Defining and Understanding Resistance to Checkpoint Inhibitor Therapy

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Relevant Disclosures

• Consulting Fees: Bristol Myers Squibb, Merck, Marengo, Novartis, Pfizer, Replimune
• Contracted Research: Merck
• Royalties: Up-to-date
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I am a melanoma specialist so much of my content is biases to melanoma study data
**Immune checkpoint inhibitors and US FDA approvals**

<table>
<thead>
<tr>
<th>Year</th>
<th>Drugs</th>
<th>Approvals</th>
<th>Diseases</th>
<th>Combos</th>
<th>Adj/Neo</th>
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<td>4</td>
<td>5</td>
<td>3</td>
<td>2</td>
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</table>
What is the unmet need?

Most patients are not receiving benefit
How do we define resistance?

Non-responder

Primary resistance

Secondary resistance
SITC PD-1 Resistance Taskforce (April 1, 2019; Atlanta GA)

• Who: Immunologists, Clinical Trialists, Industry Members, NCI, FDA

• Aim:
  • Come to consensus about defining resistance to single-agent anti-PD-(L)1 therapy
  • “False-resistance” rate of <5%
  • Could be adopted rapidly into clinical trials evaluating agents/combos in this space

• Chose
  • Three scenarios:
    • Primary resistance
    • Secondary resistance
    • Resistance after treatment discontinuation
SITC PD-1 Resistance Taskforce (April 1, 2019; Atlanta GA)

Workshop Attendees
- AstraZeneca
- Bristol-Myers Squibb
- CytomX Therapeutics
- Genentech
- Merck
- Other Oncology Groups
- Cancer Research Institute
- Parker Institute for Cancer Immunotherapy

Total Workshop Attendees: 36
- Academia = 14
- NCI = 3
- FDA = 6
- Industry = 8
- SITC Staff = 2
- Other Oncology Groups = 2
- SITC PD-1 Resistance Taskforce (April 1, 2019; Atlanta GA)

Leadership
- Harriet Kluger, MD
  Yale School of Medicine
- Hussein Tawbi, MD, PhD
  MD Anderson Cancer Center
May 2021 Combination Immunotherapy Resistance Workshop

- Draft Resistance Definitions Generated
  - Definitions Drafted for Various Combinations
    - IO/IO
    - IO/Chemo
    - IO/Small Molecule (targeted therapy/cytokines)

- Manuscript Development for Combination Resistance Definitions
  - Manuscript Initiation Q2 2021
  - Manuscript Submission to JITC Q2 2022
  - Acceptance of all three manuscripts to JITC late 2022/early 2023
### Defining Resistance to IO combination therapy offers different challenges

<table>
<thead>
<tr>
<th>Resistance phenotype</th>
<th>Drug exposure requirement</th>
<th>Best response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Resistance</strong></td>
<td>8–12 weeks* (2 cycles)</td>
<td>PD SD &lt; 6 months</td>
</tr>
<tr>
<td><strong>Secondary Resistance</strong></td>
<td>&gt;6 months</td>
<td>CR, PR, SD ≥ 6 months</td>
</tr>
<tr>
<td><strong>Neoadjuvant</strong></td>
<td>6+ weeks</td>
<td>&lt;50% tumor death in resection sample</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>6+ weeks</td>
<td>Recurrence on or &lt;12 week after last dose</td>
</tr>
</tbody>
</table>

*Atkins et al. accepted at JITC*
Summary of Resistance Efforts

• Published definitions for single-agent anti-PD-1/PD-L1 and combination therapies – IO/IO, IO/Chemo, IO/targeted therapy
  • Atkins et al. JITC 2023, , Rizvi et al. JITC 2023
• SITC efforts continue – next frontier is to validate the definitions
• Data is emerging about mechanisms of resistance (MOR), but no wide-scale approach has been applied to link MORs to primary or secondary resistance
• Efforts are ongoing to apply definitions of resistance and MORs into clinical trial efforts
Building on Resistance Definitions

Future Questions and Aspects Concerning Immunotherapy Resistance

1) Collecting and analyzing data concerning patients with primary/secondary resistant tumors
2) Linking definitions to mechanisms of resistance
3) Targeting resistance populations with novel therapies
Building on Resistance Definitions

Future Questions and Aspects Concerning Immunotherapy Resistance

1) Collecting and analyzing data concerning patients with primary/secondary resistant tumors

2) Linking definitions to mechanisms of resistance

3) Targeting resistance populations with novel therapies
Proposed MOA of HDAC inhibition as IO

- Entinostat (ENT) is an oral class I-selective histone deacetylase inhibitor
- ENT reduces MDSC and Treg number & function
- ENT induces pro-inflammatory cascade in TME
- ENT enhances antigen presentation
- Additional beneficial effects on Teff & NK cells
- Synergy with anti-PD1 inhibition in preclinical models

Ramalingam et al. AACR 2019
ENCORE-601: Open-Label Study Evaluating ENT + PEMBRO in Patients With Recurrent or Metastatic Melanoma and Prior Progression On or After Anti-PD-1 Therapy

**Inclusion Criteria:**
- Recurrent or metastatic melanoma, measurable by RECIST 1.1
- Prior progression on or after anti-PD-(L)1 treatment
- Prior BRAF treatment if indicated
- ECOG Performance Status < 2
- Willingness to participate in baseline and on-treatment biopsy and blood samples

**Primary Endpoint**
- ORR (irRECIST)

**Secondary Endpoints**
- CBR, PFS, OS, safety & tolerability

53 patients enrolled, last patient enrolled April 2018

Sullivan et al. AACR 2019
ENT plus pembrolizumab is associated with durable responses in patients who previously progressed on anti-PD-1 therapy.

- 10 confirmed responses of 53 treated [19% ORR (95% CI: 9%-32%)]
  - 1 CR, 9 PRs
- Median duration of response: 13 months (range 3-20)
  - 4 responders ongoing
- An additional 9 patients have had SD for >6 months
  - 36% CBR (95% CI: 23%-50%)

Sullivan et al. AACR 2019
Pharmacodynamic effects of pembro plus ENT in melanoma....

1. Consistent reduction in circulating MDSCs
2. Genes whose expression in pre-/on- tumors are most altered are immune-related (RNA seq)
3. Marked change in immune-related gene sets pre/on (Nanostring)
4. Some interesting genes come in terms of those most changed with treatment (Nanostring)
Building on Resistance Definitions

Future Questions and Aspects Concerning Immunotherapy Resistance

1) Collecting and analyzing data concerning patients with primary/secondary resistant tumors

2) Linking definitions to mechanisms of resistance

3) Targeting resistance populations with novel therapies (2)
Cryoablation can augment the immune response
TITLE: A phase II study of core needle biopsy and cryoablation of an enlarging tumor in patients with advanced lung cancer or melanoma receiving post-progression immune checkpoint inhibitor therapy

Patients with lung cancer or melanoma progressing on ICI with:

1) Enlarging tumor amenable to cryo
2) Additional disease per RECIST
3) Eligible for 2 cycles of post-cryo ICI

Objectives:

• To determine the safety and feasibility of cryo in pts receiving post-progression ICI
• To determine the ORR/DCR of cryo/ICI in ICI refractory cases

CT-guided percutaneous needle biopsy to confirm diagnosis, followed by CT-guided percutaneous cryoablation.

Monitor for radiologic response on post-progression immune checkpoint inhibitor therapy.

Monitor for progression-free and overall survival.

N=10, expansion to N=20 based on a 2-stage design.

*Meghan Mooradian, MD
*Florian Fintelmann, MD
Melanoma Cohort

**20 patients screened**

- 2 screen fails
- Lesions regressed prior to cryo (n=1)
  - No evaluable disease post-cryo per TIMC (n=1)

**18 patients treated on protocol**

- One patient enrolled in hospice prior to receiving subsequent ICI and/or scans

**17 patients evaluable**

- **Best response:**
  - PR, n=4
  - SD, n=3
  - PD, n=10

- 67% had primary ICI resistance

**ORR: 24%**

**DCR: 41%**

*Cryoaoclation of a liver lesion
-> Tumor burden ↓ 10%
= Stable disease*

*Cryoaoclation of a lung lesion
-> Tumor burden ↓ 45%
= Partial response*

*Meghan Mooradian, MD*
*Florian Fintelmann, MD*
Concluding thoughts (1)

Immune checkpoint inhibitors and US FDA approvals

Defining resistance is a critical step in developing the next breakthroughs for the ICI-resistant population

<table>
<thead>
<tr>
<th>Resistance Phenotype</th>
<th>Drug Exposure Requirement</th>
<th>Best response</th>
<th>Confirmatory Scan for PD Requirement</th>
<th>Confirmatory Scan Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Resistance</td>
<td>≥ 6 Weeks</td>
<td>PD; SD for &lt; 6 months</td>
<td>Yes</td>
<td>At least 4 weeks after initial disease progression</td>
</tr>
<tr>
<td>Secondary Resistance</td>
<td>≥ 6 Months</td>
<td>CR, PR, SD for &gt; 6 months</td>
<td>Yes</td>
<td>At least 4 weeks after disease progression</td>
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Immune checkpoint inhibitor therapy is changing the way we treat cancer
Concluding thoughts (2)

An better understanding of resistance...

...is leading to promising data in and strategies for the resistant population.
Acknowledgements

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Hussein Tawbi
David Feltquate
Theresa Levallee
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Naiyer Rizvi

SITC Staff
Peter Intile
Christian Miller
Mary Dean

ENCELE-601
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