Overview of immune aspects
- endometrial / cervical cancer-

Hans Nijman
Lisbon GCIG meeting, Thursday October 27th, 2016
Immune response against cancer

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
Tumor Infiltrating T cells
Treatment selection based on immune resistance

- Block adaptive immune resistance
- Bring T cells into tumors:
- Generate T cells:

Hot tumors
Cold tumors

Ribas et al
PBMC+OVCAR-3

+anti-CD3

CD4

CD8β

CD8α

CD103

CD4+ T cells

~70%

CD8+ T cells

~2%

PBMC+OVCAR-3

ctrl

CD4

CD8β

CD8α

CD103

CD4+ T cells

~1%

CD8- CD4-

+anti-CD3

CD56

CD103

~19%

~7%
CD103+ cells (%) for different conditions and cell lines.

- Untreated
- TGFβRI inh.
- CD3 agonist
- CD3 agonist + TGFβRI inh.

Graph showing the percentage of CD103+ cells for each condition.
Treatment selection based on immune resistance

- **Hot tumors**
  - Block adaptive immune resistance

- **Cold tumors**
  - Bring T cells into tumors:
  - Generate T cells:
Releasing the breaks on Cancer Immunotherapy

Antoni Ribas, M.D., Ph.D.
Pembrolizumab in tumors with mismatch-repair deficiency

- Phase II study

- Patients with treatment refractory progressive metastatic cancer, in 3 groups:
  - Mismatch repair deficient colorectal adenocarcinomas (N=11)
  - Mismatch repair proficient colorectal adenocarcinomas (N=21)
  - Mismatch repair deficient non colorectal cancer (N=9)
    - 2 patients with endometrial cancer in this group

- Pembroluzimab IV, 10mg/kg every 14 days

Le et al, NEJM 2015
Pembrolizumab in tumors with mismatch-repair deficiency

Le et al, NEJM 2015
Pembrolizumab in tumors with mismatch-repair deficiency

<table>
<thead>
<tr>
<th></th>
<th>Objective RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR-deficient Colorectal</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>MMR-proficient Colorectal</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>MMR-deficient Non-colorectal</td>
<td>5/7 (71%)</td>
</tr>
</tbody>
</table>

- 2 cases of EC: 1 CR & 1 PR

Le et al, NEJM 2015
Mean somatic mutations per tumor
(whole exome sequencing)

MMR- proficient: 73

MMR- deficient: 1782
Single nucleotide variants introduce neo-epitopes

Sahin et al, Current opinion immunology, 2016
EC – Four molecular subtypes

- POLE (ultra-mutated) / MSI (hyper-mutated)
- Copy number low (endometrioid)
- Copy number high (serous-like)

Kandoth et al., Nature 2013
Molecular classification of endometrial cancer

• The Cancer Genome Atlas Network:
  - Integrated genomic, transcriptomic and proteomic characterization of 373 endometrial carcinomas.

TCGA, Nature 2013
POLE-mutations

- POLE: DNA polymerase epsilon.
  - Involved in proofreading of DNA during DNA replication

- 7-12% of EC
- High frequency of base substitution mutations
- Strong association with endometrioid histology and high grade
- Excellent prognosis, but why?
Do POLE mutant endometrial cancers show increased immunogenicity?

- Analysis of immune infiltration in 150 tumor samples from PORTEC 1 and 2, LUMC and UMCG

<table>
<thead>
<tr>
<th></th>
<th>MSS</th>
<th>MSI</th>
<th>POLE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Range</td>
<td>62.5</td>
<td>68.8</td>
<td>63.5</td>
<td>65.0</td>
</tr>
<tr>
<td>FIGO stage (2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>48</td>
<td>39</td>
<td>45</td>
<td>132</td>
</tr>
<tr>
<td>III/IV</td>
<td>6</td>
<td>10</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>45</td>
<td>39</td>
<td>33</td>
<td>117</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EEC</td>
<td>54</td>
<td>49</td>
<td>47</td>
<td>150</td>
</tr>
<tr>
<td>NEEC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>54</td>
<td>49</td>
<td>47</td>
<td>150</td>
</tr>
</tbody>
</table>

Van Gool, CCR 2015
Increased density of intratumoral CD8+ lymphocytes in POLE mutants

Van Gool and Eggink et al, CCR 2015
Conclusions on POLE & MSI tumors

- High immune cell infiltration of POLE-mutant and MSI tumors.

- High PD-1 and PD-L1 expression in POLE-mutant and MSI tumors.

- Suggests sensitivity to checkpoint inhibition for these subgroups.

Additional note:

<table>
<thead>
<tr>
<th>T cell cytotoxicity</th>
<th>Checkpoint activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ CD8A 3.0x</td>
<td>↑ PD1 2.0x</td>
</tr>
<tr>
<td>↑ IFNG 3.6x</td>
<td>↑ PD-L1 2.3x</td>
</tr>
<tr>
<td>↑ PRF 2.5x</td>
<td>↑ LAG3 2.9x</td>
</tr>
<tr>
<td>↑ T-bet 1.9x</td>
<td>↑ TIGIT 3.6x</td>
</tr>
</tbody>
</table>
Treatment selection based on immune resistance

- Block adaptive immune resistance
- Bring T cells into tumors:
  - Hot tumors
  - Cold tumors
- Generate T cells: -
Antigens for vaccine development

- **Examples of vaccination trials**
  - Survivin in EC (immune response in 25% ptn) / J. Immunotherapy 2015
  - WT1 in EC (immune response in 3 out of 4) Anticancer Research 2013
  - P53 in OC (immune response in 80% of the ptn).

Schumacher et al, Cur Op Immunol 2013
Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial

Vaccination against Oncoproteins of HPV16 for Noninvasive Vulvar/Vaginal Lesions: Lesion Clearance Is Related to the Strength of the T-Cell Response
position for PhD student (MD)

UMCG, Dept. of Gyn. Oncology
Thaline Prins
Anouk Terwindt
Fenne Komdeur
Florine Eggink
Marco Versluis
Kim Brunekreeft
Stephanie van de Wall
Hagma Workel
Joyce

UMCG, Dept. of Pathology
Harry Hollema & Evelien Duiker

UMCG, Dept. of Genetics
Pieter van de Vlies & Kim de Lange

UMCG, Dept. of Virology
Toos Daemen

UMCG, Dept. of Hematology
Edwin Bremer

UMCG, Dept. of Med. Oncology
Steven de Jong & Marcel van Vught
An Reyners & Hilde Jalving

LUMC, NL
Tjalling Bosse
Mariette van Poelgeest
Vincent Smit
Carien Creutzberg
Sjoerd van der Burg

ENITEC consortium, ESGO

TRANSPORETEC consortium

University of Southampton, UK
Tim Elliott

University of Würzburg, Germany
Harald Wajant

University of Exeter, UK
Paul Eggleton

University of Oxford, UK
David Church

Aduro
Andrea v. Elsas & Hans v. Eenenaam

TRON & GANYMED
Ugur Sahin & Ozlem Türeci