March 25, 2015

Immune Checkpoint Inhibitors Drug Combinations: Patients Relevance & Ways Forward

Dr. Alexandre Passioukov
Therapeutic efficacy of agents targeting immune checkpoints

Introduction

- Deep and durable responses have been observed, with an impact on OS;
- Currently limited to certain tumor types (e.g. melanoma, NSCLC, RCC, bladder, Hodgkin lymphoma);
- Only subsets of patients respond to single agents vs. combinations
Nivolumab vs. nivolumab /ipilimumab in advanced melanoma

Therapeutic efficacy of agents targeting immune checkpoints

Combo treatment responders

Combos demonstrate a clear potential to increase the proportion of responders:

- Tumor immune infiltration seems to be a pre-requisite for clinical efficacy of this type of agents, but is not enough *per se*;
- Biomarkers susceptible to identify combo vs. s.a. responders tend to a ‘multiplex’ format
ICIs: current landscape

Ai et al. Cancer Imm. Imm, 2015
IC modulation: current landscape

Are we just exploiting pre-existing & insufficient anti-tumor response(s)?

Ai et al. Cancer Imm. Imm, 2015
CTLA-4/PD-1 inhibition preclinical synergy: adaptive up-regulation of IC-molecules

- **In vivo experiments in B16 melanoma models:**
  - inhibition of either CTLA-4 or PD-1 by single agent induced the expression of other co-inhibitor within tumor;
  - Re-tolerizing of TILs is a risk with single ICI;
  - Triple co-inhibitory blockage CTLA-4 / PD-1 / PD-L1 cured 70% of mice through increase of ratio Teff/Tregs (Curran et al. PNAS, 2010)

- **Rational for simultaneous inhibition but:**
  - CTLA-4 inhibition promotes auto-immunity
  - PD-1 inhibition overlapping toxicities, notably risk of pneumonitis
CTLA-4/PD-1inh. clinical synergy in BMS ph I: rapid long-lasting responses + OS increase

Clinical efficacy:
- RR of 53% (RESIST) with a
- Rapid onset on combo, in contrast to few months for single agents;
- OS at 2 years of 88% (*historical control: 25%, AJCC, 2008*)

Safety:
- **Grade III/IV AEs: 53%**
CTLA-4/PD-1 responders vs. single agent
key biomarker observations (Tang et al. 2013)

How responders on combo are different from responders on single agent?

1. Ki67+ T cells up to 10-fold higher (15-35%) on combo than on ipilimumab alone;
2. Double positive CTLA-4/PD-1 Teff cells in PBMCs increased ~1 week after start of combo and persisted for up to 12-weeks;
3. ICOS increase on CD4, in contract to CD8 on monotherapy
Innovative combinations: vision

- Greater percentage of patients
- Broader range of malignancies

Ai, Curran, CII, 2015
Innovative combinations: vision

- Greater percentage of patients
- Broader range of malignancies

But: how we best screen optimal ICI combos?
IC combos: key challenges

1. Multiple IO combinations are possible, many of which may have a **negative risk-benefit ratio**;

2. High complexity of interactions between the tumor and immune system requires ‘**personalized approaches**’ for different patients & different combos within the same patient segment;

3. **Deciphering immunosuppression patterns** developed by individual tumors will be critical in the rational design of IO combinations
Translational Challenges for Immune Combos

1. Relevance of preclinical models:
   - Major differences between immune systems of rodents and humans result in poor predictivity of non-clinical models
   - *PDTT, GEMM, NHP approaches*

2. Clinical study design: dose & sequence challenges

3. Patient selection challenges:
   - *trend to multiplex format*
Humanized mouse model: example

Champions Oncology (Baia et al):
- Immunodeficient mice reconstituted with human CD34+ cells;
- Expected array of human immune-components;
- Immunografted animals show expected anti-tumor immune-responses after ICI (combos)

Next steps:
- Combos with anti-PD1/PD-L1 and cytotoxics
- Co-administration of cytokines (including IL-12 or IFN-g)
- Screen ImmunoGrafts against tumors taken from responding/non-resp. patients
Non-human primates models

Advantages:
- May cross-react with human Abs;
- Similarities of basic immune system components;
- High predictive value of PK/PD

BUT:
- Rarity of representative tumor-bearing models (low spontaneous tumors incidence; induced tumors described but not routinely used);
- Relatively high costs (large animals, slow reproduction).
Translational Challenges for Immune Combos

1. Relevance of preclinical models:
   - PDTT, GEMM, NHP approaches

2. Clinical study design: dose and sequence challenges

3. Patient selection challenges:
   - trend to multiplex format
CTLA-4 & PD-1 and anti-tumor immune responses: conceptual sequence

1. T-cells activation and proliferation dampened by CTLA-4 upregulation (priming phase)
2. T-cells anti-tumor activity can be inhibited through PD-1/PD-L1 axis (effector phase)
CTLA-4 & PD-1 and anti-tumor immune responses: clinical evidence

BUT: PD-1 + Ipilimumab clinical data demonstrated superiority of concomitant approach (NEJM 6/2013)

Translational Challenges for Immune Combos

1. Relevance of preclinical models:
2. Dose and sequence challenges
3. Patient selection challenges:
   - *single agent PD read-outs are key*
   - *trend to multiplex format*
**PD-L1 expression vs. efficacy data**

**PD-L1 as a potential efficacy biomarker: response according to PD-L1 expression in NSCLC and melanoma**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>PDL-1 + ve ORR n/N (%)</th>
<th>PDL-1-ve ORR n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPDL3280A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamid et al. ASCO #9010</td>
<td>Melanoma 4/15 (27%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Melanoma 8/12 (67%)</td>
<td>6/32 (19%)</td>
</tr>
<tr>
<td>Weber et al. ASCO #9011</td>
<td>Melanoma 7/16 (44%)</td>
<td>3/18 (17%)</td>
</tr>
<tr>
<td>Nivolumab Grosso et al. ASCO #3016</td>
<td>Melanoma 9/25 (36%)</td>
<td>0/17 (0%)</td>
</tr>
<tr>
<td>Nivolumab Topalian et al. NEJM 2012</td>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>Nivolumab Antonia et al. WCLC 2013</td>
<td>NSCLC</td>
<td>5/31 (16%)</td>
</tr>
<tr>
<td>Pembrolizumab Garon et al. WCLC 2013</td>
<td>NSCLC</td>
<td>4/7 (57%)</td>
</tr>
<tr>
<td>MPDL3280A Horn et al. WCLC2013</td>
<td>NSCLC</td>
<td>8/26 (31%)</td>
</tr>
<tr>
<td>Nivolumab/ipilimumab Callahan et al. ASCO#3003</td>
<td>Melanoma</td>
<td>4/10 (40%)</td>
</tr>
</tbody>
</table>

**Large variability:**
- Different assays;
- Different quantification algorithms;
- Tumor cells vs. TILs - different biology
PD-L1 expression: tumor vs. TILs

PD-L1 prevalence in UBC tumours by IHC

<table>
<thead>
<tr>
<th></th>
<th>PD-L1-positive tumour-infiltrating immune cells (no. of specimens (%))</th>
<th>PD-L1-positive tumour cells (no. of specimens (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 205</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 3</td>
<td>18 (9)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>IHC 2</td>
<td>37 (18)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>IHC 1</td>
<td>89 (43)</td>
<td>37 (18)</td>
</tr>
<tr>
<td>IHC 0</td>
<td>61 (30)</td>
<td>146 (71)</td>
</tr>
</tbody>
</table>

Powles et al. Nature 2014
PD-L1 in TILs vs. efficacy data in bladder
high potential to enrich responders population

<table>
<thead>
<tr>
<th>Tumour-infiltrating immune cells and objective response rates</th>
<th>Objective response rate n (%)</th>
<th>Stable disease n (%)</th>
<th>Progressive disease n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC 2/3 (n = 30)</td>
<td>13 (43.3) (95% CI: 25.5–62.6)</td>
<td>8 (26.7)</td>
<td>8 (26.7)</td>
</tr>
<tr>
<td>IHC 3 (n = 10)</td>
<td>5 (50.0) (95% CI: 22.2–77.8)</td>
<td>2 (20.0)</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>IHC 2 (n = 20)</td>
<td>8 (40.0) (95% CI: 20.9–63.9)</td>
<td>6 (30.0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>IHC 0/1 (n = 35)</td>
<td>4 (11.4) (95% CI: 4.0–26.3)</td>
<td>13 (37.1)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td>IHC 1 (n = 23)</td>
<td>3 (13.0) (95% CI: 3.7–31.7)</td>
<td>8 (34.8)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>IHC 0 (n = 12)</td>
<td>1 (8.3) (95% CI: 0.4–34.9)</td>
<td>5 (41.7)</td>
<td>5 (41.7)</td>
</tr>
</tbody>
</table>

Powles et al. Nature 2014
PD-L1 expression: patterns in non-responders

Herbst et al. Nature 2014
Combination approaches overcoming dependence on PD-L1 expression?

- Tumor PD-L1 status does not predict outcome on concomitant combo;
- Additional responses on combo happen in PD-L1(-) patients (PD-L1 upreg. in TILs on trt?);
- 50% RR limit in this setting (prevalence of the relevant tumor infiltration patterns?)
Single agent vs. Combo Responders
general considerations

Obviously at least 3 patient populations need to be defined:

1. patients to be treated with single agent,
2. patients to be treated by combos:
3. Patients resistant to immunotherapies (*BUT: might be sensitized?*)
Single agent vs. Combo Responders

general considerations

Obviously at least 3 patient populations need to be defined:

1. patients to be treated with single agent,
2. patients to be treated by combos:
3. Patients resistant to immunotherapies *(BUT: might be sensitized?)*

To increase chances to identify them:

- Clear demonstrate mechanistic rationale before moving into clinical development;
- Single agent PD marker should be established prior to combining agents;
- Making effort to collect bio-samples on trt/upon progression;
- Creative & flexible trial design: dose / scheduling / biomarker set-up (‘octopus’ trials?)
T cell receptor diversity evaluation to predict patient response to ipilimumab in metastatic melanoma

Michael A. Postow, Manuari Manuel, Philip Wong, Jianda Yuan, Marlene Noel, Anaïs Courtier, Nicolas Pasqua, Jedd D. Wolchok

1. Melanoma and Immunotherapeutics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY, USA - 2. ImmunID, Grenoble, France - 3. Immune Monitoring Core Facility, Ludwig Center for Cancer Immunotherapy, Memorial Sloan Kettering Cancer Center, New York City, NY, USA

- Baseline diversity richness and evenness of the TCR repertoire are associated with clinical response to ipilimumab.

- The ImmunTracker test is being further evaluated in larger groups of patients to determine whether the kit may ultimately be used to select patients likely to respond to ipilimumab in metastatic melanoma and possibly to other cancer immunotherapies.

**Host immuno-competence: a pre-requisite for ICIs to work?**
ccRCC transcriptome analysis molecular subtypes: predictive of treatment with immune-modulators?

- ccrcc4 tumors exhibited sarcomatoid differentiation with a strong inflammatory, Th1-oriented but suppressive immune microenvironment, with high expression of PDCD1 (PD-1) and its ligands

Beuselinck et al. CCR 2015
Tumor Immuno-phenotype vs. tumor molecular features?

Chan al. TLCR, 2015
Tumor Immuno-phenotype vs. tumor molecular features?

Immune contexture vs. NGS & transcriptomics or ‘combined’?

Immune infiltration pattern 1

Immune infiltration pattern 2
IC combos efficacy predictive biomarkers: an integrative approach needed

- Ideally would differentiate between the patients responding to single agent(s) vs. combination to avoid unnecessary toxicities;
- Ideally would identify all the patients who benefit from the treatment, while excluding the non-responders;
- Would require a ‘personalized approach’ with a combination of markers or even of different technologies.

Represent unprecedented translational and clinical validation challenges: with a great ambition of CANCER CURE
Thank you