Master Protocols for Immunotherapy Combinations

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Disclosures

• Consultant: Bristol Myers Squibb, Merck, Incyte, NewLink Genetics, Novartis, Huya, Regeneron, Array Biopharma

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Stage IV Melanoma: FDA Approvals

1975 Dacarbazine
1998 HD-IL2

2011-2015: 10 approvals

Pre-2011
1-Year OS ~ 25%

2011
Ipilimumab
Vemurafenib

2013
Dabrafenib
Trametinib

2014
Nivolumab
Pembrolizumab

2015
Nivolumab + ipilimumab
T-VEC

**1-Year OS >70%**

Currently Reported Long-term Survival Outcomes for Stage IV Melanoma

KEYNOTE-001 - Overall Survival

Hamid et al. 2018 ASCO Annual Meeting.
Cancer Immune Phenotypes


Zaraour H. Clin Cancer Res; 2016; 22(8).

Coinhibitory & Costimulatory Receptors


Zaraour H. Clin Cancer Res; 2016; 22(8).
Immunotherapy Combination Strategies

- Immunotherapy + Immunotherapy
- Immunotherapy + Targeted therapy
- Immunotherapy + Chemotherapy
- Immunotherapy + Radiotherapy
Challenges Facing I-O Drug Development

- Series of clinical trials, testing 1 or 2 questions at a time in a single disease
- Time
- Cost
- Competing trials
- Unselected patient populations
- Screen failures
- Rare genetic/other subtypes
- Identifying truly predictive biomarkers
Need to Accelerate Cancer I-O Drug Development

- New more efficient strategies are essential that can test more approaches, more efficiently, in less time
- Master Protocols can be a major methodologic innovation over the traditional approach of a series of clinical trials
  - Overall systematic approach to a disease
  - More efficient screening
  - Increasing the speed of drug development and approvals

Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730
Opportunities for Master Protocols for Immunotherapy

• Improved genomic and immunologic understanding of cancers
  – Incorporation of precision medicine approaches
  – Mechanism-based trials
    • Eligibility based on mechanistic criteria (e.g., MSI-H, biomarker signatures, …)
  – Allowing target and agent prioritization

• Timely assessment of safety and clinical activity of multiple agents in parallel or rapid sequences
Opportunities for Master Protocols

• NCI sponsored cooperative groups could play a major role
  – Robust clinical trial infrastructure
  – Allowing multi-sponsor trials
  – Multi-stakeholder decision-making body
Types of Master Protocols

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• Evaluates various subgroups within a conventionally defined disease
  – Subgroups often biomarker-defined
• Patients screened for the presence of a biomarker/other characteristic and assigned a stratum
• Multiple drugs are studied in the various strata
• Design may be randomized or may use external controls

NCI-Match

- Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective
- Advanced solid tumor, lymphoma, myeloma (each, a separate “umbrella” within a “basket”)
- DNA sequencing for actionable mutations
- Multiple treatments that target gene abnormalities
- Exploratory, multicenter, non-comparative
- Endpoints: Tumor response (primary) and PFS
- Size: 35 patients per sub-study

We might envision an anti-PD1/PD-L1 backbone trial in a certain disease (“umbrella”) where patients are screened based on the presence of biomarker(s) (e.g., PD-L1, CD8, MSI-H, mutational burden, other specific markers, …) and allocated to certain strata (combinations)

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Basket Trial

- Involves multiple diseases or histologic features
- Participants screened for the presence of a target & entered
- Could contain multiple strata that test various biomarker–drug pairs
BRAF V600

• Basket trial to evaluate the efficacy of vemurafenib
• Multiple non-melanoma cancers with BRAF V600 mutations
• Phase 2, non-comparative, adaptive trial using Simon 2-stage
• Response rate

ECHO-202 / KEYNOTE-037

- Phase 2 Study
- Exploring efficacy of pembrolizumab and epacadostat
- ORR by modified RECIST v1.1
- Selected solid tumors and DLBCL
- Sample size 25 - 42 subjects

ClinicalTrials.gov: NCT02178722
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Potential Design of a Platform Trial Involving a Single Disease.

- **Platform trial ongoing over time, with no fixed stopping date, and governed by a master protocol that envisions adding and dropping strata.**

- **Other types of adaptive designs are possible, including adaptive randomization, as are the use of other criteria for early stopping.**
I-SPY 2

- Adaptive platform Phase 2 randomized trial
- Locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures
- Biomarkers: hormone-receptor status, HER2 status, and MammaPrint risk score - define eight genetic sub-groups
- Primary endpoint: Pathological complete response

Neoadjuvant Ipilimumab in N1b, 2b, N2c, N3 Melanoma

Advantages of Neoadjuvant Therapy

Clinically,
• Improved clinical outcome

Experimentally,
• Evaluate clinical/radiologic as well as pathologic responses
• Access to tumor & blood before & after
  ➢ Investigation of antitumor mechanisms of action
  ➢ Biomarker studies
Tumor TIL by IHC (N=24): CD8+ T Cells

<table>
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<tr>
<th>TIL</th>
<th>Median Δ (Wk6 – Baseline) with 95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8+ T Cells</td>
<td>19 (4.79,39.25)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Significant increase in cytotoxic CD8+ TIL after Ipi

Tarhini et al. PLOS One 2014
RFS by Baseline Expression Level

KM curves for PFS

Pt.

Tarhini et al. Oncoimmunology 2017
Neoadjuvant Ipi: Circulating MDSC and T-reg by Flow (N=27)

**Summary of most significant changes (%) at week 6**

<table>
<thead>
<tr>
<th></th>
<th>Δ at Wk 6</th>
<th>Sd Dev of Δ at Wk6</th>
<th>P-value</th>
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<tr>
<td><strong>T-Regs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ %</td>
<td>+6.79</td>
<td>9.09</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CD4+CD25hi+CD39+ %</td>
<td>+5.39</td>
<td>8.63</td>
<td>0.001</td>
</tr>
<tr>
<td>CD4+CD25hi+Foxp3+ %</td>
<td>+4.05</td>
<td>8.13</td>
<td>0.02</td>
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**Conclusion:** ↑ in CD4+ T-Cells is mostly accounted for by the ↑ in Tregs

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<tr>
<td><strong>MDSC</strong></td>
<td></td>
<td></td>
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<tr>
<td>% lymphocytes Lin1-/HLA-DR-/CD33+/CD11b+</td>
<td>-0.72</td>
<td>3.19</td>
<td>0.34</td>
</tr>
<tr>
<td>% monocytes HLA-DR+low/CD14+</td>
<td>-12.84</td>
<td>12.06</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% monocytes Lin1-/HLA-DR-/CD33+/CD11b+</td>
<td>-2.99</td>
<td>16.18</td>
<td>0.19</td>
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Greater ↑ in circulating T-reg associate with improved RFS (p=0.034; HR=0.57)

Tarhini et al. PLOS One 2014
**BMS CA028-001: ADaptiVe Biomarker Trial that InformS Evolution of therapy after nivolumab (ADVISE)**

**Primary endpoint:** number of patients with baseline tumor biopsies samples with ≥ 30% tumor content

**Secondary endpoints:** Change from baseline in histopathologic features and biomarker expression patterns; safety

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<th>Biomarker Defined Treatment Selection</th>
<th>nivo + relatlimab (LAG3)</th>
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<tr>
<td></td>
<td>nivo + BMS-96205 (IDO)</td>
</tr>
<tr>
<td></td>
<td>nivo + cabiralizumab (CSF1R)</td>
</tr>
<tr>
<td></td>
<td>nivo + ipilimumab (FOXP3)</td>
</tr>
<tr>
<td></td>
<td>nivo + BMS-986156 (GITR)</td>
</tr>
<tr>
<td></td>
<td>nivo + lirilumab (KIR)</td>
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<tr>
<td></td>
<td>nivo + SBRT</td>
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**Current selection markers:** CD8, PDL1, LAG3, IDO, CSF1R, FoxP3, GITR, NKp46

**Future combination options could be included when appropriate combination safety data + potential IHC assays**

Pre-tx biopsy

NSCLC, MEL, RCC, Gastric, SCCHN, Urothelial

Screen (28 day)

Biomarker Defined Treatment Selection

Treat to PD, Toxicity, or 1 yr

ClinicalTrials.gov Identifier: NCT03335540

*Courtesy of Jason Luke, MD*
Considerations for Master Protocols Clinical Trial Design

- Histology specific (certain tumor type) or histology agnostic (various tumor types)
- Study Endpoints
  - RR (PR, CR), PFS
  - pCR (Neoadjuvant)
- Randomized versus historical controls
Considerations for Master Protocols Clinical Trial Design

- Eligibility Criteria
- Interim Analyses and Stopping Rules
- Biomarker and Enrichment Strategies
  - PD-L1 status
  - Microsatellite instability high (MSI-H)
  - Tumor mutation burden (TMB)
  - Immune related mRNA signatures
- Statistical Analysis Plans
- Registrational Intent
Challenges for Master Protocols in I-O and Potential Disadvantages

- Meaningful short-term study endpoints that may allow adaptive designs
- The right biomarkers that may allow adaptive designs
- Collaborations across competing pharmaceutical companies
- Logistical and Operational Considerations
- Funding & Cost
Epacadostat + Pembrolizumab in Melanoma

**ECHO-202 / KEYNOTE-037**

Treatment-Naive Melanoma Phase 1/2 (n=54)

- Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W
- Other Epacadostat doses + Pembrolizumab 200 mg Q3W

**Phase 3 ECHO-301/KEYNOTE-252**

- **Response, n (%)**
  - Epacadostat + Pembrolizumab (n=354): 121 (34.2%)
  - Placebo + Pembrolizumab (n=352): 111 (31.5%)

- **Progression-Free Survival (RECIST v1.1, BIRC)**
  - E + P: 218 (61.8%)
  - Placebo + P: 219 (62.2%)

- **Overall Survival**
  - E + P: 106 (29.9%)
  - Placebo + P: 96 (27.8%)

What went wrong?

• RR as the primary endpoint
  – ? Central review …

• Single arm/historical control prior to Phase III
  – ? Randomization

• Eligibility / representative population
  – ? Mandating evaluation of low & high risk

• Right dose
  – ? Careful PK/PD

• Biomarker, pCR, …
  – ? Neoadjuvant evaluation
Recommendations

- Unique designs for unique questions
- Study arms that may provide options for “Screen Failures”
- The importance of obtaining tumor tissues in I-O clinical trials to investigate biomarkers & resistance pathways
- Standardized biospecimen acquisition and storage
- Consider neoadjuvant evaluation
- Collaboration & coordination between the pharmaceutical industry, NCI, FDA, academia, community oncology programs
- Taking advantage of NCI sponsored cooperative group infrastructure
- Guidance to community sites to allow broader participation
- Patient & health care provider education
- Reward participation and team work