Building rational combinations in immunotherapy

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Disclosure slide

- Consultant or advisory role: BMS, GSK, Roche, Astex
- Steering committees: Roche, GSK
- Research grants: BMS, Astex
Kaplan-Meier Plot of Overall Survival

- DTIC + 10 mg/kg Ipi
- DTIC + Placebo
- Censored

Proportion Alive

Patients at Risk

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>DTIC + Ipi</th>
<th>DTIC + Placebo</th>
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Maio M, ESMO 2013

26-30 September 2014, Madrid, Spain
Ipilimumab/Nivolumab Combo

Can we design novel combinations/sequences in immunotherapy?

Vemurafenib/Cobimetinib Combo

Medan OS NE
1 year OS 83%, estimated
It takes two to tango
Potential partner agent(s) for novel combinations/sequences in immunotherapy

- Vaccines
- Cytokines
- Tumor microenvironment modulating agents
- Selected chemotherapeutic agents
  - Targeted therapies
  - Hypomethylating agents
## Immunological properties of BRAF/MEK inhibitors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Host?</th>
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<tbody>
<tr>
<td>↑ expression of HLA molecules</td>
<td>↑ circulating anti-tumor T cells</td>
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<tr>
<td>↑ expression of tumor-associated antigens</td>
<td>↓ peripheral lymphocyte counts</td>
</tr>
<tr>
<td>↑ tumor infiltrating lymphocytes</td>
<td>modifications of CD4^+ T cells</td>
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<tr>
<td></td>
<td>phenotype and functions</td>
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<tr>
<td>↓ immunosuppressive cytokines or molecules (e.g., IL-6, IL-8, B7-H1)</td>
<td>↑ maturation and antigen processing functions of DC</td>
</tr>
</tbody>
</table>
Treatment with BRAFi can modulate circulating TAA-specific T lymphocytes
Points to consider

• Long-term efficacy of the combinations of ipilimumab plus nivolumab or BRAFi plus MEKi

• Acquired resistance to BRAF/MEK inhibitors

• Disease progression is often rapid after resistance to BRAF inhibitors develops: about 50% of patients died within 28 days of their last dose of vemurafenib (BRIM-2/-3 data)$^1$

• Preemptively switching to immunotherapy with ipilimumab before the development of resistance to vemurafenib could be a useful strategy in the daily practice$^2$

• Combination vs sequencing

Immuno–Targeted vs Targeted–Immuno sequencing: the NIBIT-M3 Study

Switch at Disease Control

TARGETED THERAPY

IMMUNOTHERAPY

TARGETED THERAPY

IMMUNOTHERAPY

Endpoint: OS/PFS for switchers at Disease Control

W1

W12

W18

W24

W36

W48

Endpoint: OS2/PFS2 for switchers at Progressive Disease

DC

PD

Tumor Assessment
Potential partner agent(s) for novel combinations/sequences in immunotherapy

• Vaccines
• Cytokines
• Tumor microenvironment modulating agents
• Selected chemotherapeutic agents
• Targeted therapies
• Hypomethylating agents
EPIGENETICALLY DOWN-REGULATED

HLA I

Endoplasmic Reticulum

ERp57

ERAAP

tapasin

TAP-1/2

peptides

proteasome

intracellular protein
DNA hypomethylating agents (DHA)

- 1\textsuperscript{st} generation: Zebularine, 5-azacytidine, 5-aza-2’-deoxycytidine
- 2\textsuperscript{nd} generation: SGI-110
Tumor immunomodulatory activity of DHA \textit{in vitro}
Gene expression profiles modulated by DHA in syngeneic murine breast tumor TS/A

Significantly modulated pathways

- Innate immune response (5 genes)
- Defense response to bacterium (5 genes)
- Response to virus (5 genes)
- Antigen processing and presentation (5 genes)
- G-protein coupled receptor protein signaling pathway (6 genes)
- Spermatogenesis (8 genes)
- Signal transduction (12 genes)
- Transport (16 genes)
- Immune response (19 genes)
Gene expression profiles modulated by DHA in activated human PBMC

Significantly modulated pathways

- immune response: 10
- regulation of transcription, DNA-dependent: 8
- negative regulation of cell cycle: 4
- sensory perception of sound: 4
- chemotaxis: 4
- transcription: 7
- 4 genes down-regulated
- 191 genes up-regulated

Cut-off: at least 4 genes per biological process

P≤0.05; FC≥3

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Host immunomodulatory activity of DHA *in vitro*

**HLA class I expression**

**Mixed lymphocyte reaction**
DHA do not impair cellular cytotoxicity

**LAK**

- LAK
- LAK DAC 0.5 uM
- LAK DAC 1 uM
- LAK SG1-110 0.5 uM
- LAK SG1-110 1 uM

**gp100-restricted CTL**

- Hurley vs Mel 275
- Hurley DAC vs Mel 275
- Mel 40
- K562

E/T ratio

Percent of lysis

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Epigenetic immuno-sequencing

HOST

DHA + Anti-CTLA-4 mAb

TUMOR

Modulate Tumor immunogenicity and immune recognition

Extending life and function of activated T cell

COMBOS

DHA

Anti-CTLA-4 mAb

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Antitumor activity of SGI-110 plus α-CTLA-4 mAb in murine TS/A breast tumor

Volume cm³

- CTRL
- SGI-110
- α-CTLA-4
- SGI-110+α-CTLA-4

84%
Tumor CD3 infiltrates

Control

SGI-110

\(\alpha\)-CTLA-4 mAb

SGI-110 + \(\alpha\)-CTLA-4 mAb

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Antitumor activity of SGI-110 plus α-CTLA-4 mAb in TS/A-grafted immunocompromised mice

**Graphs:**

- **Graph 1:** Volume cm³ over Days showing the growth of tumors in athymic nude mice.
  - SGI-110
  - α-CTLA-4 mAb
  - COMBO
- **Graph 2:** Volume cm³ over Days showing the growth of tumors in SCID/Beige mice.
  - SGI-110
  - α-CTLA-4 mAb
  - COMBO
Epigenetic immuno-sequencing: the NIBIT-M4 Study

SGI-110
5 days q21

Anti-CTLA-4
4x q21
Aiming to an even better future with novel combinations