Immuno Oncology in Regional Treatments of Metastases

Giovanni Mauri, MD
Division of Interventional Radiology,
European Institute of Oncology,
Milan, Italy
Consultant for Elesta SRL
Tumor Infiltrating Lymphocytes (TIL)
Immuno oncology & IR

1. (TILs) Dendritic cells in surrounding tissues encounter tumor antigens

2. Dendritic cells enter lymphatic tissue and mature on the way to the lymph node

3. Mature dendritic cells present antigen to T cells

4. Activated T cells leave node

5. T cells recognize and kill tumor cells
Relationship Between Tumor Infiltrating Lymphocyte Levels and Response to Pembrolizumab* In Metastatic Cancer

*PEMBROLIZUMAB is an antibody used in cancer immunotherapy. It blocks a protective mechanism of cancer cells, and allows the immune system to destroy cancer cells. It targets the programmed cell death 1 (PD-1) receptor of lymphocytes.
KEYNOTE-086: Phase 2 Study of Pembrolizumab Monotherapy For mTNBC

Cohort A
- ≥1 prior systemic treatment for mTNBC with documented PD
- PD-L1 positive or negative

Cohort B
- No prior systemic treatment for mTNBC
- PD-L1 positive

All Patients
- Centrally confirmed TNBC
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample
- No radiographic evidence of CNS metastases

Pembrolizumab 200 mg IV Q3W
- for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

Primary end points: ORR and safety
Secondary end points: DOR, DCR, PFS, OS

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\textsuperscript{a}≤1\% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative.
\textsuperscript{b}DCR = disease control rate = SD ≥24 wk + CR + PR.
ClinicalTrials.gov identifier NCT02447003.
Objectives

- Assess stromal TIL (sTIL) levels in previously treated and previously untreated mTNBC
- Explore relationship between sTIL levels and PD-L1 expression in mTNBC
- Explore relationship between sTIL levels and response to pembrolizumab monotherapy in mTNBC
sTIL Levels Overall and by Cohort

- Wilcoxon rank sum (one sided). Red font indicates statistical significance.
- Box = 25th and 75th percentiles; line = median; whiskers = 1.5 × IQR.
- Data cutoff date: Nov 10, 2016.

**Combined Cohorts**

<table>
<thead>
<tr>
<th>TIL Level, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>5% (3-20)</td>
</tr>
<tr>
<td>n</td>
<td>193</td>
</tr>
</tbody>
</table>

**Cohort A vs Cohort B**

<table>
<thead>
<tr>
<th>TIL Level, %</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td>5% (1-10)</td>
</tr>
<tr>
<td>n</td>
<td>147</td>
</tr>
</tbody>
</table>

\( p < 0.001 \)

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sTIL Levels by Sample Site

### LN vs Lung vs Breast vs Liver vs Skin vs Chest Wall vs Other

#### Median (IQR)

<table>
<thead>
<tr>
<th>Sample Site</th>
<th>LN</th>
<th>Lung</th>
<th>Breast</th>
<th>Liver</th>
<th>Skin</th>
<th>Chest Wall</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39</td>
<td>16</td>
<td>51</td>
<td>25</td>
<td>17</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10% (5-50)</td>
<td>12.5% (5-36)</td>
<td>10% (5-30)</td>
<td>5% (3-25)</td>
<td>3% (1-10)</td>
<td>5% (1-8.5)</td>
<td>5% (1.25-13.75)</td>
</tr>
</tbody>
</table>

### LN vs Non-LN

#### Median (IQR)

<table>
<thead>
<tr>
<th>Sample Site</th>
<th>LN</th>
<th>Non-LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39</td>
<td>154</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10% (5-50)</td>
<td>5% (2-16.25)</td>
</tr>
</tbody>
</table>

### P

- **0.003** \(^a\)
- **0.010** \(^b\)

\(^a\)Kruskal-Wallis test (one sided). \(^b\)Wilcoxon rank sum (one sided). Red font indicates statistical significance.

- Box = 25\(^{th}\) and 75\(^{th}\) percentiles; line = median; whiskers = 1.5 × IQR.
- Data cutoff date: Nov 10, 2016.
sTIL Levels by Tumor Response

**Cohort A**
- **Responder**: Median 10% (IQR 5-30)
- **Non-Responder**: Median 5% (1-10)

**Cohort B**
- **Responder**: Median 50% (IQR 35-70)
- **Non-Responder**: Median 15% (5-40)

**Combined Cohorts**
- **Responder**: Median 37.5% (8.75-66.25)
- **Non-Responder**: Median 5% (2-15)

- **n**: 7, 140, 11, 35, 18, 175

- **P**
  - **Cohort A**: 0.062
  - **Cohort B**: 0.009
  - **Combined Cohorts**: <0.001

- **a**Wilcoxon rank sum (one sided).
- Box = 25th and 75th percentiles; line = median; whiskers = 1.5×IQR.
- Data cutoff date: Nov 10, 2016.

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What did we learn?

- sTILs assessed by H&E were significantly associated with response to pembrolizumab, particularly in the first-line setting.
- sTILs levels, LDH concentration, and cohort were independent predictors of response to pembrolizumab monotherapy in this study.
- sTILs and PD-L1 CPS showed significant positive correlation.
- sTILs can identify patients with mTNBC with a greater chance of responding to pembrolizumab monotherapy.
Short-term ‘induction’ or “priming” with “local therapy” can modulate the anticancer immune response resulting in an increased activity of anti-PD1

- **Local tumor damage** can induce immunogenic cell death, overcome T-cell exclusion and promote antigen presentation\(^1\)

- Doxorubicin increases production of interferons, reduces myeloid-derived suppressor cells (MDSC)-induced immune suppression\(^2,3\)

- **Cyclophosphamide (low dose)** depletes Tregs in human breast tumors\(^4\)

- **Cisplatin** stimulates class I HLA and vulnerability of tumor cells for T cell killing\(^5,6\)

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4. Ghiringhelli et al. CII 2007
5. Lesterhuis et al. JCI 2011
6. Ramakrishnan et al. JCI 2010

M.Kok et al. abstract LBA14
The cancer-immune set point of a particular person is already determined by the time of clinical presentation, driven by the inherent immunogenicity of the tumour and by the responsiveness of the individual’s immune system.

The features that determine the set point may therefore reflect genetic factors that are specific to a given tumour, the genetics of the person with cancer, or the extent to which antitumour immunity had developed initially.
**Immunology & IR**

**Immunogram and immunogenicity**

- **Tumor sensitivity to immune effector**
  - MHC expression, IFN-γ sensitivity

- **Tumor foreignness**
  - Mutational load

- **Optimal Immunogenicity**
  - Absence of inhibitory tumor metabolism
  - LDH, glucose utilization

- **Immune cell infiltration**
  - Intratumoral T cells

- **General immune status**
  - Lymphocyte count

- **Absence of soluble inhibitors**
  - IL-6, CRP

- **Absence of checkpoints**
  - PD-L1
**Immuno oncology & IR**

**PRIMING with CHT/RT or “IR”**

- CHT or RT or “IR”
- Heat Shock Protein
- Immature dendritic cells
- «Eat-me» signal

- Translocation of Calreticulin to the cell surface
- Activation of HSP90
- Release of High Mobility Group Box 1 protein

- Live tumor cell
- Stressed tumor cell
- Dying tumor cell

- HSP90
- HMGB1
- CRT
Immuno oncology & IR

The ABSCOPAL effect

“the action of local therapy upon distant ‘out-of-field’ foci of tumors”
USgHIFU: the ABSCOPAL effect

75yo: anaplastic/undifferentiated pancreatic cancer (stage IV)

CDDP + GEM

March 2014

June 2014
USgHIFU: the ABSCOPAL effect

FOLFIRI

June 2014

September 2014
USgHIFU: the ABSCOPAL effect

FOLFIRI

- September 2014
- October 2014
- January 2015
- November 2017
- July 2015
IR in the ERA of Immuno Oncology

**DIAGNOSIS**
- Biopsy
  - Gene profiling
  - TIL level
  - Immunogram

**THERAPY**
- Local therapy
  - Tumor Tx
  - Promoting immuno response
Thank you!!
giovanni.mauri@ieo.it
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Giovanni Mauri, MD
Division of Interventional Radiology,
European Institute of Oncology,
Milan, Italy