Through the looking glass:
Anti-cancer treatments for the non-oncologist

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May 4th 2016
Outline

- Basic stats
- Anti-cancer therapies – a historical perspective
- Ehrlich’s “magische Kugel” – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions
## Cancer Incidence and mortality in WA (2013)

<table>
<thead>
<tr>
<th>Site</th>
<th>Cases</th>
<th>%</th>
<th>ASR</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>1569</td>
<td>30.8</td>
<td>86.1</td>
<td>11</td>
</tr>
<tr>
<td>Melanoma</td>
<td>498</td>
<td>9.8</td>
<td>26.5</td>
<td>35</td>
</tr>
<tr>
<td>Uterus</td>
<td>200</td>
<td>3.9</td>
<td>10.7</td>
<td>78</td>
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<tr>
<td>Ovary</td>
<td>113</td>
<td>2.2</td>
<td>6.1</td>
<td>152</td>
</tr>
<tr>
<td>Cervix</td>
<td>77</td>
<td>1.5</td>
<td>5.0</td>
<td>223</td>
</tr>
<tr>
<td>Lung</td>
<td>333</td>
<td>19.1</td>
<td>14.4</td>
<td>60</td>
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<tr>
<td>Breast</td>
<td>256</td>
<td>14.7</td>
<td>12.2</td>
<td>75</td>
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<tr>
<td>Ovary</td>
<td>78</td>
<td>4.5</td>
<td>3.2</td>
<td>285</td>
</tr>
<tr>
<td>Uterus</td>
<td>49</td>
<td>2.8</td>
<td>2.0</td>
<td>438</td>
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<tr>
<td>Cervix</td>
<td>22</td>
<td>1.3</td>
<td>1.3</td>
<td>804</td>
</tr>
</tbody>
</table>

Department of Health, Western Australia, Perth. Statistical Series Number 101

Figure B29.1: Ovarian cancer incidence and mortality rates, 1991–2012

Figure B29.2: Ovarian cancer incidence (2009) and mortality (2010) rates by age group

Figure B17.1: Melanoma of the skin incidence and mortality rates, 1991–2012

Figure B17.2: Melanoma of the skin incidence (2009) and mortality (2010) rates by age group

AIHW Australian Cancer Database 2009, AIHW National Mortality Database
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Cancer and the immune system

• 1863 – Virchow observed that tumours were infiltrated by leukocytes
• A link was proposed between cancer and inflammation

Rudolph Carl Virchow
(1821-1902)
“The father of immunotherapy”

- 1891 – Coley injected streptococcal bacterial toxins around tumours

- ‘Coley’s toxin’ was used in soft tissue sarcoma for 40 years with variable success

William Coley (1862-1936)
Paul Ehrlich
(1854–1915)
Paul Ehrlich: Birth of Targeted Therapy

(1) Antibodies: Nobel Prize for serum therapy in 1908
(2) Targeted chemotherapy: 1910-1911

Receptors on cells

A bacterial toxin and a targeted chemotherapy

Postulated “side-chains,” or “receptors” specific for external substances (dyes), antigens, and nutrients

Model: bifunctional agent, containing a chemical structure that binds to the “receptor” linked to a toxic molecule

The first targeted therapies

- Huggins demonstrated the hormone-dependency of prostate cancer

- In 1940, oestrogen therapy for prostate cancer became the first targeted systemic therapy, against receptors or pathways upon which a cancer was dependent

Charles Huggins (1901-1997)
Chemotherapy – emerging from the horrors of chemical warfare

2 Dec 1943 - The ‘Bari incident’

SS John Harvey
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The Nobel Prize in Physiology or Medicine 1984

Niels K. Jerne
Prize share: 1/3

Georges J.F. Köhler
Prize share: 1/3

César Milstein
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein “for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies”.

Figure 1. Fusion of Mouse Myeloma Cells and Immune Spleen Cells.

The magic bullet “magische Kugel”

1997 – Rituximab (NHL)

1998 – Herceptin (breast ca)

2001 – Imatinib (CML)
Number of targeted therapy publications

Year


Number of publications

0 2,000 4,000 6,000 8,000 10,000 12,000
BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 6 1957

CANCER—A BIOLOGICAL APPROACH
I. THE PROCESSES OF CONTROL

Sir MACFARLANE BURNET, M.D., F.R.S.
Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

Theory of clonal selection

Sir Frank Macfarlane Burnet
(1899-1985)
The Danger Model: A Renewed Sense of Self

e) 1994, 4th modification (Danger model: major change) APCs are activated by endogenous cellular alarm signals from distressed or injured cells.

Fatal Melanoma Transferred in a Donated Kidney
16 Years after Melanoma Surgery

Figure 1. Affected Kidney from Patient 2.
The excised kidney is necrotic and contains a large, central mass of melanoma tissue (Panel A). An S-100-stained specimen of the kidney shows striking cytologic atypia and strong S-100 positivity (Panel B).
6 steps of the anti-tumour immune response

1. Tumour cells
2. Dendritic cells (APCs)
3. CD8+ T cell priming
4. CD8+ T cells proliferate
5. Memory T cells
6. Chemotherapy
   - Targeted therapy
   - Radiotherapy

Tumour antigens

Diagram shows the interaction between tumour cells, dendritic cells, CD8+ T cells, and memory T cells, highlighting the steps involved in the anti-tumour immune response.
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- Future directions
Immune checkpoints

PD-1/PD-L1 inhibition

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O’Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.
Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Rapid Eradication of a Bulky Melanoma Mass
with One Dose of Immunotherapy

doi:10.1056/NEJMc1501894

*Figure 1. Response of a Large Chest-Wall Melanoma Metastasis to One Dose of Ipilimumab plus Nivolumab*
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
Five-Year Survival Rates for Treatment-Naive Patients With Advanced Melanoma Who Received Ipilimumab Plus Dacarbazine in a Phase III Trial

Michele Maio, Jean-Jacques Grob, Steinar Aamdal, Igor Bondarenko, Caroline Robert, Luc Thomas, Claus Garbe, Vanna Chiarion-Sileni, Alessandro Testori, Tai-Tsang Chen, Marina Tshaikia, and Jedd D. Wolchok
Swinging for the Fences: Long-Term Survival With Ipilimumab in Metastatic Melanoma

Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma

Fig 1. Overall survival in the temozolomide (thick line) and DTIC (thin line) treatment groups.

Pembrolizumab versus Ipilimumab in Advanced Melanoma

Figure 1. Kaplan–Meier Estimates of Progression-free and Overall Survival.

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

Nivolumab (anti-PD-1) in Patients with Platinum-Resistant Ovarian Cancer

The DNA damage response

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

Hannah Farmer1,2, Nuala McCabe1,3, Christopher J. Lord5, Andrew H. J. Tutt3,4, Damian A. Johnson5, Tobias B. Richardson5, Manuela Santamaria3,1, Krystyna J. Billen1, Ian Nicolson3, Charlotte Knights1, Niall M. G. Martin1, Stephen P. Jackson1, Graeme C. M. Smith1 & Alan Ashworth1,2

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

Helen E. Brysset1, Niklas Schueler1, Huw D. Thomas1, Kayan M. Parker1, Dan Flower1, Elena Lopez1, Suzanne Kyle1, Mark Mould1, Nicola J. Curtin1 & Thomas Helleday1,2
Figure 3: Best percentage change from baseline in CA-125 concentrations in the ovarian-cancer cohorts, by platinum sensitivity and resistance.

Best change in CA-125 (U/mL) is maximum reduction from baseline or minimum increase in the absence of reduction.
As maintenance treatment, gBRCAm patients derive most PFS benefit: 7.1 months median PFS improvement

**Graphical Representation**

**Probability of PFS**

- **gBRCA**
- **Olaparib**
- **Placebo**

**HR = 0.17**

(95% CI: 0.09, 0.31)

p < 0.00001

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Olaparib (N=83)</th>
<th>Placebo (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>11.2 mo</td>
<td>4.1 mo</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(8.3, NC)</td>
<td>(2.9, 5.1)</td>
</tr>
</tbody>
</table>

**Number at Risk**

<table>
<thead>
<tr>
<th>Olaparib gBRCAm</th>
<th>53</th>
<th>44</th>
<th>26</th>
<th>11</th>
<th>4</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo gBRCAm</td>
<td>43</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Overall Survival in Patients With BRCA Mutation

- 14/62 (22.6%) placebo patients switched to a PARP inhibitor
- OS in BRCA WT patients: HR = 0.98; 95% CI, 0.62–1.55; P = .946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months

J Ledermann et al. Lancet Oncology 2014 15 852- 861
<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib (N = 136)</th>
<th>Placebo (N = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Any</td>
<td>130 (95.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Nausea</td>
<td>93 (68.4)</td>
<td>71 (52.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>66 (48.3)</td>
<td>32 (23.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43 (31.6)</td>
<td>27 (19.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31 (22.8)</td>
<td>23 (16.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (18.4)</td>
<td>16 (11.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (18.4)</td>
<td>17 (12.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24 (17.6)</td>
<td>11 (8.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>23 (16.9)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22 (16.2)</td>
<td>19 (14.0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>19 (14.0)</td>
<td>17 (12.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (13.2)</td>
<td>14 (10.3)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>18 (13.2)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16 (11.8)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>17 (12.5)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (12.5)</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (12.5)</td>
<td>14 (10.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>16 (11.8)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>16 (11.8)</td>
<td>9 (6.6)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>5 (3.7)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>14 (10.3)</td>
<td>13 (9.6)</td>
</tr>
</tbody>
</table>
Current status of olaparib (Lynparza)

- **Australia** – TGA approved
  
  “Olaparib is indicated as monotherapy for the **maintenance treatment** of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.”

- **Europe** – approved as **maintenance treatment** for platinum sensitive relapsed BRCA m ovarian cancer –patients in remission following platinum-based therapy

- **USA** - approved as monotherapy
  - For patients who have received ≥ 3 lines of chemotherapy
  - **Not** approved as maintenance therapy
  - Approval also for companion diagnostic (Myriad Genetics BRCA analysis CDx)
Table 2  Ongoing phase III studies of PARP inhibitors for ovarian cancer treatment

<table>
<thead>
<tr>
<th>Trial and NCI trial number</th>
<th>Study arms</th>
<th>Trial population</th>
<th>Primary endpoint</th>
<th>Total accrual</th>
<th>Trial status</th>
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<tbody>
<tr>
<td>Newly diagnosed ovarian cancer</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>SOLO1 (NCT01844986)</td>
<td>Olaparib versus placebo post-platinum-based chemotherapy</td>
<td>BRCAm only, HGSOCC, or endometrioid stage III and IV only</td>
<td>PFS</td>
<td>344</td>
<td>Accrual completed; results pending</td>
</tr>
<tr>
<td>GOG-3005 (NCT02470585)</td>
<td>Carboplatin and paclitaxel versus carboplatin, paclitaxel, and veliparib versus carboplatin, paclitaxel, and veliparib followed by veliparib maintenance therapy</td>
<td>Advanced HGSOCC, both BRCAm and BRCAwt</td>
<td>PFS</td>
<td>1100</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>PAOLA1 (NCT02477644)</td>
<td>Platinum/taxane/bev, bev maintenance versus platinum/taxane/bev, bev/olaparib maintenance</td>
<td>Newly diagnosed high-grade ovarian cancer</td>
<td>PFS</td>
<td>642</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>Recurrent ovarian cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOVA (NCT01847274)</td>
<td>Niraparib versus placebo post-platinum-based chemotherapy</td>
<td>Platinum-sensitive, HGSOCC, BRCA-stratified</td>
<td>PFS</td>
<td>360</td>
<td>Accrual completed; results pending</td>
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<tr>
<td>SOLO2 (NCT01847233)</td>
<td>Olaparib versus placebo post-platinum-based chemotherapy</td>
<td>Platinum-sensitive BRCAm only, HGSOCC, or endometrioid</td>
<td>PFS</td>
<td>264</td>
<td>Accrual completed; results pending</td>
</tr>
<tr>
<td>ARIEL3 (NCT01968213)</td>
<td>Rucaparib versus placebo post-platinum-based chemotherapy</td>
<td>Platinum-sensitive recurrence, HGSOCC or endometrioid BRCA-stratified</td>
<td>PFS</td>
<td>540</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>SOLO3 (NCT0282020)</td>
<td>Olaparib versus MD choice non-platinum chemotherapy</td>
<td>Platinum-sensitive BRCAm HGSOCC</td>
<td>PFS</td>
<td>411</td>
<td>Accrual ongoing</td>
</tr>
<tr>
<td>NRG-GY004 (NCT02446600)</td>
<td>Olaparib versus olaparib/cediranib versus platinum doublet</td>
<td>Platinum-sensitive recurrent high-grade ovarian cancer BRCA-stratified</td>
<td>PFS</td>
<td>450</td>
<td>Accrual ongoing</td>
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<tr>
<td>NRG-GY005 (NCT02502266)</td>
<td>Olaparib/cediranib versus single-agent chemotherapy</td>
<td>Platinum resistant recurrent high-grade ovarian cancer</td>
<td>PFS (ph 2) OS (ph 3)</td>
<td>680</td>
<td>Accrual ongoing</td>
</tr>
</tbody>
</table>

HGSOCC high-grade serous ovarian cancer, BRCAm BRCA mutation carrier, PFS progression-free survival, Bev bevacizumab
What about toxicity?

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Targeted therapies</th>
<th>Immunotherapy</th>
</tr>
</thead>
</table>
| • Neutropenia / immune suppression  
  • Hair loss  
  • Nausea and vomiting  
  • Lethargy | • Skin rash  
  • GI effects (diarrhoea, nausea)  
  • Drug induced liver injury  
  • ‘off-target toxicity’ e.g. skin SCC | • NOT immune suppressive  
  • Immune-related side effects  
  • Skin (rash, pruritis)  
  • Diarrhoea / colitis (<5%)  
  • Pneumonitis (<3%)  
  • Endocrine  
  • Any auto-immune ‘-itis’ |
Immune checkpoint blockade (ICB) toxicities

<table>
<thead>
<tr>
<th>Frequent (&gt;10%) ICB toxicities</th>
<th>Rare (&lt;10%) life-threatening ICB toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain</td>
<td>• Colitis and risk of gastrointestinal perforation</td>
</tr>
<tr>
<td>• Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea</td>
<td>• Pneumonitis including acute interstitial pneumonia / ARDS</td>
</tr>
<tr>
<td>• Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue</td>
<td>• Infusion reaction and anaphylactic shock</td>
</tr>
<tr>
<td></td>
<td>• Type 1 diabetes and risk of diabetic ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>• Severe skin reactions, DRESS, Stevens Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>• Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk</td>
</tr>
<tr>
<td></td>
<td>• Neutropenia and sepsis risk</td>
</tr>
<tr>
<td></td>
<td>• Encephalopathy and neurological sequelae</td>
</tr>
<tr>
<td></td>
<td>• Guillain–Barré syndrome and respiratory risk</td>
</tr>
<tr>
<td></td>
<td>• Myelitis and motor sequelae</td>
</tr>
<tr>
<td></td>
<td>• Myocarditis and cardiac insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Acute adrenal insufficiency and hypovolemic shock</td>
</tr>
<tr>
<td></td>
<td>• Pleural and pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>• Nephritis</td>
</tr>
</tbody>
</table>

The five pillars of immunotherapy toxicity management

Spectrum of toxicity of immune checkpoint blockade agents

Outline

- Basic stats
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- Ehrlich’s “magische Kugel” – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions
Immune biomarkers: the promises and pitfalls of personalized medicine

Joanna C. D. Willis and Graham M. Lord

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Neoantigens in cancer immunotherapy

Fig. 2. Estimate of the neoantigen repertoire in human cancer. Data depict the number of somatic mutations in individual tumors. Categories on the right indicate current estimates of the likelihood of neoantigen formation in different tumor types. Adapted from (50). It is possible that the immune system in melanoma patients picks up on only a fraction of the available neoantigen repertoire, in which case the current analysis will be an underestimate. A value of 10 somatic mutations per Mb of coding DNA corresponds to ~150 nonsynonymous mutations within expressed genes.

Neoantigens in cancer immunotherapy

Fig. 4. Strategies to target the patient-specific neoantigen repertoire. (A) Immunotherapy is given in combination with interventions such as radiotherapy that enhance exposure to autologous neoantigens. (B) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, a patient-specific vaccine is produced, and this vaccine is given together with adjuvant and T cell checkpoint-blocking antibodies. (C) Potential neoantigens are identified as in Fig. 1 steps 1 to 3, T cells that are specific for these neoantigens are induced or expanded in vitro, and the resulting T cell product is given together with T cell checkpoint-blocking antibodies.

Translational Implications of Tumor Heterogeneity

Biomarkers of PARPi response

- BRCA1/2 germline mutations (~14% of high-grade serous EOC)
- BRCA ½ somatic mutations (~6%)
- Other genetic and epigenetic alterations in HR genes ?>30%
Approximately 50% of high-grade serous EOCs have alterations in HR repair genes.

Konstantinopoulos et al. Cancer Discov 2015;5:1137-1154
Homologous recombination deficiency (HRD) assays

Validation, validation, validation!!
Defining a BRCA-like signature through single gene analysis is complex – not all genes are functionally relevant

Rucaparib IC50 Fold Change After siRNA Knockdown in OVCAR-3 Cell Line

IC50 = half maximal inhibitory concentration.
HRD causes genome-wide loss of heterozygosity (LOH) that can be measured by comprehensive genomic profiling based on NGS.

**Hypothesis 1:**
Ovarian cancer patients with high genomic LOH suggesting BRCA-like signature will respond to PARPi.

**Hypothesis 2:**
Ovarian cancer patients who are "biomarker negative" (ie, with low genomic LOH) will not respond to PARPi.

mut=mutation; NGS=next-generation sequencing; wt=wild type.
Diagnostic development: Cutoff defined for BRCA-like signature, being tested and refined

TCGA and AOCS Overall Survival Data Used to Develop LOH Cutoff to Identify High-Grade Ovarian Cancer Patient Tumors with BRCA-Like Signature

Prospective testing of prespecified cutoff in ARIEL2 and ARIEL3

Greatest rucaparib activity observed in BRCA\textsuperscript{mut} patients...

- Robust clinical activity observed in BRCA\textsuperscript{mut} patients (n=23)
  - 61% ORR (RECIST)
  - 70% ORR (RECIST & CA-125)
  - 83% of patients continuing on treatment (+)

- Responses observed in germline and somatic BRCA\textsuperscript{mut} tumors
...and differential rucaparib activity seen in patients with/without BRCA-like signature

- Clinical activity observed in BRCA\textsuperscript{wt} patients \textbf{with} BRCA-like signature (n=25)
  - 32\% ORR (RECIST)
  - 40\% ORR (RECIST & CA-125)
  - 52\% of patients continuing on treatment (+)

- Few responses observed in BRCA\textsuperscript{wt} patients \textbf{without} BRCA-like signature (n=13)
  - 8\% ORR (RECIST)
  - 8\% ORR (RECIST & CA-125)
  - 38\% of patients continuing on treatment (+)

\textsuperscript{16}EORTC-NCI-AACR SYMPOSIUM ON 
"MOLECULAR TARGETS & CANCER THERAPEUTICS"
Outline

- Basic stats
- Anti-cancer therapies – a historical perspective
- Ehrlich’s “magische Kugel” – a dream realised
- Immunotherapy comes of age
- The search for biomarkers
- Future directions
Combined Nivolumab and Ipilimumab
or Monotherapy in Untreated Melanoma

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A Intention-to-Treat Population

No. at Risk

| Treatment                      | Months | 0  | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|-------------------------------|--------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Nivolumab                     |        |    | 316| 292| 271| 177| 170| 160| 147| 136| 132| 124| 106| 86 | 50 | 38 | 14 | 9  | 6  | 2  | 1  | 1  | 1  | 0  |
| Nivolumab plus ipilimumab     |        |    | 314| 293| 275| 219| 208| 191| 173| 164| 163| 151| 137| 116| 65 | 54 | 18 | 11 | 7  | 2  | 1  | 0  | 0  | 0  |
| Ipilimumab                    |        |    | 315| 285| 265| 137| 118| 95 | 77 | 68 | 63 | 54 | 47 | 42 | 24 | 17 | 7  | 4  | 3  | 0  | 0  | 0  | 0  | 0  |

Novel combinations


**Box 1 | Immunotherapies that are approved or in development**

**Vaccines**
- Dendritic cell-based vaccines
- Autologous granulocyte-macrophage colony-stimulating factor (GM-CSF)-transfected vaccines

**Viral vector vaccines**

**mRNA-based vaccines**

**Multipeptide-based vaccines**

**Locally released virotherapy**

**Targets of modulatory monoclonal antibodies**
- Cytotoxic T lymphocyte-associated antigen 4 (CTLA4)
- Programmed cell death protein 1 (PD1)
- PD1 ligand 1 (PDL1)
- CD137
- OX40
- Lymphocyte activation gene 3 protein (LAG3)
- T cell immunoglobulin and mucin-domain containing 3 (TIM3)
- Glucocorticoid-induced tumour necrosis factor receptor family-related protein (GITR)
- CD27

**Adoptive T cell therapy**
- Tumour-infiltrating lymphocytes
- Chimeric antigen receptors (CARs)
- CAR-transduced T lymphocytes

Improving Survival

% Survival

Time

Control
Conventional Therapies
Immune Checkpoint Blockade
Thank you!!