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UK
A case study of anti-angiogenics in ovarian cancer
71 yr old LGSOC (dx 2006)

- Diagnosed LGSOC 2006
  - Carbo/taxol x 4 cycles
  - Interval de-bulking surgery + short small bowel resection
  - Carbo/taxol x 2 cycles


2nd palliative treatment Oct 2008 - Jan 2010 Phase III trial carbo ± phenoxodiol [OVATURE] (best response PR)

3rd palliative treatment Nov 2010 - Apr 2011 Phase II IGF-1R inhibitor (linsitinib) + weekly taxol x 5 cycles (best response SD)

4th palliative treatment May 2011 - Jul 2011 Carbo/caelyx x 2 cycles (best response PD)

5th palliative treatment Sept 2011 - Feb 2013 Phase I trial ombrabulin + bevacizumab trial (best response PR)
  - Feb 2013: Right internal capsule stroke

6th palliative treatment Mar 2013 - Jul 2013 Carbo/Gem (best response PR)

7th palliative treatment Nov 2013 - Mar 2014 Phase I trial combining RAFi + MEKi (best response SD)

8th palliative treatment May 2014 - Aug 2014 Phase I trial targeting folate receptor (best response SD)

9th palliative treatment Oct 2014 - Sep 2015 Phase II low dose cyclophosphamide ± nintedanib [Metro-BIBF] (best response SD)

10th palliative treatment Sep 2015 - Oct 2015 Carbo monotherapy re-challenge x 2 cycles

11th palliative treatment Dec 2015 - Apr 2016 Phase I trial with ATR inhibitor + concomitant carbo (best response SD)

12th palliative treatment Nov 2016 - ongoing Weekly Paclitaxel

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**MUTATIONS DETECTED***:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Allele Frequency in sample</th>
<th>COSMIC @ position</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>G12V</td>
<td>19%</td>
<td>8890</td>
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<tr>
<td>FANCD2</td>
<td>F386V</td>
<td>23%</td>
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<tr>
<td>ATM</td>
<td>F858L; P1054R</td>
<td>51% ; 48%</td>
<td>9 ; 6</td>
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Multiple anti-angiogenic agents (n=4)

- Diagnosed LGSOC 2006
  - Carbo/taxol x 4 cycles
  - Interval de-bulking surgery + short small bowel resection
  - Carbo/taxol x 2 cycles

  - Phase III Carbo / taxol ± cediranib x 2 cycles [ICON-6] (best response PD)

- 2nd palliative treatment Oct 2008-Jan 2010
  - Phase III trial carbo ± phenoxodiol [OVATURE] (best response PR)

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- 10th palliative treatment Sep 2015-Oct 2015
  - Carbo monotherapy re-challenge x 2 cycles

- 11th palliative treatment Dec 2015-Apr 2016
  - Phase I trial with ATR inhibitor + concomitant carbo (best response SD)

- 12th palliative treatment Nov 2016-ongoing
  - Weekly Paclitaxel
Multiple clinical trials (n=8; 50% PI)

- **Diagnosed LGSOC 2006**
  - Carbo/taxol x 4 cycles
  - Interval de-bulking surgery + short small bowel resection
  - Carbo/taxol x 2 cycles

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For consideration/discussion

- Integration of clinical trials into patient care
- NGS in ovarian cancer
- Diversity of anti-angiogenic agents
- Toxicities of anti-angiogenics
1) Types of anti-angiogenic agents

**Anti-VEGFR Ab**
Bevacizumab, humanised MoAb inhibits VEGFA binding to VEGFR-1 & 2 and prevents formation of new tumour vessels/regression of tumour vasculature

**Small molecule kinase inhibitors**
Multikinase/multipathway inhibition (VEGF/PDGF/FGF)
E.G. cediranib, sorafenib, sunitinib, pazopanib, nintenanib

**Vascular disrupting agents (VDAs)**
Vessel shutdown and tumour necrosis
Either derivatives of flavone acetic acid (invoke cytokine release such as TNFa) or tubulin-binding agents such as combretastatin.
E.G. vadimezan (DMXAA), fosbretabulin (CA4P), ombrabulin
**Bevacizumab**

**First line** Bev+chemo ➔ mBev
- GOG-0218, ICON-7, ROSiA

Extended duration of bev demonstrated mPFS 25.5m (ICON7 PFS 19.3m)
- AGO-OVAR-17 (Engot Ov-15) {BOOST} comparing bev 30m vs 15m (as in GOG-0218).
  Mendiola et al. ASCO poster 2012

**Relapse/recurrent**
- PLAT resistant = AURELIA: improved PFS (3.4 vs 6.7m), not OS
- PLAT sensitive = OCEANS: improved PFS (8.4 vs 12.4), not OS
- GOG-0213: ORR 58.5% vs 78.7% / 37.3m vs 42.2m HR 0.829, p=0.056 / mPFS 10.4 vs 13.8
- MITO-16-MANGO-OV-2 (ongoing)

**Neoadjuvant**
Bev+chemo prolongs PFS, no effect on survival or surgical safety
**Small molecule TKIs**

- **CEDIRANIB**
  - PI: 18% PR yet PFS was 5.2m
    - Matulonis et al JCP 2009, Friedlander et al Gynecol Oncol 2010
  - **ICON6**: Phase III first plat-S relapse (cediranib/placebo)
    - mPFS 11.0m vs 8.7m (p<0.0001, HR 0.56).
    - Cediranib+chemo without maintenance= 9.9m mPFS
      - Ledermann et al Lancet 2016
    - PII olaparib+cediranib in plat-S recurrent ov ca
      - mPFS 17.7m vs 9.0m with olaparib alone, HR 0.42
      - Liu et al. Lancet Oncol 2014
- **PAZOPANIB**
  - **MITO-11**: + weekly paclitaxel mPFS 3.5m vs 6.4m, NO OS
- **NINTEDANIB**
  - **AGO-OVAR-12**: PIII nintedanib/placebo,
    - mPFS 17.2m vs 16.6m in placebo (p=0.024, HR 0.84)
      - De Bois et al Lancet Oncol 2016
    - Randomised PII maintenance trial nintedanib/placebo
      - 36wk PFS rate 16.3% vs 5.0% in placebo, HR 0.65
      - Ledermann et al JCO 2011
- **TREBANANIB**
  - **TRINOVA-1**: + weekly paclitaxel mPFS 5.4m VS 7.2m, NO OS
  - **TRINOVA-2/ENGOT-OV-6**: + PLD; no PFS or OS benefit

**ESMO PRECEPTORSHIP PROGRAM**

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- ![ESMO logo]
- ![European Society for Medical Oncology]
- ![Better Medicine. Best Practice.]

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Vascular disruptive agents (VDAs)

<table>
<thead>
<tr>
<th>VDA</th>
<th>Derivatives of flavone acetic acid</th>
<th>Tubulin-binding agents (e.g. combretastatin)</th>
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<tbody>
<tr>
<td>Mechanism</td>
<td>Invoke cytokine release such as TNFa</td>
<td>Cause distortion of immature endothelial cells lacking pericyte coating inducing thrombosis &amp; vessel collapse</td>
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<tr>
<td>OPSALIN: PII carbo/taxol ± ombrabulin (NCT01332656) negative</td>
<td>Sanofi-Aventis since discontinued development</td>
<td>Single-arm phase IIs shown addition of VDAs (vadimezan or fosbretabulin/combretastatin) to chemo is well tolerated &amp; possibly higher response rate, e.g. 29% response in plat-R</td>
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<tr>
<td>PII Bev ± fosbretabulin in plat-S ov (NCT01305213)</td>
<td>mPFS 4.8 for bev alone vs 7.3m for combo</td>
<td>Zweifel et al, Ann Oncol 2011</td>
</tr>
<tr>
<td>ORR 28.2% vs 35.7%</td>
<td>Monk et al JCO 2016</td>
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- Minimal single-agent activity as residual rim repopulates cancer
- Greater efficacy with combination therapy
2) Bev toxicity & risk of AVTE

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<th>2008 meta-analysis [n=7956 from 15 RCTs]</th>
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<tr>
<td>• All grade &amp; HG VTE, 11.9% &amp; 6.3% respectively</td>
</tr>
<tr>
<td>• 1.33 RR of increased VTE with Bev</td>
</tr>
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<td>Nalluri et al. JAMA 2008</td>
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<th>2011 meta-analysis [n=6055 in 10 non-ovarian RCTs]</th>
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<td>• TTE risk varied according to tumour type</td>
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<tr>
<td>• All-grade VTE 10.9% with bev vs 9.8%</td>
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<tr>
<td>• G3-5 VTEs 6.4% vs 6.3%</td>
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<td>Hurwitz et al JCO 2011</td>
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Incidence of VTE in advanced ovarian cancer 11% - 42% (in clear cell subgroup)
Duska et al Gynaecol Oncol 2010
Khorana Cancer 2013

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<th>Bev + chemo greater risk of AVTE than chemo alone in elderly pts &gt; 65 yrs [3007 pts from 4 CRC trials]</th>
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<tr>
<td>• ATE rate 5.75% vs 2.5%</td>
</tr>
<tr>
<td>• VTE rate 1-2% more frequent with bev</td>
</tr>
<tr>
<td>Cassidy et al. Cancer Res Clin Oncol 2010</td>
</tr>
</tbody>
</table>
THANK YOU

- Duska LR, Garrett L, Henretta M. Why never-events occur despite adherence to clinical guidelines: the case of venous thromboembolism in clear cell cancer of the ovary compared with other epithelial histologic subtypes, Gynaecol Oncol 2010; 116: 374-377