Immune Checkpoint Inhibition in Hematologic Malignancies
- Focusing on Multiple Myeloma

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COI disclosure

Name of author: Yoon Seok Choi

I have no personal or financial interests to declare:

I have no financial support from an industry source at the current presentation.
• **T cell dysfunction** following persistence of (tumor) antigens

**T cell dysfunction in cancer**

- **T cell dysfunction** following persistence of (tumor) antigens


- **T cell rejuvenation after blocking T cell inhibitory receptor/ligand(s).**

Immune checkpoint inhibition

- Clinical success of immune checkpoint inhibitors in selected solid tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Target</th>
<th>Agent(s)</th>
<th>FDA approval</th>
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<td>Melanoma</td>
<td>CTLA-4</td>
<td>Ipilimumab</td>
<td>yes</td>
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<tr>
<td></td>
<td>PD1</td>
<td>Nivolumab</td>
<td>yes</td>
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<tr>
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<td>PD1</td>
<td>Pembrolizumab</td>
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<tr>
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<td>PD-1</td>
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Immune checkpoint inhibition

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- Limited single-agent anti-myeloma efficacy of immune checkpoint inhibitors

# Phase Ib of nivolumab monotherapy

<table>
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<th>Prior systemic therapies</th>
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<tr>
<td>2–3 lines: 12 (44%)</td>
</tr>
<tr>
<td>4–5 lines: 8 (30%)</td>
</tr>
<tr>
<td>≥6 lines: 6 (22%)</td>
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<th>Efficacy</th>
<th>Nivolumab (n=27)</th>
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<td>ORR, n (%)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (4)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>17 (63)</td>
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<td>Median PFS, weeks (95% CI)</td>
<td>10 (5–15)</td>
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Prerequisite for successful immune checkpoint inhibition

- Presence of reactive T cell precursors and tumor antigens
- Tumor-specific T cells with potential to be functionally restored
Prerequisite for successful immune checkpoint inhibition

- Presence of reactive T cell precursors and tumor antigens
- Tumor-specific T cells with potential to be functionally restored

Study objective

- Immunologic characterization of BM T cells (and tumor-specific T cells) in MM patients
- Immunologic reservoir of T cells to be restored by immune checkpoint blockade
T cells in BM of patient with MM

- BM of patients with MM is enriched with CD8\(^+\) T cells, suggesting compartmentalization of BM from peripheral circulation.
Immune checkpoint receptors on BM T cells in MM

- BM contains more PD-1+ and PD-1+TIGIT+ CD8+ T cells, compared to peripheral blood in MM patients.
Immune checkpoint receptors on BM T cells in MM

- Predominance of PD-1$^+$ T cells in myeloma marrow does **not** result from selective trafficking of T cells of specific differentiation stages.

  Predominance of PD-1$^+$ T cells

- Rather, high expression of PD-1 by marrow-infiltrating T cells is attributed to **abundant expression by T_{EM} population per cell basis.**

High expression of PD-1
PD-1 is a major T cell inhibitor receptor in BM of MM patients, when compared to BM of extranodal marginal zone lymphoma of MALT free from lymphoma involvement.
Immune checkpoint receptors on BM T cells in MM

- **Simultaneous** expression of **multiple** inhibitory receptors in CD8⁺ T cells

![Flow cytometry plots showing expression of TIM-3, LAG-3, TIGIT in different subjects.](image)

- **Subject 008**
- **Subject 011**
- **Subject 019**
Checkpoint ligands on malignant plasma cells

- Flow cytometric definition of **malignant plasma cells** in BM of MM patients

  \[
  \text{CD14}^{-}\text{CD19}^{-}\text{CD138}^{+}\text{CD319(CS1)}^{+}\text{CD56}^{\text{hi}}
  \]

- **PD-L1** expression by **malignant plasma cells**

  ![Flow cytometry plots and PD-L1 expression graph](image)
Checkpoint ligands on myeloma microenvironment

- PD-L1 and Galectin-9 expression in myeloma microenvironment
Detection of antigen-specific CD8\(^+\) T cells

CD8\(^+\) T cells recognizing the HLA-A2-restricted epitope “LLLGIGILV”, included in myeloma tumor antigen HM1.24
Characterization of myeloma-specific CD8$^+$ T cells

CD8$^+$ T cells recognizing the HLA-A2-restricted epitope “LLLLGIILV”, included in myeloma tumor antigen HM1.24

Further immunophenotyping
Characterization of myeloma-specific CD8\(^+\) T cells

- HLA-A2 Dextramer
- NY-ESO-1\(^{157-165}\)

- PD-1\(^+\)
- TIM-3\(^+\)
- Lag-3\(^+\)
- TIGIT\(^+\)
Extremely exhausted myeloma-specific T cells

- Myeloma-specific T cells show “extremely” exhausted phenotypes ($\text{EOMES}^{\text{hi}}$), suggesting poor responsiveness to PD-1 blockade.

Extremely exhausted myeloma-specific T cells

- Myeloma-specific T cells show “extremely” exhausted phenotypes (EOMES^{hi}), suggesting poor responsiveness to PD-1 blockade.
Extremely exhausted myeloma-specific T cells

- Myeloma-specific T cells express “multiple” inhibitory receptors, suggesting poor responsiveness to PD-1 single blockade.
Extremely exhausted myeloma-specific T cells

- Myeloma-specific T cells show “extremely” exhausted phenotypes (EOMES\textsuperscript{hi}), suggesting poor responsiveness to PD-1 blockade.
Summary

• **PD-1/PD-L1 axis** acts as a major component of immunosuppressive microenvironment in multiple myeloma.

• The clinical efficacy of blocking immune checkpoint blockades is hampered by (1) **heterogeneity and multiplicity** in expression patterns of T cell inhibitor receptors and (2) **molecular depth** of T cell exhaustion.

• Combination approach might be useful to overcome the refractoriness to PD-1 blockade in multiple myeloma.
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Minsuk Kwon, M.D.
Jeewon Lee, Ph.D.
T cells in BM of patient with MM

- Tissue-resident (CD69⁺CCR7⁻) CD8⁺ T cells are distributed more abundant in BM than in PB of patients with MM.