Cancer Immunotherapy – Where We Are and Where We’re Heading

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Faculty Disclosure

• Osama Rahma declares no existence of a financial interest in any amount related to the content of this activity.

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

1. Recognize the current status of immune checkpoint inhibitor (ICI) indications
2. Identify trends for the next wave of ICIs including bi-specific antibodies and adaptive T-cell therapy in solid tumors
3. Recognize the toxicities of these novel immunotherapy approaches
History of Cancer Immunotherapy: Key Milestones

IFN-α as adjuvant for melanoma

Immune component to spontaneous regressions in melanoma

Adoptive T-cell immunotherapy

IL-2 approved for RCC & melanoma

First tumor-associated antigen cloned (MAGE-1)

BCG approved for bladder cancer

Discovery of dendritic cell

Tumor-specific monoclonal Abs

Discovery of checkpoint inhibitors

IFN-α as adjuvant for melanoma

Pembrolizumab & nivolumab approved for melanoma

First IO approved for prostate cancer (sipuleucel-T)

Nivolumab approved for RCC

Nivolumab approved for HL

Pembrolizumab approved for NSCLC

Pembrolizumab approved for PD-L1+ NSCLC

Nivolumab approved for RCC

Nivolumab approved for HL

Pembrolizumab for PD-L1+ gastric

Pembrolizumab for HNSCC

Nivolumab for HCC

Antibodies, vaccines, cytokines

Immune Checkpoint Inhibitors

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History of Cancer Immunotherapy: Key Milestones

- **1970s**: IFN-α as adjuvant for melanoma
- **1980s**: BCG approved for bladder cancer
- **1990s**: Adoptive T-cell immunotherapy
- **2000s**: First tumor-associated antigen cloned (MAGE-1)
- **2011**: Pembrolizumab & nivolumab approved for melanoma
- **2014**: First IO approved for prostate cancer (sipuleucel-T)
- **2015**: First CTLA-4 (ipilimumab) approved for melanoma
- **2016**: First tumor-associated antigen cloned (MAGE-1)
- **2017**: BCG approved for bladder cancer
- **2018**: Pembrolizumab and nivolumab approved for HNSCC

Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Name</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTLa-4</td>
<td>Ipilimumab</td>
<td>3mg/kg IV over 90min q3 weeks</td>
<td>Melanoma</td>
</tr>
<tr>
<td>PD-1</td>
<td>Pembrolizumab</td>
<td>200 mg IV over 30 min q3weeks</td>
<td>Melanoma, NSCLC, Hodgkin Lymphoma, Head and Neck CA, Urothelial CA, MSI-H/dMMR CA, Gastric CA</td>
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<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>240 mg IV over 30 min q2week or 480 mg IV over 30 min q4weeks*</td>
<td>Melanoma, NSCLC, Renal cell CA, Hodgkin Lymphoma, Head and Neck CA, Urothelial CA, MSI-H/dMMR Colorectal CA, Hepatocellular CA</td>
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<tr>
<td>PD-L1</td>
<td>Atezolizumab</td>
<td>1200 mg IV over 60 min q4weeks</td>
<td>NSCLC, Urothelial CA</td>
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<tr>
<td>PD-L1</td>
<td>Avelumab</td>
<td>10 mg/kg IV over 60 min q4weeks</td>
<td>Merkel Cell, Urothelial CA</td>
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<tr>
<td>PD-L1</td>
<td>Durvalumab</td>
<td>10 mg/kg IV over 60 min q4weeks</td>
<td>NSCLC, Urothelial CA</td>
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</tbody>
</table>
Immune Checkpoints Resistance

Cancer antigen presentation
- TNF-α
- IL-10
- IFN-α
- IL-13
- CD40L/CD40
- CD4
- ATP
- HMGB1
- TLR

Release of cancer cell antigens
- Immunogenic cell death
- Tolerogenic cell death

Primers and activators
- CD28/B7.1
- CD137/CD137L
- OX40/OX40L
- CD27/CD70
- HVEM
- GITR
- IL-2
- IL-12
- CTLA-4/B7.1
- PD-L1/PD-1
- PD-L1/B7.1
- prostaglandins

Stimulatory factors

Inhibitors
Immune Checkpoints Resistance

**Cancer antigen presentation**
- TNF-α
- IL-1
- IFN-α
- CD40L/CD40
- CD31  
- ATP
- HMGB1
- TLR

**Stimulatory factors**
- CX3CL1
- CXCL10
- CXCL9
- CCL5

**Inhibitors**
- CTCLL
- CXCL10
- CCL2

**Release of cancer cell antigens**
- Immunogenic cell death
- Tolerogenic cell death

**Priming and activation**
- CD28/B7.1
- CD137/CD137L
- CD40/CD40L
- CD40L/CD40
- HVEM
- GITR
- IL-2
- IL-12
- CTLA-4/BD1
- PD-L1/PD-1
- PD-L1/B7.1
- prostanoids

**Trafficking of T-cells to tumors**
- CX3CL1
- CXCL10
- CXCL9
- CCL5

**Immunogenic cell death**
- LFA1/ICAM1
- Selectins
- VEGF
- Endothelin B receptor

**Release of cancer cell antigens**
- Immunogenic cell death
- Tolerogenic cell death


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T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions

- T-cell response to antigen is mediated by peptide-MHCs recognized specifically by TCR (first signal)
- B7 family of membrane-bound ligands binds both activating and inhibitory receptors (second costimulatory signal)
- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus

T-Cell Antigen-Presenting Cell

- MHC class I or II
- Peptide
- CD137L
- OX40L
- CD70
- CD40L
- GAL9
- TIM3
- Adenosine

T-Cell

- PD-L2
- PD-L1
- CD80 or CD86
- CD80 or CD86
- B7RP1
- B7-H3
- B7-H4
- HVEM
- CD137
- OX40
- CD70
- CD40
- GAL9
- Adenosine

Costimulatory receptors

- CD28
- CTLA-4
- ICOS
- BTLA
- KIR
- CD137
- TIM3

Inhibitory receptors

- PD-1
- TIM-3
- LAG-3
- A2aR

- TCR
- LAG3
- A2aR

- Cytokines (TGF-β, IL-1, IL-6, IL-10, IL-12, IL-18)
T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions

- T-cell response to antigen is mediated by peptide-MHCs recognized specifically by TCR (first signal)
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T-Cell Regulation via Multiple Costimulatory and Inhibitory Interactions

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- Targeting CTLA-4 and PD-1 inhibitory receptors has been a major clinical focus
Anti–PD-1 Antibodies

ORR
- Melanoma: 28%
- NSCLC: 18%
- Renal cell cancer: 27%

Confirmed ORR
- Melanoma: 38% (comparable ± previous ipilimumab)

Nivolumab + Ipilimumab vs Nivolumab vs. Ipilimumab in Melanoma

PFS (Intent-to-Treat)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NIVO + IPI (N=371)</th>
<th>NIVO (N=356)</th>
<th>IPI (N=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>(1.6–16.1)</td>
<td>(6.9–16.1)</td>
<td>(3.9–16.4)</td>
</tr>
<tr>
<td>HR (95% CI) vs. IPI</td>
<td>0.42</td>
<td>0.52</td>
<td>0.73</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.66 (0.36)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Log-rank P=0.0001 vs. IPI

**Exploratory endpoint

ICI Expansion Beyond Melanoma

- Pembrolizumab
- Nivolumab
- Atezolizumab
- Avelumab
- Durvalumab
- Durvalumab + platinum doublet
- Durvalumab + tremelimumab
- Pembrolizumab + ipilimumab
- Nivolumab + ipilimumab

* MSI high tumors only; **1–49% tumor cells PD-L1+; *** ≥50% tumor cells PD-L1+
Biomarkers to Determine Response

PD-L1 on Tumor or Immune Cells
Biomarkers to Determine Response

PD-L1 on Tumor or Immune Cells

TMB

Biomarkers to Determine Response

PD-L1 on Tumor or Immune Cells

TMB

CD8 (TILs)
**PD-L1 as Biomarker**

Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes in the nivolumab phase I trial

![Graph showing PD-L1 expression](image)

49 patients: 20 with melanoma, 13 NSCLC, 7 colon, 6 kidney, and 3 prostate cancer.


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**Mutational Load in Cancer**

![Graph showing mutational load](image)

FDA Approved Pembrolizumab for TMB > 10

* LB Alexandrov et al. Nature 2013

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Pembrolizumab in MSI high CRC

- Mismatch repair–proficient colorectal cancer
- Mismatch repair–deficient colorectal cancer
- Mismatch repair–deficient noncolorectal cancer

- Progressive metastatic carcinoma ± mismatch repair deficiency (N = 41)
- ORR: 40% for MSI high CRC, 0% for MSS CRC
- Median PFS and OS: NR for MSI high CRC

Immune Gene Signature as Predictor for Response

T-cell–Inflamed GEP Score by Response (n = 144)

T-cell–inflamed GEP score significantly associated (P = 0.014) with improved response to pembrolizumab
**PD-1 Resistance (Melanoma)**

- **PD-1 THERAPY**
  - Primary resistance 30%
  - Response 60%
  - Secondary resistance 10%

  - Ribas et al, JAMA. 2016 Apr 19; 315(15):1600-9

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**Resistance to Anti–PD-1 Antibodies**

- **ORR**
  - Melanoma: 28%
  - NSCLC: 18%
  - Renal cell cancer: 27%

- **Confirmed ORR**
  - Melanoma: 38% (comparable ± previous ipilimumab)

- Nivolumab
  - First occurrence of new lesion
  - Pt off study

- Pembrolizumab
  - Prior ipilimumab treatment
  - No prior ipilimumab treatment

Resistant to Anti–PD-1 Antibodies

- **ORR**
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Immune Checkpoints Resistance

- **Priming and activation**
  - CD28/CD80, CD137/CD137L
  - OX40/OX40L, CD27/CD70
  - GITR
  - IL-3, IL-12
  - CTLA-4/B7.1, PD-L1/PD-1, PD-L1/B7.1
  - prostaglandins

- **Cancer antigen presentation**
  - TNF-α, IL-10
  - IFN-α, IL-13
  - CD40/CD40L
  - G2M, IL-15
  - HMGB1

- **Stimulatory factors**
  - CXCL1, CXCL10, CXCL9
  - IFN-γ
  - T-cell granule content
  - PD-L1/PD-1, LAG-3

- **Inhibitors**
  - CTLA-4/B7.1
  - PD-L1/B7.1
  - prostaglandins

- **Trafﬁcking of T-cells to tumors**
  - LFA-1/ICAM1
  - Selectins
  - VEGF
  - Endothelin B receptor

- **Recognition of cancer cells by T-cells**
  - T-cell receptor
  - Reduced pMHC on cancer cells

- **Killing of cancer cells**
  - IFN-γ
  - T-cell granule content
  - PD-L1/PD-1, LAG-3
  - IDO
  - MICA/MICB
  - TGF-β
  - B7-H4
  - BTLA
  - TIM-3/phospholipids

- **Release of cancer cell antigens**
  - Immunogenic cell death
  - Tolerogenic cell death

- **Inﬁltration of T-cells into tumors**
  - LFA-1/ICAM1
  - Selectins
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  - B7-H4
  - BTLA
  - TIM-3/phospholipids

Immune Checkpoints Resistance

- **Stimulatory factors**
  - IFN-γ
  - IL-2
  - IL-4
  - IL-15

- **Inhibitors**
  - PD-L1/PD-1
  - PD-L1/B7.1
  - Arginase
  - IDO
  - MICA/MICB
  - TGF-β
  - BTLA/TIM-3
  - 3-phospholipids

- **Cancer antigen presentation**
  - TNF-α
  - IL-10
  - IL-1
  - IL-4
  - IFN-α
  - IL-13
  - CD40L/CD40
  - CDN
  - ATP
  - HMGB1
  - TLR

- ** Killing of cancer cells**
  - IFN-γ
  - T-cell granule content
  - PD-L1/PD-1
  - PD-L1/B7.1
  - Arginase
  - IDO
  - MICA/MICB
  - TGF-β
  - B7-H4
  - BTLA/TIM-3
  - 3-phospholipids
  - VISTA

- **Trafficking of T-cells to tumors**
  - CX3CL1
  - CXCL10
  - CXCL19
  - CCL5

- **Infiltration of T-cells into tumors**
  - LFA1/ICAM1
  - Selectins
  - Endothelin B receptor

- **Recognition of cancer cells by T-cells**
  - T-cell receptor
  - Reduced pMHC on cancer cells

- **Release of cancer cell antigens**
  - Immunogenic cell death
  - Tolerogenic cell death
  - No TILs
  - Or Loss of Neoantigens

- **Defects in INF-Ɣ & antigen presentation**
  - JAK 1-2, B2M

- **Priming and activation**
  - CD28/CD71
  - CD137/CD137L
  - OX40/OX40L
  - CD27/CD70
  - HVEM
  - GITR
  - IL-2
  - IL-12
  - CTLA4/B7.1
  - PD-L1/PD-1
  - PD-L1/B7.1
  - prostaglandins

- **Recognition of cancer cells by T-cells**
  - T-cell receptor
  - Reduced pMHC on cancer cells

- **No TILs or Loss of Neoantigens**
Tumor Immune Classification

1. Release of cancer cell
2. Inflamed
3. Recognition of cancer cells by T-cells
4. Infiltration of T-cells into tumors
5. Infiltration of T-cells to tumors
6. Killing of cancer cells
7. Recognition of cancer cells by T-cells
8. Priming and activation
9. Trafficking of T-cells to tumors
10. Cancer antigen presentation

Overcoming Immune Resistance

1. Cancer antigen presentation
2. Priming and activation
3. Immune Desert
4. Blood vessel
5. Lymph node
6. Tumor
7. Release of cancer cell

Overcoming Immune Resistance

1. Cancer antigen presentation
2. Priming and activation
3. Immune Desert
4. Blood vessel
5. Lymph node
6. Tumor
7. Radiation
8. Release of cancer cell
Overcoming Immune Resistance

Cancer antigen presentation
Release of cancer cell

Immune Desert
Radiation
Chemo
Oncolytic Viruses

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Chemo+Pembro in NSCLC Better than Chemo


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Chemo+Pembro in TNBC Better Than Chemo Only in PD-L1+


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CRT+anti-PD-1 in Panc Cancer

Pembrolizumab

Neoadjuvant
Capcitabine-based Chemoradiation

Post-operative Recovery

Adjuvant
Gemcitabine

OR

Staging CT/MRI

Restaging CT/MRI

Follow-up CT/MRI

ON FOLLOW-UP

CD8

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CRT+anti-PD-1 in Panc Cancer

- Pembrolizumab

- Neoadjuvant
  - Capecitabine-based Chemoradiation

- Post-operative Recovery

- Adjuvant
  - Gemcitabine

- OR

- Staging CT/MRI
- Restaging CT/MRI
- Follow-up CT/MRI

- ON FOLLOW-UP

- Gemcitabine

- ON FOLLOW-UP

CD8

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Overcoming Immune Resistance

[Diagram showing the trafficking of T-cells to tumors and immune exclusion with a focus on anti-angiogenesis.]
Overcoming Immune Resistance

Trafficking of T-cells to tumors

Immune Exclusion

Anti-Angiogenesis

Targeting co-inhibitory molecules

Bi-specific Antibodies

Overcoming Immune Resistance

 Trafficking of T-cells to tumors

 Lymph node

 Blood vessel

 Tumor

 Anti-Angiogenesis

 Immune Exclusion


 Angiogenesis and Immune Regulation

 VEGF → inhibits dendritic cell maturation and
 → Inhibits antigen presentation
 → Inhibits tumor infiltration by lymphocytes
 → Promotes regulatory T cell (Treg) and MDSCs

 Rahma et al, CCR, 2019
The Predictive and Prognostic Value of ANGPT2 for Immune Checkpoint

Pembrolizumab (anti-PD-1) and AMG386 (angiopoietin-2 (Ang-2) peptibody in Patients with Advanced Solid Tumor
Pembrolizumab (anti-PD-1) and AMG386 (angiopoietin-2 (Ang-2) peptibody in Patients with Advanced Solid Tumor

- RR 13% (2 PR response for 24+ months)
- DCR 40%, with 4 stable disease
- Median PFS 3.1 months
- Median OS 8.5 months

Patient# 5

- Feb 2014: Dx met mod diff rectal CA to liver
- MSS, RAS/BRAF WT, Her-2+ (IHC)
- March 2014: FOLFOX/Avastin with Vitamin D with response
- Sept 2015: Rt hepatectomy and partial left hepatectomy.
- February 2016: Supraclavicular biopsy showed recurrent colonic adenocarcinoma
- February 2016: FOLFIRI/Cetuximab
- August 2017: PD in his retroperitoneum.
- Sept-Nov 2017 FOLFOX/Avastin with PD
- November 2017: He started the phase 1 trial of pembrolizumab and trebananib with PR
- Feb 2018: Last dose pembro per protocol
Patient # 15

- May 2015 MSS met mucinous CRC to liver KRAS mutated
- June-Nov 2015- FOLFOX6
- Dec 2015 Y90 TARE to the R hepatic artery
- Jan 2016 Y90 TARE to the L hepatic artery
- April 2016 PET CT showed new FDG avid metastatic disease mesentery
- May- Sept 2016 Capecitabine
- Oct 2016- March 2018 FOLFIRI + Avastin
- April 2018-2020 Pembro+Trebananib with PR
- On pembro off trial

Overcoming Immune Resistance

Overcoming Immune Resistance


PD-1 Adaptive Resistance Associated with Upregulation of Co-Inhibitory Molecules

PD-1 Adaptive Resistance Associated with Upregulation of Co-Inhibitory Molecules

Antigen-Presenting Cell → T-Cell

- PD-L2 → ?
- PD-L1 → PD-1
- CD80 or CD86 → CD28
- CD80 or CD86 → CTLA-4
- B7RP1 → ICOS
- B7-H3 → ?
- B7-H4 → ?
- HVEM → BTLA

Peptide → KIR

MHC class I or II → CD137L, OX40L, CD70, CD40, GAL9, Adenosine

Cytokines (TGF-β, IL-1, IL-6, IL-10, IL-12, IL-18)

PD-1, CD28, CTLA-4, ICOS, CD80

KIR, TCR, LAG3

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PD-1 Adaptive Resistance Associated with Upregulation of Co-Inhibitory Molecules

Antigen-Presenting Cell

- PD-L2
- PD-L1
- CD80 or CD86
- CD80 or CD86
- B7RP1
- B7-H3
- B7-H4
- HVEM

Peptide

- MHC class I or II

T-Cell

- PD-1
- PD-1
- CD28
- CTLA-4
- ICOS
- ?
- ?
- ?

CD137L
- CD137

CD40L
- CD40
- CD27
- CD40L

B7-H3
- B7-H4

HLA-A, HLA-B, HLA-C

BTLA

KIR

TIRAP

CTLA-4

PD-1

BTLA

TIM-3

VISTA

LAG-3

CTLA-4

PD-1

Tim-3

BTLA

VISTA

LAG-3

TCR

LAG-3

Ongoing Combinations

- Chemotherapy
- Radiotherapy
- Targeted Therapy
- Immunotherapy
Bi-specific Antibodies Targeting CD3-CEA

- Bivalent binder to human CEA (avidity 0.2 nM)
- Human specific, not cross-reactive to Cynomolgus monkey CEA
- High affinity/bivalency favors tumor targeting & retention
- Monovalent binding to CD3 epsilon chain (affinity 80 nM)
- Cross-reactive to human and Cynomolgus monkey CD3ε
- No T-cell activation without simultaneous binding to CEA
- Functionally inert Fc-part
- Extended half-life

CEA = carcinoembryonic antigen; Fc = Fc portion of IgG.

Overcoming Immune Resistance

Overcoming Immune Resistance

CAR-T Solid Tumors


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Akce et al, Front. Immunol, 2018

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Challenges of CAR-T in Solid Tumors

Strategies to improve efficacy of CAR-T
Immune-Related AEs (irAEs): Mechanism of Action

- “Achilles heel” of checkpoint inhibitors: autoimmunity via irAEs
- Unique toxicities of immunomodulators caused by dysregulation of the host immune system, similar to autoimmune disease

Blockade of CTLA-4

- T-cell activation and proliferation
- Autoimmunity
- Antitumor responses (de novo memory based)


irAEs With Immunotherapy

If not vigilant, may result in more serious immune-related AEs
## Ipilimumab (Anti–CTLA-4): Suspected irAEs in Pts With Melanoma

<table>
<thead>
<tr>
<th>irAE, %</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
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<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>24.4</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Rash</td>
<td>19.1</td>
<td>0.8</td>
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<tr>
<td>Vitiligo</td>
<td>2.3</td>
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<td>0</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>27.5</td>
<td>4.6</td>
<td>0</td>
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<tr>
<td>Colitis</td>
<td>7.6</td>
<td>5.3</td>
<td>0</td>
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<tr>
<td><strong>Endocrine</strong></td>
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<tr>
<td>Hypothyroidism</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Hypopituitarism</td>
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<tr>
<td>Hypophysitis</td>
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<td>1.5</td>
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<tr>
<td>Adrenal insufficiency</td>
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<tr>
<td>Increase in ALT</td>
<td>1.5</td>
<td>0</td>
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<td>Colitis</td>
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<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>2.3</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1.5</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in ALT</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0.8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Kinetics of Appearance of Immune-Related AEs with Ipilimumab

Rash, pruritus (3%)
Liver toxicity (7%)
Diarrhea, colitis (12%)
Endocrine (3%)

Combined analysis of 325 participants with 10 mg/kg IV Q3W x 4

Nivolumab (Anti–PD-1): Suspected irAEs in Pts with Melanoma

• n = 206 pts with malignant melanoma and wild-type BRAF

<table>
<thead>
<tr>
<th>Suspected irAE, %</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>ALT increase</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>Bilirubin increase</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Renal</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

# Nivolumab (Anti–PD-1): Suspected irAEs in Pts with Melanoma

- **n = 206 pts with malignant melanoma and wild-type BRAF**

## Suspected irAE, %

<table>
<thead>
<tr>
<th>Suspected irAE, %</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increase</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Bilirubin increase</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>1.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

## Suspected irAE, %

<table>
<thead>
<tr>
<th>Suspected irAE, %</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>37.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Rash</td>
<td>17</td>
<td>0.5</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>15</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17</td>
<td>1.5</td>
</tr>
<tr>
<td>Colitis</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4.4</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>3.4</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune Diabetes mellitus</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>7.3</td>
<td>1</td>
</tr>
</tbody>
</table>


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Time to Onset of First Treatment-Related Select AE With Nivolumab (Any Grade)

Majority of treatment-related AEs occurred within first 3 mos of treatment

<table>
<thead>
<tr>
<th>Mos</th>
<th>Skin</th>
<th>Gastrointestinal</th>
<th>Pulmonary</th>
<th>Endocrine</th>
<th>Renal</th>
<th>Hypersensitivity/infusion reaction</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 3-6</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6-12</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 12-24</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Pts still on study, n

131

Pts still on treatment, n

131

Total pts with first event, n

24

Number of Pts With First Event in Category

Pts (%)

131

112

85

52

73

51

25

6

2

1

95

Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition

Distribution of Grade 1/2 Immune-Related AEs

Distribution of Grade 3-5 Immune-Related AEs

## Combination Immunotherapy: irAEs

<table>
<thead>
<tr>
<th>Treatment-Related AEs, %</th>
<th>Ipilimumab + Nivolumab (n = 94)</th>
<th>Ipilimumab + Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any tx-related AE</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Immune-related AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Dermatologic</td>
<td>71.3</td>
<td>9.6</td>
</tr>
<tr>
<td>▪ Gastrointestinal</td>
<td>51.0</td>
<td>21.3</td>
</tr>
<tr>
<td>▪ Endocrine</td>
<td>34.0</td>
<td>5.3</td>
</tr>
<tr>
<td>▪ Hepatic</td>
<td>27.7</td>
<td>14.9</td>
</tr>
<tr>
<td>▪ Pulmonary</td>
<td>11.7</td>
<td>2.1</td>
</tr>
<tr>
<td>▪ Renal</td>
<td>3.2</td>
<td>1.1</td>
</tr>
</tbody>
</table>

IrAE Management

- Vast majority of irAE can be managed effectively if recognized and addressed early
  - Trained teams of oncologists, nurses and pharmacists
  - Education of oncology providers
  - Laboratory testing in all patients to ascertain structured assessment
  - Early involvement of multidisciplinary teams with disease specialists

General Management

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contine ICPI</td>
<td>Suspend ICPI</td>
<td>Suspend ICPI, Start high-dose corticosteroids (Pred or MethylPred 1-2 mg/kg; taper over 4-6 weeks)</td>
<td>Discontinue therapy</td>
</tr>
<tr>
<td>Monitor for symptoms every 2-3 days</td>
<td>Consider restarting when grade I Corticosteroids may be started (Pred or MethylPred 0.5 mg/kg)</td>
<td>Additional immune suppression for refractory patients</td>
<td>Hospitalize</td>
</tr>
</tbody>
</table>

ICPI, immune checkpoint inhibitor; MethylPred, methylprednisolone; Pred, prednisolone

Key Takeaways

• Immunotherapy is breakthrough in cancer treatment
• There is no standard biomarker to determine response to immunotherapy
• However, PD-L1, TILs, mutational load have been associated with better response
• Primary and secondary resistance are related to multiple defects during the cancer immune cycle
• Large efforts to overcome resistance with combinational immunotherapy, bi-specific antibodies and CAR-T cells
• We must be vigilant for irAEs
Thank You