The State-of-the-Art of PD-1/PD-L1 Development, Clinical Use & Outcomes

Ramy Ibrahim, MD
Chief Medical Officer
Disclosure

- Scientific Advisory Board:
  Arcus
  Harpoon
  ImaginAb
  Immunovaccine
- Honoraria:
  PER
  GLG
Cancer Immunotherapy has Arrived

**SURGERY**
- 1800s
- Limitations

**RADIATION**
- Early 1900s
- Limitations

**CHEMOTHERAPY**
- Late 1940s
- Limitations

**TARGETED DRUGS**
- 2000s
- Limitations

**IMMUNOTHERAPY**
- 2010s
- Benefits

- Durable
- Adaptable
- Targeted
- Synergistic
- Systemic
- Universal
We have made enormous progress with approved drugs, first-in-class treatments and novel treatments.

But none of them are fully curative and many tumors can’t be treated.
So what have we accomplished so far?

✓ Single agent CTLA4:
  ✓ Long term OS benefit in a small subset of patients
  ✓ Durable effect
  ✓ Unique kinetics of response
  ✓ irAEs that are mostly manageable and reversible with the use of toxicity management guidelines
  ✓ No definitive biomarker

✓ Single agent PD(L)1:
  ✓ Approvals based on survival benefit across multiple indications
  ✓ Well established toxicity management guidelines
  ✓ Benefit is no longer limited to “immunogenic” tumor types
  ✓ Molecular based approvals rather than histology: MSI-H tissue agnostic
  ✓ PDL1 expression can inform patient selection in certain settings
  ✓ Unlikely to be the only biomarker. Need a composite biomarker
  ✓ Synergy when combined with standard of care in some settings
So what have we accomplished so far?

✓ Combinations:
  ✓ When combined with right chemotherapy regimen, meaningful clinical benefit was reported (NSCLC)
  ✓ Sequential therapy (Durvalumab Pacific study)
  ✓ CTLA4+PD1 showed higher rate of adverse events in melanoma and risk:benefit is unclear when compared to PD1 monotherapy
  ✓ TMB
  ✓ Many combinations have been investigated in the PD1 resistant population and some results are disappointing

✓ CAR-T:
  ✓ Impressive data in hematological malignancies (CD19)
  ✓ Not ready for prime time in solid tumors
  ✓ New enabling technologies are under development
Ten Years Follow Up: Long-Term Benefit

Only 1 in every 5 treated metastatic melanoma patients

Ipilimumab Analysis: Pooled OS Analysis Including EAP Data (4846 Patients)

Median OS, months (95% CI): 9.5 (9.0-10.0)

3-year OS rate, % (95% CI): 21 (20-22)
PD1 demonstrates superiority over chemotherapy (Melanoma and NSCLC)

Efforts to replace chemotherapy with many studies conducted with IO vs chemotherapy.

Nivolumab FDA approved 2015

1st line pembro FDA approved 2016

Pembrolizumab FDA approved 2015

Atezolizumab FDA approved 2016
Immunotherapy FDA Approvals

10 FDA immunotherapy approval milestones in 6 years

- Anti-CTLA-4 2011
- BiTE 2014
- Anti-PD-1 2014
- Oncolytic Virus 2015
- Anti-PD-L1 2016-17
- CAR-T 2017

Tumor agnostic approval MSI-H
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<th>Event</th>
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<td>First vaccine developed</td>
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<td>Discovery of dendritic cell (Steinman)</td>
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https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.html
By Sep 2017, 163 active agents with 50 in clinical phase

Tang, Shalabi, Lucey-Hubbard; Ann Oncol; 2017
Not just PD1 phenomenon……

2,004 IO agents in development

940 AGENTS ARE IN CLINICAL STAGES, AND 1,064 IN PRECLINICAL OR DISCOVERY PHASES
How to build on the monotherapy successes?
COMBINATION STUDIES
THE LANDSCAPE OF COMBO TRIAL TYPE

COMBINATION WITH OTHER IO AGENTS IS THE MOST COMMON APPROACH

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<th>Combination type</th>
<th>Number of Total Trials</th>
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<td>IO</td>
<td>399</td>
</tr>
<tr>
<td>Targeted</td>
<td>114</td>
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<tr>
<td>Chemotherapy</td>
<td>340</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>169</td>
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<td>92</td>
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<td>86</td>
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<th>Pembrolizumab</th>
<th>Nivolumab</th>
<th>Durvalumab</th>
<th>Atezolizumab</th>
<th>Avelumab</th>
<th>Others</th>
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<tr>
<td>IO</td>
<td>161</td>
<td>73</td>
<td>71</td>
<td>124</td>
<td>32</td>
<td>49</td>
</tr>
<tr>
<td>Targeted</td>
<td>92</td>
<td>31</td>
<td>22</td>
<td>23</td>
<td>4</td>
<td>9</td>
</tr>
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<td>340</td>
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<td>71</td>
<td>33</td>
<td>14</td>
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<td>161</td>
<td>7</td>
<td>17</td>
<td>49</td>
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506 more new PDx trials since Sep 2017

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<tr>
<th>Phase 1</th>
<th>Phase 1/2</th>
<th>Phase 2</th>
<th>Phase 2/3</th>
<th>Phase 3</th>
<th>Phase 4</th>
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<tr>
<td>435</td>
<td>281</td>
<td>619</td>
<td>12</td>
<td>150</td>
<td>5</td>
</tr>
<tr>
<td>542</td>
<td>380</td>
<td>872</td>
<td>16</td>
<td>191</td>
<td>7</td>
</tr>
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10. Phases (group)
- Phase 1
- Phase 1/2
- Phase 2
- Phase 2/3
- Phase 3
- Phase 4

- **1502** active anti-PDx trials as of Sep 2017.
- **2008** active anti-PDx trials as of Jun 2017, 508 new trials.
334 new PDx Combo trials have started in 9 months

1105 combo trials as of Sep 2017

1449 combo trials as of Jun 2018
Synergy: 1+1=3 if we target different IO pathways?

FIGURE: Selected immune checkpoint pathways. Adapted from P. Sharma 2012 ASCO Annual Meeting.
Exploring Combinations for Cancer Treatments

Chemotherapy and/or Radiation + Immunotherapy

1. Release of cancer 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
Sound scientific rational but not the desired clinical outcome: ipilimumab + radiation in castrate resistant prostate cancer
PD(L)1 can be combined or sequenced with Standard of care

Pacific study: unresectable stage III NSCLC durvalumab following chemo-rad

1L NSCLC: Combination with Carboplatin and Pemetrexed (KN021G)

• Approved based on significant improvement in ORR and PFS
• Trend toward OS benefit is emerging despite the high rate of crossover (75%)


Antonia et al, NEJM 2017
Early signal of activity doesn’t always translate to definitive clinical benefit in phase 3

Background: Rationale for Combination and Dosing

ECHO-202 / KEYNOTE-037
- Phase 1: Epacadostat 50, 100, or 300 mg PO BID + Pembrolizumab 200 mg IV Q3W
- MTD of epacadostat not reached
- Phase 2: Epacadostat 100 mg PO BID
  - Phase 1/2 efficacy in treatment-naive melanoma:
    - ORR = 55%
    - Median PFS = 22.8 mo (12.4 mo all melanoma)

Overall Survival

<table>
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<th>Events</th>
<th>Median OS, months (95% CI)</th>
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<tr>
<td>E + P</td>
<td>105 (9.39)</td>
</tr>
<tr>
<td>Placebo + P</td>
<td>99 (7.8)</td>
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HR (95% CI): 1.13 (0.86–1.49)
P = 0.807

ORR = 55%

Median PFS = 22.8 mo (12.4 mo all melanoma)
Is this the best approach for combinations?
Clinical Data Deconvolution is Needed
It is not a matter of generating more data but it is important to learn from existing data.

There is an overwhelming amount of data:

- Pharma and academia
- To make sense of this data and harness it to inform the next generation of trials and therapies, we must develop novel methods to explore and analyze big biological data.

TRIAL DATA

COMBINE WITH OTHER RELEVANT DATASETS (Public data, other published clinical trials)

AUTOMATED PIPELINES

PICI Informatics is building infrastructure to do cloud-based data analytics using pipelines that are rapid and reproducible.

This lets scientists spend less time crunching data, and more time asking questions and discovering treatments.
PICI worked with MSKCC to identify neoantigens predictive of surviving Pancreatic Cancer (PDAC)

(Balachandran et al., Nature 2017)

PICI worked with Stanford to track long-lived clones following engineered T cell therapy in a “super-responder” patient.

(Provisionally accepted, Cancer Discovery)
**PICI Informatics Examples**

**PICI** worked with **UCLA** to show a high response rate to PD-1 blockade in patients with demoplastic melanoma.

(Eroglu et al., Nature 2017)

**PICI** worked with **UCLA & DFCI** on an analysis of colorectal cancer and identified mutations contributing to immune evasion suggesting a path for immunotherapy treatment.

(Grasso et al., Cancer Discovery, 2018)
Non-profit organizations

Role of philanthropic funding
April, 2016: Billionaire tech entrepreneur Sean Parker announced a $250 million donation to establish the Parker Institute for Cancer Immunotherapy to speed research into innovative cancer treatments.
PICI Connects Academia, Industry, Nonprofit
Comprehensive Resources and Tools

- Best and the Brightest Researchers and Ideas
- Centralized IP Infrastructure
- Dedicated IO Research Team
- Clinical Trials Management Team
- Enabling Broad and Specific Collaborations
- Menu of Access to Therapeutics
- Bioinformatics Team: Data Analysis
- Core Research Infrastructure
- Biorepository and Standardized SOPs
A comprehensive organization to accelerate science and research

- Clinical Trials Management
- Bioinformatics
- Technology Development
- Shared Research Tools & Infrastructure
- Strategic Partnerships
- Data Sharing & Collaboration Platform

- Data sharing and centralized IP management
- Access to global pipeline for combination clinical trials
- Involving other nonprofits
- With industry
- Investments in startups and product development

Among PICI academic researchers

- Involving other nonprofits
- With industry
- Access to global pipeline for combination clinical trials
- Data sharing and centralized IP management
- Investments in startups and product development
Single Exploratory Studies with Predefined Drugs and Arms

1,105 PD(L)-1 combos (60% in academia)

- Study 1
- Study 2
- Study 3
- Study 4
- Study 5
- Study 6

Single company, single institute and limited resources

- Inconsistencies
- Uncoordinated
- Duplication
- Inefficient
- Data quality
Where Will We Go From Here?
PICI Clinical Trial Platform 2.0

Multiple companies
Combinations not restricted to one portfolio/pipeline
Combinations based on a strong hypothesis or existing data

Ideas coming from scientists
Multiple institutes to participate
Data monitoring
eCRF library
PICI – IND sponsor

Collaborative Master Protocols
Adaptive Design

Combo 1
Iterative learning

Combo 2
Iterative learning

Combo 3
Iterative learning

Combo 4
IO Master Neoadjuvant Protocol to generate mechanistic data

- **Monotherapy Arm**
- **Combo 1**
- **Combo 2**
- **Combo 3**
- **Combo 4**

**TIME: Trial Start**

- **Diagnostic bx**
- **Surgical resection specimen**

- **Dose 1**
- **Dose 2**
- **Dose 3**

8-12 weeks depending on the indication

MOA data inform future selection

Signal seen ➔ expanded cohort
Developing new technologies
T-Cell Response Predicts Benefit of Immunotherapy “Replacing the Need for a Biopsy with a Scan”

**ImaginAb Disruptive Solution:**
Non-invasive imaging of CD8⁺ T cells to see whether checkpoint inhibitors and other immuno-modulators are working

**Compelling Value Proposition:**
- Track CD8⁺ T cells before, during and after treatment for patient selection and treatment monitoring
- Early detection of response to therapy (weeks vs months)
- Utility in many mono- or combination- immunotherapies
- Expedite the clinical development and market launch of immunotherapy drugs
Patient 1: Lowest Dose Level

\[ ^{89}\text{Zr-DFO-IAB22M2C} \] Patient 1, Malignant Melanoma

~ 2 h  ~ 6 h  ~ 24 h  day 3  day 6
CD8 positive tumor