Clinical evaluation of response to immunotherapy

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  – BMS; MSD; GSK; Roche

• Research grants:
  – BMS; GSK; MSD
Aim of presentation

- Highlight the differences in MOA of IT compared to targeted therapy of chemotherapy
- Summarize the response types observed with IT
- Discuss the evaluation possibilities
MOA of cancer treatments

DNA damage

Chemotherapy

Radiotherapy

Cell death
MOA of cancer treatments

Targeted agents

Inhibition of mutated or overexpressed proteins in cancer cells

Cell death or stop of cell growth
MOA of cancer treatment

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)
MOA of cancer treatment

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Anti-CTLA4

TIL infusion

DC vaccination

Anti-PD1/PDL1
IT versus TT or CT

• Targeted and chemotherapy work directly
  – Target tumor cells (and normal cells)

• Immunotherapy works indirectly
  – Stimulates cells from the immune system
    • Anti-CTLA4
    • Anti-PD1/PD-L1
    • DC vaccination or other vaccine platforms
  – Augments the pool of tumor-specific T cells
    • TIL therapy
    • TCR of CAR gene therapy
Time-to-response to treatment

• Chemotherapy: if present usually within 6 weeks (2 courses)
• Targeted therapy:
  – BRAFi (+MEKi) within days, mostly within 2 weeks (PET)
• Immunotherapy: highly variable
  – Ipilimumab: weeks to months
  – Anti-PD1/PD-L1: weeks to months
  – TIL: weeks to months
Patterns of response to ipilimumab

Wolchok et al., Clin Canc Res 2009
Response patterns with ipilimumab

Ledeza et al. J Clin Oncol Nurs 2011
Response patterns with ipilimumab

Saenger and Wolchok Cancer Immunity 2008
Response pattern following ipilimumab treatment

Dense infiltrate of T cells in resected lesion

*Note.* The lesion remained relatively stable in size throughout treatment. No lesion was evident following resection.

Ledezma et al. J Clin Oncol Nurs 2011
Is progression truly progression?

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,1 Axel Hoos,2 Steven O'Day,3 Jeffrey S. Weber,4 Omid Hamid,3 Celeste Lebbé,5 Michele Maio,6 Michael Binder,7 Oliver Bohnsack,8 Geoffrey Nichol,9 Rachel Humphrey,2 and F. Stephen Hodi10
# Immune related Response Criteria

<table>
<thead>
<tr>
<th>WHO</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, measurable lesions (i.e., ≥5 × 5 mm)</td>
<td>Always represent PD</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (i.e., &lt;5 × 5 mm)</td>
<td>Always represent PD</td>
</tr>
<tr>
<td>Non-index lesions</td>
<td>Changes contribute to defining BOR of CR, PR, SD, and PD</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>SD</td>
<td>50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions</td>
</tr>
<tr>
<td>PD</td>
<td>At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)</td>
</tr>
</tbody>
</table>

Wolchok et al., Clin Cancer Res 2009
….simplify irRC from bidimensional

### WHO based irRC

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurable lesions</td>
<td>≥5 × 5 mm² by bidimensional measurements</td>
</tr>
<tr>
<td>Measurement of each lesion</td>
<td>The longest diameter × the longest perpendicular diameter (cm²)</td>
</tr>
<tr>
<td>The sum of the measurements</td>
<td>The sum of the bidimensional measurements of all target lesions and new lesions if any</td>
</tr>
<tr>
<td>Response assessment</td>
<td>PD: ≥25% increase from the nadir</td>
</tr>
<tr>
<td></td>
<td>PR: ≥50% decrease from baseline</td>
</tr>
<tr>
<td></td>
<td>CR: Disappearance of all lesions</td>
</tr>
<tr>
<td>New lesions</td>
<td>The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.</td>
</tr>
<tr>
<td>Confirmation</td>
<td>Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD</td>
</tr>
</tbody>
</table>

Nishino et al., Clin Canc Res 2013
...simplify irRC from bidimensional to unidimensional...

<table>
<thead>
<tr>
<th>WHO based irRC</th>
<th>RECIST 1.0 based irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bidimensional assessment (the original irRC)</strong></td>
<td><strong>Unidimensional assessment</strong></td>
</tr>
<tr>
<td>Measurable lesions</td>
<td>≥10 mm in the longest diameter</td>
</tr>
<tr>
<td>Measurement of each lesion</td>
<td>The longest diameter (cm)</td>
</tr>
<tr>
<td>The sum of the measurements</td>
<td>The sum of the longest diameters of all target lesions and new lesions if any</td>
</tr>
<tr>
<td>Response assessment</td>
<td>PD: ≥20% increase from the nadir</td>
</tr>
<tr>
<td></td>
<td>PR: ≥30% decrease from baseline</td>
</tr>
<tr>
<td>New lesions</td>
<td>CR: Disappearance of all lesions</td>
</tr>
<tr>
<td>Confirmation</td>
<td>The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.</td>
</tr>
<tr>
<td></td>
<td>Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD</td>
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</table>

Nishino et al., Clin Canc Res 2013
Best immune related response according to 2-dimensional vs 1-dimensional measurement

<table>
<thead>
<tr>
<th>Best response by unidimensional assessment</th>
<th>irCR</th>
<th>irPR</th>
<th>irSD</th>
<th>irPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>irCR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>irPR</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>irSD</td>
<td>0</td>
<td>0</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>irPD</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE: $\kappa_w = 0.881$.

Nishino et al., Clin Canc Res 2013
RECIST 1.0 vs RECIST 1.1

- 10 lesions
- Max 5 per organ
- Min. size clinical lesion: 20 mm
- Not mentioned

- 5 lesions
- Max 2 per organ
- Min. size clinical lesion 10 mm
- LN target lesion ≥15 mm
irRC, but now based on RECIST 1.1

71 Patients ranked by the percent changes of measurements at the 1st follow-up using irRC simulating RECIST 1.0

Nishino et al., J Immunother Cancer 2014
RECIST 1.1 based irRC capture patterns of response to immunotherapy

Nishino et al., J Immunother Cancer 2014
Which parameter should we measure for response evaluation to IT

• Objective response?
• Progression free survival?
• Overall survival?
  – Median
  – Survival at 3 years
  – ?
Chemotherapy

Saltz et al., NEJM 2000
Targeted therapy

Short duration of response

McArthur Lancet Oncol 2014

26-30 September 2014, Madrid, Spain
Survival in BRIM-3 trial

Mc Arthur Lancet Oncol 2014

26-30 September 2014, Madrid, Spain
## Objective response to ipilimumab

### Evaluation of therapy

<table>
<thead>
<tr>
<th>Induction</th>
<th>Best overall response — no. (%)</th>
<th>P value for comparison with gp100 alone</th>
<th>P value for comparison with ipilimumab alone</th>
<th>Disease control rate — % (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (0.2)</td>
<td>0.04</td>
<td>—</td>
<td>20.1 (16.3–24.3)</td>
</tr>
<tr>
<td>Partial response</td>
<td>22 (5.5)</td>
<td>0.001</td>
<td>—</td>
<td>28.5 (21.1–36.8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>58 (14.4)</td>
<td>0.04</td>
<td>—</td>
<td>11.0 (6.3–17.5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>239 (59.3)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Not evaluated</td>
<td>83 (20.6)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Best overall response rate</td>
<td>5.7 (3.7–8.4)</td>
<td>10.9 (6.3–17.4)</td>
<td>1.5 (0.2–5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Hodi et al., NEJM 2010
Progression Free Survival

Hodi et al., NEJM 2010

26-30 September 2014, Madrid, Spain
Median overall survival

Hodi et al., NEJM 2010
Long-term overall survival

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Overall survival rate, % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year</td>
</tr>
<tr>
<td>Ipi + DTIC (N=250)</td>
<td>47.6</td>
</tr>
<tr>
<td></td>
<td>[41.2-53.7]</td>
</tr>
<tr>
<td>Placebo + DTIC (N=252)</td>
<td>36.4</td>
</tr>
<tr>
<td></td>
<td>[30.4-42.4]</td>
</tr>
</tbody>
</table>

Maio et al ESMO 2013
MK-3475 produced a reduction in tumor size in 74% of evaluable patients.

Ribas et al., ASCO 2014
Time to PR or CR & Durability of Response
Central Review, RECIST v1.1

First tumor assessment

Individual Patients

Time, weeks

IPI treated
IPI naive
Response ongoing and alive
Complete response
Partial response
Progression

26-30 September 2014, Madrid, Spain
Ipilimumab + nivolumab

ORR: 40%

After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients still in response

Overall Survival of pembrolizumab

- Median OS not reached
- 69% OS rate at 12 months (74% for IPI-N, 65% for IPI-T)
- 62% OS rate at 18 months

Ribas et al., ASCO 2014
Overall Survival with ipilimumab + nivolumab

Weber ASCO 2014

26-30 September 2014, Madrid, Spain

esmo.org
Conclusions

- Immunotherapy’s mechanism of action is very different from classical chemotherapy or targeted therapy.

- This is reflected by very different patterns and kinetics of response (mostly seen in ipi, much less in anti-PD1/PDL1 and ipi + nivo combination).

- In order to capture these different responses during clinical evaluations, irRC have been developed (recently simplified to RECIST 1.1 based irRC).

- For anti-CTLA4 not ORR, PFS, nor median OS, but long-term survival was the most meaningful endpoint for clinical evaluation.

- For anti-PD1/PD-L1 or ipi + nivo ORR and duration of response may be good endpoints, but long-term OS remains the most important endpoint for clinical evaluation.