Immuno-Oncology Combinations: Clinical Trial Design Consideration

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Disclosures (2017)

I have the following financial relationships to disclose:

• Consultant for: Merck (compensated), AstraZeneca/Medimmune (compensated), Symphogen (compensated), Morphosys (compensated)
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• Stockholder in: None
### 26 Immuno-Oncology Agents Approved Globally

#### Mostly Discovered by Experts in Academic Centers

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Therapy name</th>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell targeted Immunomodulator (6 in total)</td>
<td>Ipilimumab</td>
<td>Bristol-Myers Squibb Co</td>
<td>CTLA-4</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
<td>Bristol-Myers Squibb Co</td>
<td>PD-1</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Merck &amp; Co Inc</td>
<td>PD-1</td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Roche/Genentech Ltd</td>
<td>PD-L1</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>Merck KGaA</td>
<td>PD-L1</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>AstraZeneca/MedImmune LLC</td>
<td>PD-L1</td>
</tr>
<tr>
<td>Other Immunomodulator (8 in total)</td>
<td>Aldesleukin</td>
<td>Novartis AG</td>
<td>IL2R</td>
</tr>
<tr>
<td></td>
<td>Imiquimod</td>
<td>Valeant Pharmaceuticals Intl Inc</td>
<td>TLR7</td>
</tr>
<tr>
<td></td>
<td>Interferon alfa</td>
<td>Sumitomo Dainippon Pharma Co Ltd</td>
<td>IFNAR1; IFNAR2</td>
</tr>
<tr>
<td></td>
<td>Interferon alfa-1b</td>
<td>Shenzhen Kexing Biotech Co Ltd</td>
<td>IFNAR1</td>
</tr>
<tr>
<td></td>
<td>Interferon alfa-2a</td>
<td>Cadila Healthcare Ltd</td>
<td>IFNAR1; IFNAR2</td>
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<tr>
<td></td>
<td>Interferon alfa-2b</td>
<td>Merck &amp; Co Inc</td>
<td>IFNAR1; IFNAR2</td>
</tr>
<tr>
<td></td>
<td>Interferon beta</td>
<td>Toray Industries Inc</td>
<td>IFNAR1</td>
</tr>
<tr>
<td></td>
<td>Interferon gamma-1a</td>
<td>Otsuka Pharmaceutical Co Ltd</td>
<td>IFNAR1</td>
</tr>
</tbody>
</table>

#### Cancer Vaccine (7 in total)

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Name of Therapy</th>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BCG live</td>
<td>Shire Plc</td>
<td>TLR</td>
</tr>
<tr>
<td></td>
<td>Immucyst</td>
<td>Sanofi</td>
<td>TLR</td>
</tr>
<tr>
<td></td>
<td>Immuno BCG</td>
<td>Ataulpho Palva Foundation</td>
<td>TLR</td>
</tr>
<tr>
<td></td>
<td>Mycida-C</td>
<td>Cadila Pharmaceuticals Ltd</td>
<td>TLR2</td>
</tr>
<tr>
<td></td>
<td>Sipuleucel-T</td>
<td>Dendreon</td>
<td>Unspecified TAA</td>
</tr>
<tr>
<td></td>
<td>TICE BCG</td>
<td>Merck &amp; Co Inc</td>
<td>TLR</td>
</tr>
<tr>
<td></td>
<td>Uro-BCG</td>
<td>Medac Inc</td>
<td>TLR</td>
</tr>
</tbody>
</table>

#### Cell Therapy (2 in total)

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Name of Therapy</th>
<th>Company</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Tisagenlecleucel</td>
<td>Novartis AG</td>
<td>CD19</td>
</tr>
<tr>
<td></td>
<td>Axicabtagene choleucel</td>
<td>Gilead</td>
<td>CD19</td>
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</table>

#### Oncolytic Virus (2 in total)

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Name of Therapy</th>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oncorine</td>
<td>Shanghai Sunway Biotech Co Ltd</td>
<td>CD40L</td>
</tr>
<tr>
<td></td>
<td>Talimogene laherparepvec</td>
<td>Amgen Inc</td>
<td>GMCSFR</td>
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</tbody>
</table>

#### CD3-targeted Bispecific ab

<table>
<thead>
<tr>
<th>Therapy type</th>
<th>Name of Therapy</th>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blinatumomab</td>
<td>Amgen Inc</td>
<td>CD19 X CD3</td>
</tr>
</tbody>
</table>

A REVOLUTION IS UNDERWAY: 2,004 IO AGENTS IN DEVELOPMENT

940 AGENTS ARE IN CLINICAL STAGES, AND 1,064 IN PRECLINICAL

T-cell targeted immunomodulator

Other immunomodulator

Cancer vaccine

Cell therapy

Oncolytic virus

CD3-targeted bispecific antibody

Clinical agent count

- 99
- 170
- 344
- 224
- 69
- 34

### Increase of New PD-1/L1 Combo Trials, But Smaller Studies

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Clinical phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase 4</td>
<td>Phase 3</td>
<td>Phase 2</td>
<td>Phase 1/2</td>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Number of new trials</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>13</td>
<td>20</td>
<td>58</td>
<td>190</td>
<td>329</td>
<td>469</td>
</tr>
<tr>
<td>Planned new enrollment</td>
<td>136</td>
<td>2,473</td>
<td>582</td>
<td>4,867</td>
<td>5,031</td>
<td>11,276</td>
<td>39,821</td>
<td>46,153</td>
<td>52,539</td>
</tr>
<tr>
<td>Planned enrollment per new trial</td>
<td>136</td>
<td>495</td>
<td>291</td>
<td>374</td>
<td>252</td>
<td>194</td>
<td>210</td>
<td>140</td>
<td>112</td>
</tr>
</tbody>
</table>

Immunotherapy can be Used in Combination with Other Therapeutic Agents

**Personalized combinations guided by biomarkers**

- Costimulatory mAbs targeting:
  - CD137
  - OX40
  - CD40
  - GITR

- Conventional agents inducing immunogenic cell death:
  - Chemotherapy
  - Radiotherapy
  - Anti-angiogenics
  - Targeted therapies

- Other checkpoint inhibitory molecules:
  - CTLA-4
  - LAG3
  - TIM3
  - BTLA
  - TIGIT

- Cancer vaccines using individual neo-antigens

- Functional modification of immuno-suppressive enzymes such as:
  - IDO1
  - iNOS

- \( T_{reg} \) cell targeting or inhibition

- Adoptive cell therapy

- Myeloid cell modulation

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2. Drake CG. *Ann Oncol* 2012;23(suppl 8):viii41-viii46

Figure adapted from *Clin Cancer Res*. Copyright 2012, vol 18 (2): pp336-341.
Management of Cancer in the Post-Anti-PD-1/L1 Era

1. Anti-PD-1/L1 naive

2. Progress with interval therapy

3. Progress without interval therapy

4. Bring T cells into tumors

5. Generate/Expand T cells

Inflamed

Response to Anti-PD-1/PD-L1

Immune excluded, Immune Dessert

Likely primarily resistant to Anti-PD-1/L1
Management of Cancer in the Post-Anti-PD-1/L1 Era

Generate/Expand T cells:
- + anti-CTLA4, other immune checkpoint inhibitors
- + radiation/SBRT
- + immune activating antibodies or cytokines
- + TLR agonists or oncolytic viruses
- + IDO or macrophage inhibitors
- + targeted therapies
- + chemotherapy

Bring T cells into tumors:
- Vaccines
- TCR engineered ACT
- CAR engineered ACT
- Expanded T cells/TIL
What are the Key Challenges with IO Combinations?

• What nonclinical data are sufficient to support rational IO combinations?
• How to make go-no-go decisions from early phase IO combination trials?
• How do we optimize efficiencies and reduce redundancies in performing IO combination trials?
What are the Key Challenges with IO Combinations?

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## Presented IO Combinations in Clinical Trials: Basis for Combination – Limited Nonclinical Data

<table>
<thead>
<tr>
<th>Phase</th>
<th>Agents</th>
<th>Targets</th>
<th>Basis for Combination</th>
<th>NCT</th>
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</thead>
<tbody>
<tr>
<td>Ib</td>
<td>PF-05082566 (atumilumab) pembrolizumab</td>
<td>4-1BB PD-1</td>
<td>B16F10 melanoma and MC38 colorectal cancer models</td>
<td>02179918</td>
</tr>
<tr>
<td>Ib</td>
<td>MOXR0916 atezolizumab</td>
<td>OX40 PD-L1</td>
<td>MC38 colorectal model</td>
<td>02410512</td>
</tr>
<tr>
<td>I/II</td>
<td>BMS-986205 nivolumab</td>
<td>IDO PD-1</td>
<td>Not shown</td>
<td>02658890</td>
</tr>
<tr>
<td>I/II</td>
<td>Epacadostat various PD-1/PD-L1 inhibitors</td>
<td>IDO PD-1/PD-L1</td>
<td>B16.SIY melanoma model</td>
<td>multiple trials</td>
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<tr>
<td>I/II</td>
<td>Indoximod nivolumab</td>
<td>IDO PD-1/PD-L1</td>
<td>4T1 breast cancer model</td>
<td>01866319</td>
</tr>
<tr>
<td>I/II</td>
<td>BMS-986156 nivolumab</td>
<td>GITR PD-1</td>
<td>MC38 colorectal cancer</td>
<td>02598960</td>
</tr>
</tbody>
</table>
"Humanized" Mouse Models to Test IO Drugs

- Co-grafting human CD8+/CD4+ T cells with A375 (melanoma, MHC-II, PDL1+) s.c. in NOD/scid mice

![Graph showing tumor volume over days post tumor inoculation for different treatments: Vehicle, Keytruda, and PD1 Lead. Treatment schedule: 10 mg/kg, 3x weekly, 6 doses.]
Phase 0 Evaluation of Novel IO Agents

- Cutaneous melanoma
- Breast cancer
- Skin squamous cell cancer
- Squamous cell cancer of head and neck

**IT novel immuno-oncology agent X**

- Single agent X
- Agent X+anti-PD-1/L1

**IT novel immuno-oncology agent Y**

- Single agent Y
- Agent Y+anti-PD-1/L1
What are the Key Challenges with IO Combinations?

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- How to make go-no-go decisions from early phase IO combination trials?
- How do we optimize efficiencies and reduce redundancies in performing IO combination trials?
# Common IO Phase I Study Design

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Cohort Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamics</td>
<td>Targeted Subgroups</td>
</tr>
</tbody>
</table>

- **Novel IO agent mono-therapy**
- **Novel IO agent + anti-PD-1/L1 antibody**

- **Tumor biopsies for immune biomarker evaluations** e.g. TILs
- **Hot vs cold tumors**
- **IO naïve vs exposed pts**
Phase 1/2a Study of BMS-986156 ± Nivolumab in Patients With Advanced Solid Tumors (NCT02598960)

Monotherapy Dose Escalation in Advanced Solid Tumors

- BMS-986156 IV Q2W
- 10 mg → 30 mg → 100 mg → 240 mg → 800 mg

Monotherapy Cohort Expansion
- Advanced solid tumors
- MTD/MAD/alternate dose

Combination Dose Escalation in Advanced Solid Tumors

- BMS-986156 IV Q2W Nivolumab IV Q2W
- 30 mg + 240 mg → 100 mg + 240 mg → 240 mg + 240 mg → 800 mg + 240 mg

Combination Cohort Expansion
- Advanced solid tumors
- MTD/MAD/alternate dose

Data cutoff: March 31, 2017

**Primary objectives**
- Safety, tolerability, DLTs, and MTD, MAD, or alternate dose

**Secondary/exploratory objectives**
- Immunogenicity
- PK
- PD
- Preliminary antitumor activity

Siu et al. ASCO 2017

*Dose currently being evaluated in the expansion phase.
DLT, dose-limiting toxicity; IV, intravenously; MAD, maximum administered dose; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; Q2W, every 2 weeks.
Pros and Cons of Seamless Phase I-II Trials

Pros:
• Efficiency, time-saving
• Compelling data can lead to accelerated regulatory approval
• Frequent investigator-sponsor communications are critical to ensure safety

Cons:
• Often huge studies with 100s-1000s of patients
• Increased complexity often with multiple amendments
• Objectives, endpoints and statistical analysis plans often lacking
• Diluted clinical experience due to large number of participating sites
Objective Response Rate is not the Best Predictor of Clinical Benefit

**Overall Survival**

*Nivolumab in R/M SCCHN After Platinum Therapy*

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5, 9.1)</td>
<td>0.70 (0.51, 0.96)</td>
<td>0.0101</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 121)</td>
<td>5.1 (4.0, 6.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- ORR (Nivo) = 13%
- ORR (IC) = 5.8%

Challenges in Designing Rational IO Combinations

• Need to understand the effects different IO agents have on T cells, other immune cells and the tumor microenvironment to design rational combinations.

• Beyond ORR, what are the best endpoints for go-no-go decisions? What thresholds define potential antitumor efficacy? The readouts are complicated by heterogeneous pt populations some of whom may be responding to anti-PD1/L1 antibody alone.

• Optimal sequencing of IO agents in combination is also uncertain.

• Biomarker-driven combination studies that are agnostic of histology (e.g. high TMB, POLE mutations, LAG3 overexpression, etc) are being developed.
Biomarker profile of anti-PD1 antibody

Siu, Ohashi et al unpublished data
LAG-3 Expression Enriches for Response

Melanoma Prior-IO Cohort

- **LAG-3 ≥1%**
  - n = 22
  - ORR, 20%

- **LAG-3 <1%**
  - n = 12
  - ORR, 7.1%

- **LAG-3 Unknown**
  - n = 8
  - ORR, 0

- LAG-3 expression enriched for responses in IO-experienced patients
- Nearly a 3-fold increase in ORR was observed in patients with LAG-3 ≥1% vs LAG-3 <1% (20% vs 7.1%)
- Overall response rate was 13%

6 PRs: 2 prior PD; 3 prior PR; 1 unk

DCR, disease control rate; ORR, objective response rate.

- LAG-3 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections.
- Immune cell LAG-3 expression (≥1% or <1%) determined using mouse antibody clone 17B4.
- Response-evaluable patients (n = 48; all progressed on prior anti–PD-1/PD-L1 therapy).
- Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline >30% had an unconfirmed best response of SD.

Ascierto et al. ASCO 2017
Predictive Biomarkers for IO Agents

• **PD-L1** – Not a perfect predictive biomarker
• **Microsatellite status/Mismatch repair proteins**
• **Genomics-based** – Tumor mutation burden, neoantigens, other genomic-based biomarkers, TCR sequencing, single cell sequencing
• **Immunophenotyping** – Flow cytometry, CyTOF, multiplexed immunohistochemistry/ immunofluorescence
• **Transcriptomic based** – RNAseq, Nanostring
• **Imaging-based** – Radiomics, PET functional imaging
• **Microbiome-based**
What are the Key Challenges with IO Combinations?

• What nonclinical data are sufficient to support rational IO combinations?
• How to make go-no-go decisions from early phase IO combination trials?
• How do we optimize efficiencies and reduce redundancies in performing IO combination trials?
<table>
<thead>
<tr>
<th>Question</th>
<th>MDICT 2018</th>
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<tbody>
<tr>
<td>MDICT</td>
<td>Strong hypothesis? Yes, but preferably not the only data supporting</td>
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<tr>
<td></td>
<td>Each agent active? Preferred, if not, robust hypothesis and non clinical data</td>
</tr>
<tr>
<td></td>
<td>Non clinical efficacy? Preferred, but may not be directly relevant to human</td>
</tr>
<tr>
<td></td>
<td>Combo toxicology Has limitations</td>
</tr>
<tr>
<td></td>
<td>Combo PK, PD PD critical</td>
</tr>
<tr>
<td></td>
<td>Explore sequence? Yes, and in clinic</td>
</tr>
<tr>
<td>Trial design</td>
<td>Formal phase 1? More important than ever to have formal phase I/ PD studies</td>
</tr>
<tr>
<td></td>
<td>Escalation plan</td>
</tr>
<tr>
<td></td>
<td>Randomise? Yes, for schedule and to evaluate efficacy</td>
</tr>
<tr>
<td></td>
<td>PK in all? If DDI possible</td>
</tr>
<tr>
<td></td>
<td>PD in all PD critical prior to go/no-go decisions</td>
</tr>
<tr>
<td></td>
<td>Adaptive? Novel designs critical to maximize knowledge</td>
</tr>
<tr>
<td></td>
<td>Other Clear objectives and Go/No-Go criteria</td>
</tr>
<tr>
<td>Other</td>
<td>Drugs Best in class, do not retest failed combo unless justified</td>
</tr>
<tr>
<td></td>
<td>Sharing Critical</td>
</tr>
</tbody>
</table>

courtesy L Seymour on behalf of MDICT
Adaptive/Preemptive IO Basket Trial

Tumor Biopsy → Anti-PD1/L1 → Biomarker Profiling

- **TIGIT**
  - Anti-TIGIT + Anti-PD1/L1 vs Anti-PD1/L1

- **IDO**
  - Anti-IDO + Anti-PD1/L1 vs Anti-PD1/L1

- **LAG3**
  - Anti-LAG3 + Anti-PD1/L1 vs Anti-PD1/L1
Adaptive/Preemptive IO Dynamic Trial

• Can we individualize each patient’s treatment dynamically?
Conclusions

• PD-1/PD-L1 inhibition is safe and broadly active; serves as the backbone of I/O combination therapy
• There are more rationale combinations than can be feasibly tested
  • Selection of patients and early demonstration of proof of concept
  • How to determine if there is additivity or synergy beyond just objective response rate
• Important to understand the effects of different IO agents on immune cells and TME
• Innovative trial designs and integration of validated predictive and resistance biomarkers are critical to inform the most effective way to deliver IO regimens