Immuno-Oncology (I-O) Combinations

- Jeffrey A. Sosman, MD
- Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Presenter Disclosure Information

Jeffrey A. Sosman

- Advisory Boards: BMS, Incyte, Array, Novartis
- Research funding: BMS, Amgen
Overview of Talk

• What’s required for effective Cancer Immunotherapy
• Options for Combination Therapy
  • Examples
    • Vaccines
    • IDOi
    • Anti-LAG-3
    • Adoptive Cell Therapy
• Improving Patient Selection
The Cancer–Immunity Cycle

1. Release of cancer cell 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 (Immune and cancer cells)
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle

Each step of the Cancer-Immunity Cycle requires the coordination of numerous factors, both stimulatory and inhibitory in nature. Stimulatory factors shown in green promote immunity, ...
Where will Improvements come from?

• Combinations:
  – Based on Template: anti-PD-1/PD-L1 or with anti-PD-1/anti-CTLA-4
    • Block other co-inhibitory: LAG3, TIM3, KIR, VISTA
    • Activate co-stimulatory: 4-1BB, OX-40, GITR, CD27, ICOS
    • Block inhibitory molecules- IDOi, TGFbi, CSF1Ri, anti-IL-6 or anti- IL-10
    • Effect trafficking- anti-VEGF, CCL5, CXCR4i
    • Vaccines- TVEC- oncolytic virus, Neoantigen, other cellular
    • Adoptive Cellular therapy- TIL, CAR-T cells, TCR T-cells
Where will Improvements come from?

• Combinations:
  – Based on Template: anti-PD-1/PD-L1 or with anti-PD-1/anti-CTLA-4
    • Signal Inhibition, BRAF directed (BRAFi+MEKi), MEKi, PI3K inhibition (PTEN effects)
    • Cytokines- IL-2, IFN a,b,g,, Directed cytokines (FAP-IL-2v or CEA-IL-2v)
    • Epigenetic modulation- gene expression and EVR expression
    • Microbiome modification- fecal transplants
    • Chemotherapy other cytotoxics
    • Localized Irradiation SBRT, SRS
T cells in Tumors Express Multiple Immunoinhibitory Receptors

These regulate the balance between T cell activation and tolerance and are druggable targets for tumor immunotherapy.

- CD137
- OX40
- GITR
- TIGIT
- CD40
- VISTA
- ICOS
- CD73
  (Adenosine R)
- NKG2D
- IL2v-FAP or CEA-IL-2v
- TCR-CD3
- TLR agonist
- IODi
- CSF1R ab or sm
- CXCR2
- CXCR4
- STAT3i
- PI3Kd
- ANG2
- Anti-VEGF
- TKI
- PI3Kg,d inh
- NeoAg vac
- TVEC
- PARPinh
- Glutaminase inh
- NTRK-14
- Anti-KIR

CAR-T cell
CD19, CD33, BMSA, IL13R
TCR ag spec-transf T cell
TIL

G Freeman and A Sharpe
Nature Immunol 2012; 13:113
T cells can coexpress multiple inhibitory receptors

Co-blockade enables better rescue of exhausted T cells and therapeutic efficacy than blockade of a single inhibitory pathway, but ONLY anti-PD-1 monotherapy has substantial effects.
A dramatic and unprecedented increase in clinical cancer immunotherapy combination studies (across Phase I, II and III trials) has occurred in recent years. The studies in this figure represent many of the current studies that include a PD-L1/PD-1 pathway inhibitor in combination with other immune modulators, targeted therapy, chemotherapy and/or radiation therapy. These studies are designed to characterize the efficacy, safety and biology related to combinability, synergy or antagonism associated with these combinations. Adapted from Vanessa Lucey of the Cancer Research Institute.
Enhancing Efficacy of anti-PD-1/L1

Modified from Ribas, Cancer Discovery 2016
Blocking CTLA-4 and PD-1

**Activation**
(cytokines, lysis, proliferation, migration to tumor)

**CTLA-4 Blockade (ipilimumab)**
- Dendritic cell
  - B7
  - CD28
  - CTLA-4
- T cell
  - MHC
  - TCR

**PD-1 Blockade (nivolumab)**
- T cell
  - MHC
  - TCR
  - PD-1
  - PD-L1
- Tumor cell
  - PD-1
  - PD-L2
  - anti-PD-1

**Tumor Microenvironment**
Overall Survival in All Randomized Melanoma Patients: 067 Ipi+ Nivo vs Nivo vs Ipi

Patients at risk:

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Can PD-L1 IHC Determine Cohort that Benefits from Combination Therapy vs Single agent Therapy?

PD-L1 Expression Level <1%

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- ORR of 54.5% for NIVO+IPI and 35.0% for NIVO

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- ORR of 65.2% for NIVO+IPI and 55.0% for NIVO
Where will Improvements come from?

• Combinations:
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Potential Role of LAG-3 in T-Cell Exhaustion and Anti–PD-1 Resistance

- LAG-3 regulates a checkpoint pathway that limits the activity of T cells\(^1\)
- LAG-3 and PD-1 receptors are overexpressed and/or co-expressed on tumor-infiltrating lymphocytes in melanoma\(^2,3\)

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Nivolumab
Relatlimab (BMS-986016/anti–LAG-3)

Antitumor Activity of Relatlimab (anti-LAG3) + Nivolumab
Change in Tumor Size by LAG-3 Expression

- **Pink**: PD-L1 ≥ 1%
- **Blue**: PD-L1 < 1%
- **Gray**: PD-L1 unknown

![Graphs showing change in tumor size by LAG-3 expression](image)

\[n = 29\]
\[n = 17\]
\[n = 8\]

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<th>LAG-3 ≥ 1%</th>
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<td>45% with tumor reduction</td>
<td>24% with tumor reduction</td>
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\[a\]Six patients with clinical progression prior to their first scan and 1 with PD due to a new symptomatic brain metastasis prior to getting full scans were not included.

\[b\]One patient with best change from baseline > 30% had a best response of SD.
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Rationale for IDO1 Inhibitor Plus Anti–PD-1 Combination Therapy

- IDO1 enzyme inhibits T-cell function through local depletion of tryptophan and production of immunosuppressive kynurenine and downstream metabolites.
- High IDO1 expression is associated with a decrease in immune cell tumor infiltration and an increase in regulatory T cells.
- IDO1 expression in tumors has also been associated with poor prognosis, increased progression, and reduced survival.
- Anti–PD-1 treatment upregulates IDO1 expression in patients.

Adapted from Moon YW et al. *J Immunother Cancer*. 2015;3:51. Published under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).
Recent Results of anti-PD-1 + IDOi

• Phase I/II results from the KEYNOTE-37 trial, the combination Pembrolizumab and Epacadostat induced objective responses in 29 of 53 (55%) treatment-naïve patients, including seven CRs.

• 22 of 38 evaluable patients (58%) responded to the recommended phase II dose of epacadostat (100 mg).

• Median progression-free survival (PFS) of 22.8 months in the treatment-naïve pts, and NR in the patients who received the phase II dose of epacadostat.
Where will Improvements come from?

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Oncolytic Virus Injection Promotes Intratumoral T Cell Infiltration to Improve Anti-PD-1 Immunotherapy

Ribas et al, CELL 2017
Talimogene Laherparepvec Increases Tumor-Infiltrating Lymphocyte Density and PD-L1 Expression in Tumors

Ribas et al., CELL 2017
Where will Improvements come from?

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Cancer exome–based identification of neoantigens.
A pathway for generating autologous TCR gene therapies targeting neoantigens for patients with advanced epithelial cancers.
Summary

• What’s required for effective Cancer Immunotherapy
• Combination Therapy –
  – Underway in full gear
  – Rationale for many combinations- selection
    • IDOi
    • Anti-LAG-3
    • Vaccines
    • Adoptive Cell Therapy
• Improving Patient Selection
  • Biomarker Development- **Too many**- how to simplify
  • Use to select the most effective
  • Use to select the least toxic
Cancer-immune phenotypes.
• All inter-related
• Some tumors may have a larger sweet spot
CD8+T cell Density within the Tumor and at Invasive Margin Importance
Somatic mutations by tumor type

MS Lawrence et al. Nature 2013
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Hypothesis: PD-1 Blockade works in patients with most “mutated” / “immunogenic” cancers.

This data supports hypothesis
T cell-inflamed tumor microenvironment by tumor type in increasing frequency

No correlation observed between mutational load and increasing T cell gene signature

Presented By Jason Luke at 2016 ASCO Annual Meeting
Expanded Gene Signatures Identified During Discovery Analysis Reveal Biology of Complex Immune Synapse

Discovery analysis of entire NanoString melanoma data set led to identification of new genes:

- **IFNγ signaling**
- MHC class I and II antigen presentation machinery
- T-cell activation markers

![Diagram of immune synapse with genes and proteins labeled](image-url)
Signature Expanded in Validation Set (While Blinded to Clinical Outcome)

Melanoma Discovery Set
19 Patients

Melanoma Validation Set
62 Patients Independent Data Set

IL2Rg
CXCR6
CD3d
CD2
ITGAL
TAGAP
CIITA
HLA-DRA
PTPRC
CXCL9
CCL5
NKG7
GZMA
PRF1
CCR5
CD3e
GZMK
IFNγ
HLA-E
GZMB
PDCD1
SLAMF6
CXCL13
CXCL10
IDO1
LAG3
STAT1
CXCL11

“Preliminary Expanded Immune” (28-gene) signature: coherent set correlated with the 10-gene “Preliminary IFNγ” signature genes (in red)

Correlation Matrix of Top Significant Genes in the Discovery Set Evaluated in the Validation Set

19 Patients
Melanoma
Discovery Set

62 Patients
Independent
Data Set

Melanoma
Validation Set

Preliminary Expanded Immune (28-gene) signature: coherent set correlated with the 10-gene “Preliminary IFNγ” signature genes (in red)
Overall Survival in All Randomized Patients:
067 Ipi+ Nivo vs Nivo vs Ipi

Overall Survival (%) vs Months:

- NIVO+IPI
- NIVO
- IPI

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Can PD-L1 IHC Determine Cohort that Benefits from Combination Therapy vs Single Agent Therapy?

PD-L1 expression level $\geq 1\%$

PD-L1 expression level $< 1\%$
Outcomes Observed at a 1% Cutoff

PD-L1 Expression Level <1%

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NIVO 117 103 86 76 73 65 62 59 57 55 50 16 2 0
IPI 113 96 87 79 71 61 57 50 44 43 32 10 1 0

NIVO+IPI 155 144 132 127 116 112 105 102 101 99 85 27 3 0
NIVO 171 165 158 148 139 131 122 117 112 109 98 36 1 0
IPI 164 155 138 126 115 102 89 83 77 74 64 21 2 0
Presented by: Alexandra Snyder, M.D.

- **PD-L1**
- **ICOS**
- **Tumor Type**
- **Intratumoral FOXP3 & IDO**
- **Microbiota**
- **IL-17 CD4+ cells**
- **Intratumoral CD8+/FOXP3+**
- **Treg**
- **TCR Clonality**
- **Mutation Burden**
- **NY-ESO-1**
- **Absolute lymphocyte count**
- **“Inflamed” microenvironment**
- **Prior Therapies?**
- **MDSC**
- **CD45RO**


**Mellman et al. Nature 2011**
Presented by: Alexandra Snyder, M.D.
Tumor Interactions to Suppress the Immune System

- **T_{h2} cell**
  - IL-4
  - IL-10
  - IL-10_{hi}
  - IL-12_{low}
  - EGF

- **T_{Reg} cell**
  - IL-10
  - IL-10_{hi}
  - IFN\(^\beta\)
  - CCL5
  - IL-10_{low}
  - CD68

- **B cell**
  - IL-10
  - IL-10_{hi}
  - IL-1\beta
  - IL-12_{low}
  - CCL5
  - IL-10_{low}
  - CD68

- **Hypoxia**
  - TNF\^\text{•},
  - PGE\(_2\)^{•}
  - COX\(_2\)^{•}
  - IL-23

- **Inflammation**
  - CCL2
  - plasminogen

- **MDSC**
  - IL-10_{low}

- **Tumour**
  - S100A8
  - S100A9

- **TGF\(\beta\)**
  - PGE\(_2\)
  - COX\(_2\)
  - TGF\(\beta\)

**Resulting TAM phenotype**
- IL-10_{hi}
- IL-12_{low}
- EGF

**Tumour-associated macrophage (TAM)**
- IL-6
- CD1\(\text{d}\)^{•}
- CD11b^{•}
- F-4/80^{•}
- FIZZ1^{•}
- IL-4\(\alpha\)^{•}
- YM1^{•}
- IL-10_{hi}
- CD68^{•}
- TGF\(\beta\)^{•}
Overcome Tumor -Induced Immune Suppression
The Barriers

- Cell Populations
- Soluble Factors
- Immune checkpoints
- Loss of Tumor Antigens
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<td>pembrolizumab + durvalumab</td>
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