Are patients overdosed with the present recommendations?

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Drug Development Dpt
INSERM 1015

ESMO Advanced Course
Feb 16th, 2018
DISCLOSURES

Over the last 3 years:

• Principal Investigator of Clinical Trials from the following companies: Roche/Genentech, BMS, Merck (MSD), Pfizer, Lytix pharma, Eisai, Astra Zeneca/Medimmune, Chugai

• Member of Clinical Trial Scientific Committee: NCT02528357 (GSK), NCT03334617 (AZ)

• Member of Data Safety and Monitoring Board: NCT02423863 (Oncovir)

• Scientific Advisory Boards: Merck Serono, eTheRNA, Lytix pharma, Kyowa Kirin Pharma, Novartis, BMS, Symphogen, Genmab, Amgen, Biothera, Nektar, GSK, Oncosec, Pfizer, Seattle Genetics, Astra Zeneca/Medimmune, Servier

• Teaching/Speaker activities: Roche/Genentech, BMS, Merck (MSD), Merck Serono, Astra Zeneca/Medimmune, Amgen, Sanofi

• Scientific & Medical Consulting: Roche, Pierre Fabre, Onxeo, EISAI, Bayer, Genticel, Rigontec, Daichii Sankyo, Imaxio, Sanofi, BioNTech, Medimmune

• Co-founder: Pegascy SAS

• Patent holder: anti-CD81 (Stanford University)
Paradigm Shift in Cancer Therapy

Historical Paradigm: Targeting Tumor Cells

New Paradigm: Targeting Immune Cells

Tumor Cell

Lymphocyte
Know your Immune Checkpoint Antibodies

**Anti-CTLA-4**
- Tremelimumab (AZ)
- AGEN-1884 (Agenus)
- Ipilimumab (BMS)

**Anti-PD-1**
- Nivolumab (BMS)
- Pembrolizumab (MSD)
- spartalizumab (Novartis)
- cemiplimab (Regeneron/Sanofi)
- camrelizumab (Incyte)

**Anti-PD-L1**
- Durvalumab (AZ/Medimmune)
- Avelumab (Pfizer)
- Atezolizumab (Roche/Genentech)
- LY3300054 (Lilly)
- FAZ053 (Novartis)

Approved

YERVY™

OPDIVO™

TECENTRIQ™

BAVENCIO®

KEYTRUDA®

IMFINZI™
Anti-PD-1/PD-L1 Isotypes

αPD-1

NIVOLUMAB  PEMBROLIZUMAB

IgG4  IgG4

αPD-L1

ATEZOLIZUMAB  DURVALUMAB

Modified IgG1  Modified IgG1

NO ADCC / ADCP
### αPD-1/PD-L1:
No Dose/Efficacy/Toxicity Correlation

<table>
<thead>
<tr>
<th></th>
<th>KN001 Part D</th>
<th></th>
<th>KN006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg/kg Q3W</td>
<td></td>
<td>10 mg/kg Q3W</td>
<td>10 mg/kg Q3W</td>
</tr>
<tr>
<td><strong>ORR (%)</strong></td>
<td>33</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td><strong>PFS (median, mo)</strong></td>
<td>5.5</td>
<td>4.2</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>6-month PFS rate (%)</strong></td>
<td>50</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td><strong>12-month OS rate (%)</strong></td>
<td>72</td>
<td>64</td>
<td>68</td>
</tr>
</tbody>
</table>
\( \alpha \text{PD-1/PD-L1:} \)

No Dose/Efficacy/Toxicity Correlation


Conclusion 1:

Anti-PD-1/PD-L1 = pure antagonistic (« checkpoints blockers ») (avelumab?)
Isotypes des anti-PD-1/PD-L1

αPD-1

NIVOLUMAB  PEMBROLIZUMAB

IgG4  IgG4

Modified IgG1

αPD-L1

ATEZOLIZUMAB  DURVALUMAB  AVELUMAB

Modified IgG1

IgG1

NO ADCC / ADCP
Infusion Related Reactions ≈3%

ADCC / ADCP
IRR≈18%
Long-term PD-1 occupancy analysis in patients receiving nivolumab at 10 mg/kg

Pembrolizumab, Anti-PD-1, MSD

2nd line NSCLC: 2 mg/kg Q3W

1st line NSCLC: 200mg Q3W flat dose
Conclusion 2:

We are probably overdosing patients with anti-PD(L)1 antibodies.

**DO WE CARE?**
Anti-CTLA-4 *in vitro* based rationale: **antagonistic**
Anti-CTLA-4 THERAPY

Hodi et al. Abstract #3008 ASCO 2008

Schadendorf D, J Clin Oncol 2015.
OS ipilimumab 10 mg/kg vs 3 mg/kg

<table>
<thead>
<tr>
<th>OS</th>
<th>IPI 10 mg/kg ( n = 365 )</th>
<th>IPI 3 mg/kg ( n = 362 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>262 (72)</td>
<td>279 (77)</td>
</tr>
<tr>
<td>Median (95% CI), mo</td>
<td>15.7 (11.6, 17.8)</td>
<td>11.5 (9.9, 13.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.84 (0.70, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Log-rank ( P ) value</td>
<td>0.04</td>
<td></td>
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</table>

Minimum OS follow-up: ~43 months

Ascierto PA et al. ESMO 2016
Blocking CTLA4:
with same affinity but different isotypes
Anti-CTLA-4 *in vivo* based rationale: **depleting**

IgG1  
IgG2a  
IgG2b
CTLA-4 is highly expressed on intra-tumoral Tregs


Anti-CTLA-4 depletes intra-tumoral Tregs

Anti-CTLA-4 depletes Tumor-Specific Intratumoral Tregs


Anti-CTLA-4 Treg depletion depends on FcγR


Anti-CTLA4 in Humans

RITUXIMAB  TRASTUZUMAB  CETUXIMAB  DARATUMUMAB  IPILIMUMAB

CD20  HER2  EGFR  CD38  CTLA4

IgG1  IgG1  IgG1  IgG1  IgG1
IgG2 mAbs can do ADCC/ADCP (via Myeloid Cells)

Tremelimumab: same overall survival as ipilimumab

Zeynep Eroglu, Dae Won Kim, Xiaoyan Wang, Luis H. Camacho, Bartosz Chmielowski, Elizabeth Seja, Arturo Villanueva, Kathleen Ruchalski, John A. Glaspy, Kevin B. Kim, Wen-Jen Hwu, Antoni Ribas

Long term survival with cytotoxic T lymphocyte-associated antigen 4 blockade using tremelimumab

European Journal of Cancer, Volume 51, Issue 17, 2015, 2689–2697

http://dx.doi.org/10.1016/j.ejca.2015.08.012
IPEX syndrome: Human model of FOXP3 KO

Ipilimumab Depletes Tregs in vivo

Ipilimumab Depletes Tregs in vivo
(although it needs ADCC prone macrophages)

Conclusion 2:

Anti-CTLA-4 =
not checkpoint blockers but Treg depleters
OS ipilimumab 10 mg/kg vs 3 mg/kg

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Number of patients at risk:

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>IPI 10 mg/kg</th>
<th>IPI 3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>365</td>
<td>362</td>
</tr>
<tr>
<td>3</td>
<td>306</td>
<td>310</td>
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<tr>
<td>6</td>
<td>253</td>
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<tr>
<td>9</td>
<td>217</td>
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<tr>
<td>12</td>
<td>196</td>
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<td>18</td>
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<td>131</td>
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<tr>
<td>21</td>
<td>151</td>
<td>118</td>
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<tr>
<td>24</td>
<td>137</td>
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<tr>
<td>27</td>
<td>126</td>
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<td>45</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Minimum OS follow-up: ~43 months

Ascierto PA et al. ESMO 2016
Which Dose of $\alpha$-CTLA-4 in Combo with $\alpha$-PD-1 for bladder?

<table>
<thead>
<tr>
<th>Combination</th>
<th>Median Reduction in Target Lesion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 1 + IPI 3</td>
<td>-27.8%</td>
</tr>
<tr>
<td>NIVO 3 + IPI 1</td>
<td>0%</td>
</tr>
</tbody>
</table>

Symbols in red indicate responders.

Dashed lines indicate RECIST 1.1 response.

Sharma P et al. SITC 2016
Which dose for anti-CTLA-4 ??

• **Melanoma:**
  – ipilimumab 3mg/kg Q3W x4
  – + nivo 1mg/kg Q3W x4
  – followed by nivolumab 3m/kg Q2W

• **RCC:**
  – ipilimumab 1mg/kg x4 Q3W
  – nivolumab 3mg/kg Q3W
  – followed by nivolumab 3m/kg Q2W

• **NSCLC:**
  – ipilimumab 1mg/kg Q6W
  – nivolumab 3m/kg Q2W
Impact #1: Find the right dose to overcome resistance to immunotherapy

Impact #2: immune related adverse events
Impact #3: Address the Financial Toxicity

The cost of treating cancer is surging, with immunotherapies at the fore.

The graph shows the monthly price of treatment (thousands of dollars) over the years of FDA approval. The red line indicates the median monthly price, which surges over time.

*2010 figures adjusted for inflation.

**Nature.** 2013 May 30;497(7451)
Immunotherapy's cancer remit widens. Ledford H.
Corollary Question:
Duration of Treatment?

« Treat until unacceptable toxicity or disease progression »
Are patients overdosed with the present recommendations?

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