Targeting mesothelioma with radiation and immunotherapy

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Conflict of interest

- Bayer (speaker fees)
- Astra-Zeneca (Ad board)
Radiation in mesothelioma

• Although mesothelioma had traditionally been considered resistant to radiation, more recent evidence suggests the contrary
  – *In vitro*, epithelial mesothelioma cell lines are more sensitive to radiation than non-small cell lung cancer
  – Radiation can palliate chest pain in up to 60% of patients with mesothelioma
  – Adjuvant high dose hemithoracic radiation after surgery can improve local control
  – Induction accelerated hypofractionated hemithoracic radiation followed by surgery (SMART approach) provides encouraging results in epithelial mesothelioma
Palliative radiation with 20 Gy in 5 fractions

Data from palliative radiation suggests that total dose >40 Gy or doses >4 Gy/fraction provide the best response in mesothelioma.
Radiation doses

- Normofractionation $\sim 2$ Gy per fraction
- Hypofractionation $\geq 3$ Gy per fraction
- Ablative radiation $\geq 8$ Gy per fraction

# These doses of radiation are enabled by technological innovation such intensity modulated radiation (IMRT), image guided techniques, etc.
Mechanisms of tumor regression after radiation

Tumor regression after radiation

- DNA damage by oxygen reactive species
- Activation of the immune system

Normofractionated radiation
Hypofractionated radiation (palliative and ablative)
SMART trial
Surgery for Mesothelioma
After Radiation Therapy

Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0)
Baseline Investigations, Informed Consent

- Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week)

  1 week post-RT

  Extrapleural Pneumonectomy

  <26 weeks post-op

  - ypN0-1
    - Observation
  - ypN2
    - Adjuvant Chemotherapy
Impact of CD8+ Tumor Infiltrating Lymphocytes (TILs) on survival after SMART

![Graph showing survival rates for different TIL categories](image)

- Epithelioid CD8+ TILs >2%
- Epithelioid CD8+ TILs <2%
- Biphasic CD8+ TILs >2%
- Biphasic CD8+ TILs <2%

\[ p = 0.0001 \]

Impact of PD-L1 expression on tumor cells (>1%) on survival after SMART

![Graph showing survival rates for different PD-L1 expression types](image)

- Red line: Epithelioid PD-L1 positive
- Gray line: Epithelioid PD-L1 negative
- Blue line: Biphasic PD-L1 negative
- Green line: Biphasic PD-L1 positive

$p = 0.0002$

## Multivariate analysis of factors predicting survival after SMART

<table>
<thead>
<tr>
<th>Continuous variable</th>
<th>Patients # (total n=68)</th>
<th>P-value</th>
<th>Hazard ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8+ TILs &gt;2%</td>
<td>33</td>
<td>0.02</td>
<td>0.47</td>
<td>0.25</td>
<td>0.89</td>
</tr>
<tr>
<td>Positive lymph nodes (N+)</td>
<td>42</td>
<td>0.03</td>
<td>1.92</td>
<td>1.05</td>
<td>3.51</td>
</tr>
<tr>
<td>Epithelioid histology</td>
<td>34</td>
<td>0.0004</td>
<td>0.3</td>
<td>0.16</td>
<td>0.59</td>
</tr>
<tr>
<td>PD-L1 positive cancer cells (&gt;1%)</td>
<td>17</td>
<td>0.9</td>
<td>0.94</td>
<td>0.43</td>
<td>2.06</td>
</tr>
<tr>
<td>PD-1 cells &gt;0.3%</td>
<td>32</td>
<td>0.8</td>
<td>0.96</td>
<td>0.71</td>
<td>1.32</td>
</tr>
<tr>
<td>Male gender</td>
<td>55</td>
<td>0.2</td>
<td>1.79</td>
<td>0.79</td>
<td>4.06</td>
</tr>
</tbody>
</table>

Mice model of local accelerated hypofractionated radiation

Local Radiotherapy (LRT)
Accelerated hypofractionated non-ablative radiation in a mice model of mesothelioma
Local RT induces upregulation of tumor infiltrating T cells

De La Maza/ de Perrot et al Clin Cancer Res 2017 Sep 15
Kinetics of T cell recruitment after LRT

Mikihiro Kohno (manuscript in preparation)
CD8+ lymphocytes infiltrating AE17-OVA tumor are OVA specific

Tumor specific CD8+ T cells in AE17-OVA tumor. Radiation vs no treatment

\* p = 0.07

De La Maza/ de Perrot et al Clin Cancer Res 2017 Sep 15
Benefit of radiation (3x 5Gy) is reduced after T cells depletion
Selective depletion of Foxp3\(^+\) Tregs with LRT demonstrated synergistic antitumor effects

Mikihiro Kohno (unpublished data)
Upregulation of regulatory T cells after LRT

- Treg characterized by CD4+CD25+FoxP3+
- Combination of LRT with CTLA4 inhibitor prevent the upregulation of Treg after radiation

Wu/ de Perrot et al Oncotarget 2015 March 8
Combining CTLA-4 blockade with LRT improves local control
Impact CTLA-4 blockade with accelerated hypofractionated radiation (3x5Gy)

Abscopal effect

Secondary tumor growth

AB12
First inj

AB12
Second inj

No Rx

LRT

LRT+
CTLA-4

4 Ab

3/9 tumors rejected

Wu/ de Perrot et al Oncotarget 2015 March 8
Tumor growth was significantly reduced in mice treated with LRT and radical surgery.
CD4 and CD8 lymphocyte depletion completely abrogates tumor protection
Key steps to a successful immune response after non-ablative hypofractionated radiation and immunotherapy

1. Generate an immune response with new T cell clones
   - Adequate mutational burden, functional dendritic cells

2. Overcome the immunosuppressive tumor microenvironment
   - Tumor volume and Treg are major limiting factors

3. Overcome the mechanism of resistance from tumor cells
   - Tumor cells can upregulate of PD-L1, SerpinB9, GITRL as mechanisms of resistance to the radiation induced immune response

Adapted from Huang et al. Nature 2017; 545: 60-65
Conclusions

- Mesothelioma are sensitive to radiation, particularly the epithelial subtypes

- Accelerated hypofractionated radiation can activate the immune system with upregulation T cells in the tumor

- The immediate benefit of accelerated radiation is related to CD8+ T cells, while the long term benefit is predominantly driven by CD4+ T cells

- Surgery can optimize the benefit of radiation and immune activation by reducing the tumor antigen load

- Non-ablative hypofractionated radiation combined with surgery can provide an excellent platform for immunotherapy in mesothelioma
Acknowledgement

Thoracic Surgery
• Laura Donahoe
• Shaf Keshavjee
• Kazu Yasufuku
• Kasia Czarnecka

Radiation Oncology
• John Cho
• Andrew Hope

Medical Oncology
• Penny Bradbury
• Geoff Liu
• Natasha Leighl

Pathology
• Ming Tsao
• Michael Cabanero
• Prodipto Pal

Thoracic Surgery Research Laboratory
• Licun Wu
• Yidan Zhao
• Hanna Zhu
• Mei-Lin James Chan
• Mikihiro Kohno
• Junichi Murakami
• Masaki Anraku
• Tetsuzo Tagawa
• Matthew Wu
• Luis De La Maza Borja

Collaboration
Dept of Immunology
• Tania Watts
• Pam Ohashi
• Marcus Butler
• Naoto Hirano
• Li Zhang

University of Zurich
• Emanuela Folley-Bosco

University of Lausanne
• Michele De Palma

University of Fribourg
• Beat Schwaller
Thank you