Combination Immunotherapy Approaches
Chemotherapy, Radiation Therapy, and Dual Checkpoint Therapy

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Immune Checkpoint Therapy

T-cell: Primary anti-tumor immune effector

APC: Antigen presenting cell
Immunotherapy targets immune checkpoints, which are regulators of T-cell activation. T-cells are the primary anti-tumor immune effectors, while antigen-presenting cells (APCs) are responsible for presenting antigens. Immune checkpoints, such as PD-1 and PD-L1, play a crucial role in modulating T-cell activation.
**Rationale for Combination Immunotherapy**

Anti-PD-1/PD-L1 Responses are suboptimal:

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<th>Agent</th>
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Nanda et al., SABCS 2014; Emens et al., AACR 2014 / SABCS 2014; Rugo et al., SABCS 2015; Dirix et al., SABCS 2015
Rationale for Combination Immunotherapy

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<tr>
<td>PD-L1-unselected breast cancer</td>
<td>Avelumab (anti-PD-L1)</td>
<td>5% (n=168)</td>
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***Anti-PD-1/PD-L1 monotherapy is effective only in a minority of breast cancers***

Nanda et al., SABCS 2014; Emens et al., AACR 2014 / SABCS 2014; Rugo et al., SABCS 2015; Dirix et al., SABCS 2015
Summarize current data and future directions of combination immunotherapy:

1) chemotherapy + immunotherapy
2) radiation therapy + immunotherapy
3) dual checkpoint therapy
Rationale for Chemotherapy + Immunotherapy

**Favorable effects of chemotherapy**

- Tumor cell kill $\rightarrow$ Antigen presentation
- Inflammation (IFN$\gamma$) $\rightarrow$ ↑PD-L1
- Relative depletion of suppressive immune cells (MDSCs, T-regulatory cells)
Rationale for Chemotherapy + Immunotherapy

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Pre-Clinical Efficacy of chemotherapy + anti-PD-1/L1
• Synergy in murine models

Jeong Kim, Genentech, unpublished data.
Phase I trial of atezolizumab (anti-PD-L1) + nab-paclitaxel in metastatic TNBC

- Nab-paclitaxel days 1, 8, 15 (q28d cycles), continued for at least 4 cycles
- Atezolizumab days 1, 15
- Metastatic TNBC, 1\textsuperscript{st}-4\textsuperscript{th} line treatment (median 1 prior therapy, n=24 evaluable)
- 87% with prior taxane use

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<tr>
<th>AE, %\textsuperscript{a}</th>
<th>Grade 3-4 ≥ 5% N = 32</th>
<th>All Grade\textsuperscript{b} N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>56%</td>
<td>100%</td>
</tr>
<tr>
<td>Neutropenia/ decreased neutrophil count</td>
<td>41%</td>
<td>53%</td>
</tr>
<tr>
<td>Thrombocytopenia/ decreased platelet count</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>Anemia</td>
<td>6%</td>
<td>19%</td>
</tr>
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\textsuperscript{a} With corresponding incidence of all-grade AEs.

\textsuperscript{b} Includes events attributed to either nab-paclitaxel or atezolizumab.

Clinical Responses: 1\textsuperscript{st}-line anti-PD-L1 + Abraxane

Responses: 2\textsuperscript{nd}/3\textsuperscript{rd}-line anti-PD-L1 + Abraxane

Including investigator-assessed unconfirmed responses.

- 11 of 17 responses (65%) continued on treatment at time of data cut off
- Responses were observed in both PD-L1 positive and PD-L1 negative patients

Examples of ongoing combination chemotherapy trials in breast cancer

Atezolizumab (anti-PD-L1, Genentech)
• Randomized nab-paclitaxel +/- Atezolizumab (anti-PD-L1) in 1st-line metastatic TNBC

Pembrolizumab (anti-PD-1, Merck)
• Pembrolizumab + Paclitaxel (or) Capecitabine in metastatic TNBC
• Pembrolizumab + nab-paclitaxel in ER/PR+ or TNBC
• Pembrolizumab + Doxorubicin (or) Hormone therapy in ER/PR+ or TNBC

Durvalumab (anti-PD-L1, MedImmune/AstraZeneca)
• GeparNuevo: Neoadjuvant Durvalumab + nab-paclitaxel + epirubicin + cyclophosphamide for TNBC
Agenda

Summarize current data and future directions of combination immunotherapy:
1) chemotherapy + immunotherapy
2) radiation therapy + immunotherapy
3) dual checkpoint therapy
**Rationale for Radiation + Immunotherapy**

*Ab-scopus*: *Latin* for “away from the target”

**Abscopal Effect**
- Metastatic melanoma: tumor progression on anti-CTLA-4 (ipilimumab)
- Palliative RT to spinal met
- Subsequent complete response in liver, lung, spleen

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Postow, M. et al. NEJM 2012
A Phase II Trial of GM-CSF + RT in Solid Tumors

GM-CSF immunotherapy: potent adjuvant to dendritic cell maturation

Clinical Trial
- Patients with SD or PD
- Continued on chemotherapy
- RT (35Gy/10Fx)
- GM-CSF (125μg/m²) x 14d
- Multiple tumor types (13 evaluable breast cancers)
- Endpoint: response in non-irradiated lesion

A Phase II Trial of GM-CSF + RT in Solid Tumors

Abscopal Response Rate: ORR 11/30 (37%)
Breast cancer Abscopal Response Rate: ORR 5/13 (38%)

Examples of ongoing combination radiation therapy trials in breast cancer

**Tremelimumab (anti-CTLA-4, MedImmune/AstraZeneca)**
- Tremelimumab + brain RT (whole brain or stereotactic) +/- trastuzumab in metastatic breast cancer

**Pembrolizumab (anti-PD-1, Merck)**
- Pembrolizumab + RT in metastatic TNBC

**Anti-OX40 (MedImmune/AstraZeneca)**
- Phase I anti-OX40 plus liver stereotactic RT in metastatic breast cancer
Agenda

Summarize current data and future directions of combination immunotherapy:
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Rationale for Dual Checkpoint Therapy

Phase III randomized trial: metastatic melanoma

A Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Months</th>
<th>Progression-free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
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<tr>
<td>5</td>
<td>50</td>
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<tr>
<td>6</td>
<td>40</td>
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<tr>
<td>7</td>
<td>30</td>
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<tr>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

No. at Risk

| Group                      | 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  |
Rationale for Dual Checkpoint Therapy

Phase III randomized trial: metastatic melanoma

Anti-PD-1 + Anti-CTLA-4
Median: 53% shrinkage

Anti-CTLA-4
Median: 6% growth

Examples of Dual Checkpoint Therapy in Breast Ca

**Ipilimumab + Nivolumab (CTLA-4/PD-1, BMS)**
- Metastatic TNBC → *closed, not reported*

**Tremelimumab + Durvalumab (CTLA-4/PD-L1, MedImmune)**
- Metastatic TNBC → *ongoing*
Examples of Dual Checkpoint Therapy in Breast Ca

Ipilimumab + Nivolumab (CTLA-4/PD-1, BMS)
- Metastatic TNBC → closed, not reported

Tremelimumab + Durvalumab (CTLA-4/PD-L1, MedImmune)
- Metastatic TNBC → ongoing
Preclinical studies are informative in combination immunotherapy

Anti-PD-1 + Anti-OX40 in murine mammary models

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<th>PyMT mammary model</th>
<th>4T1 mammary model</th>
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</thead>
<tbody>
<tr>
<td>(did not require vaccine for immune checkpoint efficacy)</td>
<td>(required vaccine for immune checkpoint efficacy)</td>
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### PyMT mammary model
- **Concurrent OX40+anti-PD-1**
- **Sequential OX40→PD-1**
- **No therapy**

![PyMT survival graph](image)

### 4T1 mammary model
- **Vaccine+ Concurrent OX40+anti-PD-1**
- **Sequential OX40+Vaccine→anti-PD-1**
- **No therapy**

![4T1 survival graph](image)

Sequencing of therapy potentially influences efficacy

Messenheimer DJ, et al, AACR 2016, #4361
Pre-operative trials may screen for effective combination immunotherapies

Clinical Trial
- Pre-operative immunotherapy
- Anti-CTLA-4 and/or tumor cryoablation (n=18)
Pre-operative trials may screen for effective combination immunotherapies

Group A: Cryoablation alone
Group B: Ipilimumab alone
Group C: Combination

Ipilimumab 10mg/kg IV x 1

Tumor Cryoablation
1-8d

4-10d

Core Biopsy
Mastectomy

Clinical Trial

• Pre-operative immunotherapy
• Anti-CTLA-4 and/or tumor cryoablation (n=18)

Combination was associated with intratumoral T-cell expansion

#clones expanding $>10^3$ copies

T-cell clonal expansion

CRYO

CTLA-4

COMBO
Conclusions

1) chemotherapy + immunotherapy
   • Anti-PD-L1 + nab-paclitaxel was highly active
   • Phase III studies are ongoing

2) radiation therapy + immunotherapy
   • GM-CSF + radiation therapy generated abscopal responses in breast cancer
   • Phase II studies are ongoing

1) dual checkpoint therapy
   • Efficacy is demonstrated in pre-clinical models
   • Novel pre-operative trials may screen for effective combination therapies