 deaths

Siegel: Ca 68 (1): 7-10, 2018
### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>164,690</td>
<td>266,120</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>121,680</td>
<td>112,350</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>75,610</td>
<td>64,640</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>62,380</td>
<td>63,230</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>55,150</td>
<td>40,900</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>42,680</td>
<td>36,120</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>41,730</td>
<td>32,950</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>37,160</td>
<td>26,240</td>
</tr>
<tr>
<td>Leukemia</td>
<td>35,030</td>
<td>25,270</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>30,610</td>
<td>22,660</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>556,370</strong></td>
<td><strong>873,980</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>83,550</td>
<td>70,500</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,430</td>
<td>40,290</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,390</td>
<td>23,240</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,020</td>
<td>21,310</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,540</td>
<td>14,070</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,270</td>
<td>11,350</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,650</td>
<td>10,100</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,520</td>
<td>9,660</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>8,400</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,010</td>
<td>7,340</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>323,630</strong></td>
<td><strong>286,910</strong></td>
</tr>
</tbody>
</table>
Gynecologic cancers 2018

- Ovarian cancer
  - 22,240 new cases
  - 14,070 deaths
- Endometrial cancer
  - 63,230 new cases
  - 11,350 deaths
- Cervical, vaginal, vulvar cancers
  - 24,800 new cases
  - 6,700 deaths

Total Gyn cancers

- 110,000 new cases
- 32,000 deaths
Targets in Ovarian Cancer: Mutations and Molecular Aberrations

Presented By Paul Sabbatini, MD at 2013 ASCO Annual Meeting

Katsumata et al: Lancet Oncology 2013
Ovarian cancer: High grade serous carcinomas

- Neo-adjuvant chemotherapy vs upfront debulking surgery followed by adjuvant chemotherapy
- IP chemotherapy vs dose dense chemotherapy vs weekly chemotherapy vs every 3 weeks IV chemotherapy
- HIPEC during interim debulking surgery (NEJM 2017)
Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer

Results from the MRC CHORUS trial

S Kehoe, JM Hook, M Nankivell, GC Jayson, HC Kitchener, T Lopes, DLuesley, TJ Perren, S Bannoo, M Mascarenhas, SDobbs, S Essapen, JTwigg, J Herod, WGMcCluggage, M Parmar, AMSwart on behalf of the CHORUS trial collaborators and NCRI Gynaecological Cancer Studies Group
Deaths within 28 days of surgery

<table>
<thead>
<tr>
<th></th>
<th>PS</th>
<th>NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>14 (5.6%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

- Review of deaths within 28 days of surgery
  - PS
    - Disease progression = 4
    - Pulmonary embolism = 2; infection = 3; problems with fluid balance or renal failure = 2; hemorrhage = 1; intra-operative problems = 1
    - Still under review = 1
  - NACT
    - Pulmonary embolism = 1
Overall survival

Presented By Sean Kehoe, MD at 2013 ASCO Annual Meeting; Lancet May 20, 2015

* HR adjusted for baseline stratification factors.
EORTC: NACT + IDS vs PDS: PP1
Overall Survival: Largest Metastatic Tumor Size

- <5 cm: HR, 0.64; 95% CI: 0.45-0.93

Ovarian cancer: High grade serous carcinomas

- Neo-adjuvant chemotherapy vs upfront debulking surgery followed by adjuvant chemotherapy
- IP chemotherapy vs dose dense chemotherapy vs weekly chemotherapy vs every 3 weeks IV chemotherapy
- HIPEC during interim debulking surgery (NEJM 2017)
• IP therapy remains important as predictor of survival at 10 years
• HR=0.77
Katsumata et al: Lancet Oncology 2013
• *Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer*


• DOI: 10.1056/NEJMoaa1505067
Ovarian Cancer First-Line Treatment Trials: Where Are We Now? (cont.)

- GOG 262: Randomized phase III trial for suboptimally cytoreduced patients
  - Neoadjuvant
  - Targeted/novel therapeutics
  - QOL
  - 692 patients

Bevacizumab to Progression
Start Cycle 2

IV Wkly Paclitaxel
IV Carboplatin q3wks
X
6 Cycles

IV Paclitaxel q3wks
IV Carboplatin q3wks
X
6 Cycles

US NIH, 2011c.
Primary and Subgroup Analyses of Progression-free Survival, According to Treatment Group.
Ovarian Cancer First-Line Treatment Trials: Where Are We Now? (cont.)

- GOG 252: Randomized phase III trial for optimally cytoreduced patients
  - IP vs. IV
  - Targeted/novel therapeutics
  - QOL
  - Maintenance
  - 1,500 pts

Bevacizumab
Cycles 2–22

- IV Wkly Paclitaxel
  - IP Carboplatin q3wks
  - X
  - 6 Cycles

- IV Wkly Paclitaxel
  - IV Carboplatin q3wks
  - X
  - 6 Cycles

- IV q3wks Paclitaxel
  - IP Cisplatin
  - IP Paclitaxel
  - X
  - 6 Cycles

IV = intravenous.
US NIH. 2011b
### Progression Free Survival Optimal Stage II-III (10% stage II)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>Median PFS</th>
<th>HR [95% CI]</th>
<th>Logrank</th>
<th>Logrank</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Carbo</td>
<td>461</td>
<td>303</td>
<td>26.8 months</td>
<td>Reference arm</td>
<td>P-value</td>
<td>Chi square</td>
</tr>
<tr>
<td>IP Carbo</td>
<td>464</td>
<td>300</td>
<td>28.7 months</td>
<td>0.947 [0.808-1.11]</td>
<td>0.416</td>
<td>0.661</td>
</tr>
<tr>
<td>IP Cisp</td>
<td>456</td>
<td>307</td>
<td>27.8 months</td>
<td>1.01 [0.858-1.18]</td>
<td>0.727</td>
<td>0.122</td>
</tr>
</tbody>
</table>

- Estimated hazard ratios, and logrank tests are adjusted for stage of disease and size of residual disease micro vs ≤ 1cm.
- CT required every 6 months for surveillance (not required in GOG 114/172)
Study design

Random

Control arm
- **Carboplatin** AUC 6, d1 q21
- **Paclitaxel** 175 mg/m², d1 q21
- Treatment repeated for 6 cycles

Experimental arm
- **Carboplatin** AUC 2, d1, 8, 15 q21
- **Paclitaxel** 60 mg/m², d1, 8, 15 q21
- Treatment repeated for 6 cycles

Strata:
- Center
- PS (0, 1, 2)
- Residual disease after surgery (absent, ≤1 cm, >1 cm, no surgery)

ClinicalTrials.gov NCT00660842

Presented by: S. Pignata

Pignata, MD, PhD 2013 ASCO Annual Meeting; Lancet Oncology 2014
Overall survival

Analysis: March 2013, median follow-up 19.9 months

**Median OS**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3-week</td>
<td>403</td>
<td>76</td>
</tr>
<tr>
<td>Weekly</td>
<td>405</td>
<td>89</td>
</tr>
</tbody>
</table>

Log-rank test $p = 0.24$

Unadjusted $HR: 1.20$ (0.88 – 1.63)
In all scales, higher values represent better outcome.
All tests are adjusted by performance status, stage, residual disease after surgery, age category, and size of the institution.
Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer


23 References  7 Citing Articles

January 18, 2018
DOI: 10.1056/NEJMo1708618
Chinese Translation 中文翻译
Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer

Leena Gandhi, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Shirish Gadgeel, M.B., B.S., Emilio Esteban, M.D., Enriqueta Felip, M.D., Ph.D., Flávia De Angelis, M.D., Manuel Domine, M.D., Ph.D., Philip Clingan, M.B., B.S., Maximilian J. Hochmair, Ph.D., Steven F. Powell, M.D., Susanna Y.-S. Cheng, M.D., Helge G. Bischoff, M.D., et al., for the KEYNOTE-189 Investigators*
Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jamie E. Chafft, M.D., Kellie N. Smith, Ph.D., Valsamo Anagnostou, M.D., Ph.D., Tricia R. Cottrell, M.D., Ph.D., Matthew D. Hellmann, M.D., Marianna Zaharak, M.S., Stephen C. Yang, M.D., David R. Jones, M.D., Stephen Broderick, M.D., Richard J. Batta farano, M.D., Ph.D., Moises J. Velez, M.D., et al.
A Percentage of Pathological Regression, According to Subgroup

- Current/ex-smoker
- Never smoked
- AC
- SCC
- Other
- PR
- SD
- LN+
- LN−

Smoking Status
Histologic Subtype
RECIST Response
LN Metastases

Regression (%)
- PD-L1+
- PD-L1−
- Unknown

B Biopsy Sample before Nivolumab

C Biopsy Sample after Nivolumab
Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer: Results from the I-SPY 2 Trial


This presentation is the intellectual property of I-SPY. Contact randa@medicine.bsd.uchicago.edu for permission to reprint and/or distribute.
I-SPY 2 TRIAL Eligibility

Screening Consent → Assess Eligibility → Core Biopsy

Screening

- Tumor size ≥ 2.5 cm
- Candidate for preoperative chemotherapy
- Study MRI and biopsy
- MammaPrint (MP)
- Adequate organ function, PS<2
I-SPY 2 TRIAL Schema: HER2- Signatures

Control
Paclitaxel 80 mg/m2 every wk x 12

Experimental
Paclitaxel 80 mg/m2 every wk x 12
Pembro 200 mg every 3 wks x 4
Pembrolizumab graduated in all HER2- signatures: Both HR+/HER2- and TN

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% probability interval)</th>
<th>Probability pembro is superior to control</th>
<th>Predictive probability of success in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>All HER2-</td>
<td>0.46 (0.34 – 0.58)</td>
<td>0.16 (0.06 – 0.27)</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>TNBC</td>
<td>0.60 (0.43 – 0.78)</td>
<td>0.20 (0.06 – 0.33)</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>0.34 (0.19 – 0.48)</td>
<td>0.13 (0.03 – 0.24)</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population. The raw pCR rates (not shown) are higher than the model estimate of 0.604 in TNBC.
BRCA mutated and HRD Ovarian Cancers: Future

• Upfront maintenance PARP inhibitors
• Maintenance rucaparib or niraparib or olaparib following relapse
• Evaluation of PARP inhibitors and checkpoint inhibitors
RELAPSED OVARIAN CANCER (70% of all cases)

- Don’t forget about debulking surgery
- Angiogenesis inhibitors: bevacizumab
- PARP inhibitors: olaparib, rucaparib, niraparib
- PARP inhibitors plus anti-angiogenesis: olaparib and cediranib
- Monoclonal antibodies and immuno-conjugates
- Immunotherapy (checkpoint inhibitors)
- PARP inhibitors and checkpoint inhibitors
- Cyclin kinase 1,2 inhibitors
Progression-free survival (PFS).
PFS by BRCAm status

- 82% reduction in risk of disease progression or death with olaparib
Results of ARIEL2: A phase 2 trial to prospectively identify ovarian cancer patients likely to respond to rucaparib using tumor genetic analysis

Iain McNeish, Amit Oza, Robert L. Coleman, Clare Scott, Gottfried Konecny, Anna Tinker, David M. O'Malley, James Brenton, Rebecca Kristeleit, Katherine Bell-McGuinn, Ana Oaknin, Alexandra Leary, Kevin K. Lin, Mitch Raponi, Heidi Giordano, Sandra Goble, Lindsey Rolfe, Roman Yelensky, Andrew Allen, and Elizabeth Swisher

1Institute of Cancer Sciences, University of Glasgow, 2Princess Margaret Cancer Centre, 3The University of Texas MD Anderson Cancer Center, 4Royal Melbourne Hospital, 5University of California, 6British Columbia Cancer Agency, 7The Ohio State University, 8Cancer Research UK Cambridge Institute, 9University College London, 10Memorial Sloan-Kettering Cancer Center, 11Vall d’Hebron University Hospital, 12Institut Gustave Roussy, 13Clovis Oncology Inc., 14Foundation Medicine Inc., 15University of Washington School of Medicine

Presented By Iain McNeish at 2015 ASCO Annual Meeting
In BRCA$^{\text{wt}}$ tumors, the BRCA-like subgroup derives enhanced benefit from rucaparib

<table>
<thead>
<tr>
<th>HRD Subgroup</th>
<th>Median PFS, mo (90% CI)</th>
<th>Overall Response Rate, % (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RECIST</td>
</tr>
<tr>
<td>BRCA$^{\text{mut}}$</td>
<td>9.4 (7.3, NR)</td>
<td>69 (27/39)</td>
</tr>
<tr>
<td>BRCA-like</td>
<td>7.1 (3.7, 10.8)</td>
<td>30 (22/74)</td>
</tr>
<tr>
<td>Biomarker Negative</td>
<td>3.7 (3.5, 5.5)</td>
<td>13 (8/62)</td>
</tr>
</tbody>
</table>

NR=not reached.

Presented By Iain McNeish at 2015 ASCO Annual Meeting
Response rate striking in BRCA\textsuperscript{mut} tumors

- ORR (RECIST or CA-125) 82%
- ORR similar in germline (81%) and somatic (88%) patients
  - 4 CRs in somatic BRCA\textsuperscript{mut} group
- Median duration of response = 9.3 months+
Proportion of OC patients with mutations in homologous recombination genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>148</td>
</tr>
<tr>
<td>BRCA2</td>
<td>78</td>
</tr>
<tr>
<td>Other</td>
<td>81</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
</tr>
</tbody>
</table>

N = 1195

No mutation 74.3%

BRCA1 12.4%
BRCA2 6.5%
Other 6.8%
Overall survival by mutation status

- **BRCA2:** 75.2 months
- **BRCA1:** 55.3 months
- **Other:** 56.0 months
- **No Mutation:** 42.1 months
## Estimated relative hazards of death by mutation category

<table>
<thead>
<tr>
<th>Mutation Category</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>BRCA2</em></td>
<td>0.36 (0.25 – 0.53)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
<td>0.74 (0.59 – 0.94)</td>
<td>0.01</td>
</tr>
<tr>
<td>Other HR</td>
<td>0.67 (0.49 – 0.90)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

- Reference group is those with no mutation
- Hazard ratios are adjusted for study treatment, stage of disease, size of residual disease, initial performance status
<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Biomarker</th>
<th>Tumor</th>
<th>Phase of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSMA-ADC</td>
<td>Progenics</td>
<td>PSMA</td>
<td>Prostate</td>
<td>II</td>
</tr>
<tr>
<td>ABT-414</td>
<td>AbbVie</td>
<td>EGFR</td>
<td>GBM, NSCLC</td>
<td>I, II</td>
</tr>
<tr>
<td>IMGN901</td>
<td>Immunogen</td>
<td>CD56</td>
<td>SCLC, MM, Ovarian, MCC</td>
<td>I, II</td>
</tr>
<tr>
<td>(Lorvotuzumab mertansine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDX-011</td>
<td>Celldex</td>
<td>Glycoprotein NMB (GNMB)</td>
<td>Breast, Melanoma</td>
<td>I, II</td>
</tr>
<tr>
<td>(glembatumumab vedotin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMGN853</td>
<td>Immunogen</td>
<td>Folateceptor α</td>
<td>Ovarian, NSCLC</td>
<td>I</td>
</tr>
<tr>
<td>SGN-75 (vorsetuzumab mafodotin)</td>
<td>Seattle Genetics</td>
<td>CD70</td>
<td>RCC</td>
<td>I</td>
</tr>
<tr>
<td>DMUC5754A</td>
<td>Roche/Genentech</td>
<td>MUC16</td>
<td>Ovarian</td>
<td>I</td>
</tr>
<tr>
<td>BAY 94-9343</td>
<td>Bayer</td>
<td>Mesothelin</td>
<td>Mesothelioma, Ovarian, Gastric, Pancreatic, Lung</td>
<td>I</td>
</tr>
<tr>
<td>Anti-NaPi2b-vc-E</td>
<td>Roche/Genentech</td>
<td>NaPi2b</td>
<td>Lung, Ovarian</td>
<td>I</td>
</tr>
<tr>
<td>SC16LD6.5</td>
<td>StemCentRx</td>
<td>SCLC surface protein</td>
<td>SCLC</td>
<td>I</td>
</tr>
<tr>
<td>IMMU-132</td>
<td>Immunomedics</td>
<td>TACSTD2 (TROP2/EGP1)</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>Labetuzumab-SN-38</td>
<td>Immunomedics</td>
<td>CEA (CD66e)</td>
<td>CRC</td>
<td>I</td>
</tr>
<tr>
<td>RG-7636</td>
<td>Genentech</td>
<td>Endothelin receptor ETB</td>
<td>Melanoma</td>
<td>I</td>
</tr>
<tr>
<td>RG-7450</td>
<td>Genentech</td>
<td>STEAP1</td>
<td>Prostate</td>
<td>I</td>
</tr>
<tr>
<td>AGS-5ME</td>
<td>Agensys</td>
<td>SLC44A4 (AGS-5)</td>
<td>Pancreatic, Stomach</td>
<td>I</td>
</tr>
<tr>
<td>AGS-22M6E</td>
<td>Agensys</td>
<td>Nectin 4</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>AGS-16M8F</td>
<td>Agensys</td>
<td>AGS-16</td>
<td>RCC</td>
<td>I</td>
</tr>
<tr>
<td>MLN-0264</td>
<td>Millennium</td>
<td>Guanylyl cyclase C</td>
<td>GI</td>
<td>I</td>
</tr>
<tr>
<td>SAR-566658</td>
<td>Sanofi</td>
<td>Mucin 1</td>
<td>Solid tumor</td>
<td>I</td>
</tr>
<tr>
<td>AMG-172</td>
<td>Amgen</td>
<td>CD70</td>
<td>RCC</td>
<td>I</td>
</tr>
<tr>
<td>AMG-595</td>
<td>Amgen</td>
<td>EGFRvIII</td>
<td>Glioma</td>
<td>I</td>
</tr>
</tbody>
</table>

Presented By Jeffrey Abrams at 2014 ASCO Annual Meeting
Response Assessment at RP2D (2.4 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Ovarian IHC 0</th>
<th>Ovarian IHC 2/3+</th>
<th>Lung IHC 0</th>
<th>Lung IHC 2/3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed RECIST Response Rate</td>
<td>0% (0/1)</td>
<td>41% (7/17)</td>
<td>0% (0/5)</td>
<td>10% (2/21)</td>
</tr>
<tr>
<td>Clinical Benefit Rate (cPR or SD ≥ 3 months)</td>
<td>0% (0/1)</td>
<td>53% (9/17)</td>
<td>20% (1/5)</td>
<td>48% (10/21)</td>
</tr>
</tbody>
</table>

None of the patients with tissue unevaluable for NaPi2b staining demonstrated response to treatment.
Banerjee et al: Lifastizumab (Anti-NaPi2b vedotin-MMAE) vs liposomal doxorubicin (Abstract 5569, ASCO 2016)

- 95 patients, randomized phase 2
- PFS: 5.3 mo vs 3.1 mo
- RR: 34% vs 15%
Prexasertib: CK1,2 Tyrosine Kinase Inhibitor
Hormonal Maintenance Therapy for Women with Low-Grade Serous Carcinoma of the Ovary or Peritoneum

David M. Gershenson, MD
The University of Texas MD Anderson Cancer Center
Results: Schema

- Stage II-IV LGSC
- Primary Cytoreductive Surgery
- Platinum-Based Chemotherapy
  - Surveillance N = 134
  - Hormonal Maintenance Therapy N = 70
Results: PFS in Patients NED at Completion of Chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (mo)</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURV (n = 121)</td>
<td>29.9</td>
<td>24.5, 35.2</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HMT (n = 27)</td>
<td>81.1</td>
<td>55.2, 106.9</td>
<td></td>
</tr>
<tr>
<td>ALL (N = 148)</td>
<td>33.0</td>
<td>28.4, 37.7</td>
<td></td>
</tr>
</tbody>
</table>
# Results: OS in Patients NED at Completion of Chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (mo)</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURV (n = 121)</td>
<td>106.8</td>
<td>72.8, 140.7</td>
<td></td>
</tr>
<tr>
<td>HMT (n = 27)</td>
<td>191.3</td>
<td>93.5, 289.1</td>
<td>.04</td>
</tr>
<tr>
<td>ALL (N = 148)</td>
<td>115.7</td>
<td>86.5, 144.9</td>
<td></td>
</tr>
</tbody>
</table>
### Results: Multivariable Analysis for PFS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group SURV (ref) HMT</td>
<td>.23</td>
<td>0.11, 0.51</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Primary site Ovary (ref) Peritoneum</td>
<td>.45</td>
<td>0.27, 0.76</td>
<td>.003</td>
</tr>
<tr>
<td>Residual disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross (ref) No gross</td>
<td>.49</td>
<td>0.28, 0.87</td>
<td>.02</td>
</tr>
<tr>
<td>Disease status at completion of chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent disease (ref) NED</td>
<td>.42</td>
<td>0.18, 0.96</td>
<td>.04</td>
</tr>
</tbody>
</table>
Phase 2 trial of everolimus and letrozole in relapsed estrogen receptor-positive high-grade ovarian cancers


Division of Hematology and Medical Oncology, Mayo Clinic, Jacksonville, FL, United States
Division of Medical Oncology, Mayo Clinic, Rochester, MN, United States
Division of Biomedical Statistics and Informatics, Rochester, MN, United States
Department of Medical & Surgical Gynecology, Mayo Clinic, Jacksonville, FL, United States
Department of Cancer Biology, Mayo Clinic, Jacksonville, FL, United States

HIGHLIGHTS

- AI therapy is associated with limited clinical activity in high-grade ovarian cancer.
- Combination of everolimus and letrozole is associated with a promising 12-week PFS.
- PDX tumor models can be generated from biopsies of ovarian tumors.
Fig. 1. Progression-Free Survival. CI, confidence interval; KM, Kaplan-Meier method.
ESR1 Alteration in Metastatic ER-Positive Breast Cancer

- 10–40% prevalence of ESR1 LBD mutations in patients with metastatic ER+ breast cancer
- ESR1 mutations are associated with prior exposure to AI treatment
- After first line treatment with non-steroidal AI, patients with ESR1 mutation have worse PFS with steroidal AI compared to patients with WT ESR1
- ESR1-mutant metastatic breast cancer patients seem to benefit from fulvestrant +/- palbociclib

• Abstract MIP-056: CONSTITUTIVELY ACTIVE ESTROGEN RECEPTOR–ALPHA LIGAND BINDING DOMAIN (ERA–LBD) MUTATIONS IN OVARIAN CARCINOMA

Elvin J et al: Clinical Cancer Research June 2017

- CGP of 3641 ovarian and peritoneal tumors
- 31/3641 (0.9%) amplifications of ESR1 and 16 (0.4%) with ESR1 LBD mutations
- 10/16 (Y537S); 4/16 (D638G); 1/16 (S341L); 1/16 (Y537N)
- 8 patients: 3/3 patients responded to fulvestrant
Gynecologic cancers 2018

- Ovarian cancer
  - 22,240 new cases
  - 14,070 deaths
- Endometrial cancer
  - 63,230 new cases
  - 11,350 deaths
- Cervical, vaginal, vulvar cancers
  - 24,800 new cases
  - 6,700 deaths

Total Gyn cancers
- 110,000 new cases
- 32,000 deaths
Mutation spectra across endometrial carcinomas.

Fig. 3 Mismatch repair deficiency across 12,019 tumors.

Dung T. Le et al. Science 2017;science.aan6733
Target Lesions

- MMR-proficient CRC
- MMR-deficient CRC
- MMR-deficient non-CRC

% Change from Baseline SLD
Fig. 1 Patient survival and clinical response to Pembrolizumab across 12 different tumor types with mismatch repair deficiency.

Dung T. Le et al. Science 2017;science.aan6733
Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx
Slomovitz BM et al: GOG3007: SGO 2018

- Randomized phase 2 trial: Everolimus and letrozole vs alternating Tamoxifen with medroxyprogesterone acetate (PT)
- 74 patients: February 2015 through April 2016
- RR: 24% with everolimus and letrozole (EL)
- Upfront setting: RR 53% EL vs 43% PT; PFS: 6.4 m vs 3.8 m; grade 3-4 SAE: 0% vs 8.3%
Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx
Santin AD and Fader AN: SGO 2018

- HER2 amplification in 30% serous carcinomas of uterus
- Randomized Phase 2 trial: TC +/- trastuzumab
- August 2011- March 2017
- 61 patients
- Median PFS 8 months vs 12.6 months (HR 0.44, p= 0.005)
- 41 patients : primary rx: PFS 9.3 mo vs 17.9 mo (HR 0.4, p=0.013)
Metastatic Endometrial cancer

- Letrozole and everolimus vs Tamoxifen alternating with Medroxyprogesterone acetate
- Pembrolizumab in MMR deficient tumors
- Pembrolizumab plus ipilimumab in MMR deficient tumors
- Trastuzumab in HER2 amplified high grade serous tumors
- Bevacizumab and temsirolimus as potential Rx in subsets

- Phase 2 randomized trial of TC bevacizumab vs TC temsirolimus vs Ixabepilone CBDCA bevacizumab
- 349 patients: advanced stage or recurrent endometrial Ca
- TSC2 somatic mutations in 5.8%; associated with improved PFS in temsirolimus arm (HR 0.11)
- CTNNB1 mutations were associated with improved PFS if bevacizumab was given.
Gynecologic cancers 2018

- Ovarian cancer
  - 22,240 new cases
  - 14,070 deaths

- Endometrial cancer
  - 63,230 new cases
  - 11,350 deaths

- Cervical, vaginal, vulvar cancers
  - 24,800 new cases
  - 6,700 deaths

Total Gyn cancers
- 110,000 new cases
- 32,000 deaths
Cervix cancer

• Data from Australia on prevention of cervical cancer with vaccination
Overall survival by treatment (log-rank $P = .8333$).

Crude HR, 1.042; 95% CI, 0.710 to 1.531

$P = .8333$

DiSilvestro PA et al. JCO 2014;32:458-464
OUTBACK TRIAL SCHEMA

Women with some types of cervical cancer

Randomisation

Max 6 Weeks

Control Arm
Concurrent chemotherapy and radiation

Intervention Arm
Concurrent chemotherapy and radiation followed by additional chemotherapy

Follow-up for 3-5 years
(A) Overall and (B) progression-free survival.

Ryo Kitagawa et al. JCO 2015;33:2129-2135
Subgroup analysis of overall survival.

<table>
<thead>
<tr>
<th>Category</th>
<th>TP (n)</th>
<th>TC (n)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>56</td>
<td>48</td>
<td>1.16</td>
<td>0.77 to 1.75</td>
</tr>
<tr>
<td>≥ 51</td>
<td>67</td>
<td>73</td>
<td>0.94</td>
<td>0.65 to 1.36</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>94</td>
<td>91</td>
<td>0.90</td>
<td>0.65 to 1.24</td>
</tr>
<tr>
<td>1 or 2</td>
<td>29</td>
<td>30</td>
<td>1.44</td>
<td>0.84 to 2.47</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>102</td>
<td>100</td>
<td>0.96</td>
<td>0.71 to 1.29</td>
</tr>
<tr>
<td>Non-SCC</td>
<td>21</td>
<td>21</td>
<td>1.28</td>
<td>0.66 to 2.48</td>
</tr>
<tr>
<td>Nonirradiated tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one tumor is nonirradiated</td>
<td>79</td>
<td>73</td>
<td>0.97</td>
<td>0.69 to 1.37</td>
</tr>
<tr>
<td>All the tumors are irradiated</td>
<td>44</td>
<td>48</td>
<td>1.03</td>
<td>0.65 to 1.64</td>
</tr>
<tr>
<td>Prior platinum therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (most CDDP)</td>
<td>59</td>
<td>68</td>
<td>0.69</td>
<td>0.47 to 1.02</td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>53</td>
<td>1.57</td>
<td>1.06 to 2.32</td>
</tr>
<tr>
<td>Platinum-free interval, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>20</td>
<td>12</td>
<td>1.69</td>
<td>0.78 to 3.65</td>
</tr>
<tr>
<td>≥ 6, &lt; 12</td>
<td>18</td>
<td>22</td>
<td>0.57</td>
<td>0.29 to 1.11</td>
</tr>
<tr>
<td>≥ 12</td>
<td>21</td>
<td>34</td>
<td>0.71</td>
<td>0.36 to 1.38</td>
</tr>
<tr>
<td>No prior platinum therapy</td>
<td>64</td>
<td>53</td>
<td>1.57</td>
<td>1.06 to 2.32</td>
</tr>
<tr>
<td>Overall</td>
<td>123</td>
<td>121</td>
<td>0.99</td>
<td>0.76 to 1.31</td>
</tr>
</tbody>
</table>

Ryo Kitagawa et al. JCO 2015;33:2129-2135

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GOG 3009: ADXS001-02
GOG Foundation Trial
CONCLUSIONS: What is new in 2018

• Heterogeneous nature of ovarian cancers; most of fallopian tube origin

• Neo-adjuvant chemotherapy is an increasingly used option for ovarian cancer. More research studies in this setting. Promise of neo-adjuvant immuno-chemo.

• Debate on roles of dose dense IV paclitaxel vs IP regimens persists. Less toxicity with dose dense IV.

• Potential role of aromatase inhibitors in low grade ovarian cancer and endometrial cancer with everolimus and less so in high grade ER positive ovarian cancers.

• Potential expanded indications for upfront PARP inhibitors in HRD ovarian cancer (still under study).

• Potential for immuno-conjugates in ovarian ca and checkpoint inhibitors +/- PARP in ovarian cancers, MMR-deficient ovarian-endometrial ca and cervical cancer.
Thank you!

Gerardo Colon-Otero, M.D.
Mayo Clinic
Jacksonvile, Florida

Cell 904-742-6002
Email: gcolonotero@mayo.edu
Questions & Discussion