Immunotherapy – The Changing Face of Cancer Treatment

Nadeem Ikhlaque MD
Medical Oncologist and Hematologist
Director Lung cancer program
Franciscan Physician Network
Disclosures

• Speakers Forum and Advisory board member for BMS and Lilly pharmaceuticals
• Advisory board member for Cardinal Oncology
Gratitude
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side affects.
- Long term follow up.
Cancer treatment

- Surgery
- Radiation Therapy
- Chemotherapy
- Targeted therapy
- Immunotherapy
IT'S TIME I GOT A BIGGER SWORD!

Search ID: jknn1304
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side affects
- Long term follow up
**U.S. FDA Approved Immune-Checkpoint Inhibitors**

1-7

**Squamous Cell Head & Neck Cancer**
1L/2L after platinum chemotherapy:
- nivolumab or pembrolizumab

**Malignant Melanoma**
Adjuvant ipilimumab, nivolumab, or pembrolizumab:
1L ipilimumab, nivolumab, or pembrolizumab
1L combination nivolumab + ipilimumab

**Merkel Cell Carcinoma**
2L avelumab or pembrolizumab

**Cutaneous Squamous Cell Carcinoma**
1L cemiplimab

**Hepatocellular Carcinoma**
2L nivolumab or pembrolizumab after sorafenib

**Adv. Renal Cell Carcinoma**
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

**MSI-H or dMMR Cancers**
2L nivolumab in CRC
2L nivolumab plus ipilimumab in CRC
2L pembrolizumab in any MSI-H/dMMR cancer

**Cervical Cancer**
2L pembrolizumab CPS≥1

**Small Cell Lung Cancer**
3L nivolumab

**Non-Small Cell Lung Cancer**
Maintenance durvalumab after chemoradiation
1L pembrolizumab TPS≥50%
1L non-squamous NSCLC
- pembrolizumab + pemetrexed & platinum-salt
- atezolizumab + bevacizumab, paclitaxel & carboplatin
1L squamous NSCLC
- pembrolizumab + carboplatin & (nab-)paclitaxel in
2L pembrolizumab TPS≥1%
2L atezolizumab or nivolumab

**Triple-Negative Breast Cancer**
1L atezolizumab + paclitaxel protein-bound PD-L1≥1%

**Gastric & GEJ Carcinoma**
3L pembrolizumab CPS≥1

**Classical Hodkin Lymphoma**
4L pembrolizumab
3L/4L nivolumab after auto-HSCT and BV

**PMBCL**
3L pembrolizumab

**Locally Adv. or Met. Urothelial Cancer**
1L/2L pembrolizumab,
1L/2L after platinum salt:
- atezolizumab, avelumab, durvalumab, or nivolumab

Copyright Photo: pixologic / 123RF

Updated on 09-Mar-2019 - citations on last page - ©medi-paper.com
Types of Cancer Immunotherapy

- Vaccines
- Immune Checkpoint Inhibitors
- Oncolytic Virus Therapy
- Adoptive Cell Therapy
KEYNOTE-189: First-line Pembrolizumab + CT vs Placebo + CT in Stage IV Nonsquamous NSCLC

- Randomized, double-blind, international phase III study

Stratified by PD-L1 TPS (≥ 1% vs < 1%), platinum agent (carboplatin vs cisplatin), smoking history (never vs former/current)

Patients with previously untreated stage IV nonsquamous NSCLC; ECOG PS 0/1; any PD-L1 status; no actionable EGFR/ALK mutations; no symptomatic CNS mets or pneumonitis requiring tx (N = 616)

Pembrolizumab 200 mg Q3W + Plt*/pemetrexed† Q3W (n = 410)  
No PD

Pembrolizumab‡ + Pemetrexed† Q3W

Placebo Q3W + Plt*/pemetrexed† Q3W (n = 206)  
No PD

Placebo‡ + Pemetrexed† Q3W

Until PD or unacceptable toxicity; crossover from placebo allowed

- Primary endpoints: OS, PFS by BICR
- Secondary endpoints: ORR, DoR, safety

Gandhi. NEJM. 2018;378:2078.

Slide credit: clinicaloptions.com
KEYNOTE-189: OS (ITT)

OS in Intention-to-Treat Population

- Pembrolizumab + CT
- Placebo + CT

OS at 1 Yr
- Pembrolizumab + CT: 69.2%
- Placebo + CT: 49.4%

HR for death: 0.49 (95% CI: 0.38-0.64; P < .001)

Gandhi. NEJM. 2018;378:2078.

Slide credit: clinicaloptions.com
Keynote 189: Met All Primary Endpoints

**OS:**
HR 0.49 [95% CI: 0.38-0.64]; p < 0.00001
12-mo rate: 69.2% 49.4%
Median (95% CI):
NR (NE-NE)
11.3 mo (8.7-15.1)

**PFS:**
HR 0.52 [95% CI: 0.43-0.64]; p < 0.00001
12-mo rate: 34.1% 17.3%
Median (95% CI):
8.8 mo (7.6-9.2)
4.9 mo (4.7-5.5)

**Response Rate**
Δ28.5
P < 0.00001
47.6%
18.9%

**Subgroup Analyses**
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%
KEYNOTE-407: Carboplatin + Paclitaxel/nab-Paclitaxel ± Pembrolizumab in Advanced Squamous NSCLC

- Randomized, double-blind phase III trial
  Stratified by PD-L1 TPS (< 1% vs ≥ 1%), taxane (paclitaxel vs nab-paclitaxel), and region (east Asia vs other)

Patients with untreated stage IV squamous NSCLC, ECOG PS 0/1, available tumor biopsy for PD-L1 assessment, no brain mets, and no pneumonitis requiring systemic steroids (N = 559)

- Pembrolizumab + Carboplatin + Paclitaxel or nab-Paclitaxel
  3-wk cycles x 4
  (n = 278)

- Pembrolizumab up to 31 cycles

- Placebo + Carboplatin + Paclitaxel or nab-Paclitaxel
  3-wk cycles x 4
  (n = 281)

- Placebo up to 31 cycles

- Pembrolizumab up to 35 cycles

Carboplatin AUC 6 Q3W, nab-paclitaxel 100 mg/m² QW, paclitaxel 200 mg/m² Q3W, pembrolizumab 200 mg Q3W.

*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy.

- Primary endpoint: PFS by RECIST v1.1 (BICR), OS
- Secondary endpoints: ORR and DoR by RECIST v1.1 (BICR), safety


Slide credit: clinicaloptions.com
KEYNOTE-407: Survival (ITT)

**PFS**
- Median PFS, Mos (95% CI)
  - Pembro + CT: 6.4 (6.2-8.3)
  - CT: 4.8 (4.3-5.7)

**HR:** 0.56
(95% CI: 0.45-0.70; P < .001)

**OS**
- Median OS, Mos (95% CI)
  - Pembro + CT: 15.9 (13.2-NR)
  - CT: 11.3 (9.5-14.8)

**HR:** 0.64
(95% CI: 0.49-0.85; P < .001)

Paz-Ares. NEJM. 2018;379;2040.

Slide credit: clinicaloptions.com
Ipilimumab/nivolumab better PFS than platinum chemotherapy in high TMB, irrespective of PD-L1

CheckMate 227

Primary endpoint PFS in high TMB (≥10Mut/Mb)
HR 1.07 in (<10Mut/Mb)

Reck, ESMO IO 2017
Evolution of Systemic Therapy in Small-Cell Lung Cancer

- **1970s**: Alkylating-Based Chemotherapy (CMV)
- **1980s**: Anthracycline-Based Chemotherapy (CAV)
- **1990s**: Platinum-Based Chemotherapy (EP)
- **Today**: Checkpoint Inhibitors

CheckMate 032: Nivolumab ± Ipilimumab in Patients With SCLC and Progression on 2 or More Lines of Therapy

**Objective Response by BICR**
- Nivo 3
- Nivo 1 + Ipi 3

**OS (Nonrandomized Cohort)**
- Events/No. at Risk:
  - Nivo 3: 82/98
  - Nivo 1 + Ipi 3: 47/61
- Median OS, Mos (95% CI):
  - Nivo 3: 4.1 (3.0-6.8)
  - Nivo 1 + Ipi 3: 7.8 (3.6-14.2)
- Minimum Follow-up, Mos:
  - Nivo 3: 19.6
  - Nivo 1 + Ipi 3: 20.2

1-yr OS: 40%
1-yr OS: 27%
2-yr OS: 26%
2-yr OS: 14%
IMpower133: Atezolizumab + Chemotherapy for Advanced SCLC

- Double-blind, randomized, placebo-controlled phase I/III trial

Stratified by sex, ECOG PS 0 vs 1, brain metastases: yes vs no

Patients with measurable ES-SCLC; ECOG PS 0/1; no prior systemic therapy for ES-SCLC; treated, asymptomatic brain mets eligible (N = 403)

Induction: 4 x 21-day cycles

- Atezolizumab 1200 mg IV on Day 1 + Carboplatin AUC 5 mg/mL/min IV on Day 1 + Etoposide 100 mg/m² on Days 1-3 (n = 201)

Maintenance*

- Atezolizumab

Placebo + Carboplatin AUC 5 mg/mL/min IV on Day 1 + Etoposide 100 mg/m² on Days 1-3 (n = 202)

PD or loss of clinical benefit

*PCI per local SoC.

- Coprimary endpoints: OS, PFS by investigator assessment
- Secondary endpoints: ORR, DoR, safety

Small cell lung Cancer

**IMpower133: PFS (Coprimary Endpoint)**

- **Atezolizumab + CP/ET (n = 201)**
  - PFS events, n (%): 175 (87.1)
  - Median PFS, mos: 5.3 (4.4-6.6)
  - HR (95% CI): 0.77 (0.62-0.96)
  - *P* Value: 0.017
  - Median follow-up, mos: 13.9

- **Placebo + CP/ET (n = 202)**
  - PFS events, n (%): 189 (93.6)
  - Median PFS, mos: 4.3 (4.2-5.5)
  - HR (95% CI): 0.77 (0.62-0.96)
  - *P* Value: 0.017

- **Patients at Risk, n**
  - Atezolizumab + CP/ET: 201
  - Placebo + CP/ET: 202

**IMpower133: OS (Coprimary Endpoint)**

- **Atezolizumab + CP/ET (n = 201)**
  - 12-mo OS: 51.7%
  - Median OS, mos: 13.4 (10.8-15.3)
  - HR (95% CI): 0.70 (0.54-0.91)
  - *P* Value: 0.006

- **Placebo + CP/ET (n = 202)**
  - 12-mo OS: 38.2%
  - Median OS, mos: 11.2 (9.3-13.2)

- **Patients at Risk, n**
  - Atezolizumab + CP/ET: 201
  - Placebo + CP/ET: 202

*Slide credit: clinicaltrials.com*
Atezolizumab + nab-Paclitaxel in Patients With Untreated Advanced TNBC (IMpassion130): Background

- Clinical outcomes for patients with mTNBC remain poor, with median OS of approximately 15-18 mos with standard chemotherapy[1-3]

- Phase III IMpassion130 previously demonstrated benefit of adding PD-L1 inhibitor atezolizumab to nab-paclitaxel in patients with untreated mTNBC and PD-L1+ ICs[4]
  - Median PFS in ITT population: 7.2 vs 5.5 mos with placebo (HR: 0.80; P = .002)
  - Median PFS in PD-L1+ IC subgroup: 7.5 vs 5.0 mos with placebo (HR: 0.62; P < .001)
    - No benefit observed in PD-L1− patients, suggesting benefit driven by PD-L1 positivity
  - Based on these findings, atezolizumab + nab-paclitaxel was granted accelerated FDA approval and is guideline recommended for patients with PD-L1+ mTNBC[5,6]

- Current analysis reports second interim OS analysis (80% mature) from IMpassion130[7]


Slide credit: clinicaloptions.com
IMpassion130: Study Design

- Randomized, double-blind, placebo-controlled phase III trial
  
  *Stratified by prior taxane use in curative setting (yes vs no), liver metastases (yes vs no), PD-L1 IC status (≥ 1% vs < 1%)*

  - Patients with metastatic or inoperable, locally advanced TNBC; no prior therapy for advanced setting (prior RT or CT in curative setting allowed if ≥ 12-mo DFI);
  - RECIST v1.1 measurable disease;
  - ECOG PS 0/1;
  - Tumor evaluable for PD-L1* (N = 902)

  **Atezolizumab 840 mg IV Q2W + nab-Paclitaxel 100 mg/m² IV on D1, 8, 15**
  **28-day cycles**
  **(n = 451)**

  **Placebo IV Q2W + nab-Paclitaxel 100 mg/m² IV on D1, 8, 15**
  **28-day cycles**
  **(n = 451)**

- Treatment until PD per RECIST v1.1 or intolerable toxicity
- No crossover Allowed
- Survival follow-up

- Coprimary endpoints: PFS and OS (ITT population and PD-L1+ subgroup)
  
  - Prespecified hierarchical OS testing in ITT population; if significant, then PD-L1+ population

*By prospective central testing with SP142 PD-L1 IHC assay.
41% of patients in each arm were PD-L1+ (≥ 1% IC).
IMpassion130 Update: OS in PD-L1+ Subgroup

**Median OS, mos (95% CI)**
- Atezolizumab + nab-Paclitaxel: 25.0 (19.6-30.7) (n = 185)
- Placebo + nab-Paclitaxel: 18.0 (13.6-20.1) (n = 184)

**24-mo OS, % (95% CI)**
- Atezolizumab + nab-Paclitaxel: 51 (43-59)
- Placebo + nab-Paclitaxel: 37 (29-45)

**HR: 0.71 (95% CI: 0.54-0.93)**

Patients at Risk, n
- Atezo + nab-Pac: 185 177 160 145 135 121 106 69 43 28 21 10 6 3 3 NE
- Pbo + nab-Pac: 184 170 147 129 111 93 81 47 26 20 15 10 1 NE NE

*Not formally tested due to prespecified hierarchical statistical design for trial.*

Renal Cell Carcinoma

CheckMate 214: ORR and DoR for IMDC Int/Poor Risk

- Phase III trial of patients with previously untreated advanced ccRCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients (N = 847)</th>
<th>ORR* (95% CI), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo + Ipi (n = 425)</td>
<td>42 (37-47)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>Sun (n = 422)</td>
<td>27 (22-31)</td>
<td></td>
</tr>
</tbody>
</table>

Best Response, * %
- CR: 9\(^\d\) vs 1\(^\d\)
- PR: 32 vs 25
- Stable disease: 31 vs 45
- Progression: 20 vs 17
- Not reported: 8 vs 12

*IRRC-assessed confirmed ORR and BOR by RECIST v1.1.
\(^\d\)P < .0001

Motzer. NEJM. 2018; 378:1277.
IMDC Prognostic Criteria

- Clinical
  - KPS < 80% ($P < .0001$)
  - Time from diagnosis to tx < 1 yr ($P = .01$)

- Laboratory
  - Hemoglobin < LLN ($P < .0001$)
  - Calcium > ULN ($P = .0006$)
  - Neutrophil count > ULN ($P < .0001$)
  - Platelet count > ULN ($P = .01$)

Favorable: 0 risk factors; intermediate: 1-2 risk factors; poor: 3+ risk factors

Heng. JCO. 2009;27:5794.
Immune Checkpoint Inhibitors Offer Survival Benefit Compared With Historical Treatment Approaches

OS for Metastatic Melanoma in Clinical Trials Completing Accrual From 1975 to 2005[1]

Survival data from 42 phase II trials of patients with stage IV melanoma (N = 2100)

Pembrolizumab Plus Reduced-Dose Ipilimumab in Metastatic Melanoma, 2017[2]

Benefits of ICIs observed in multiple malignancies

Gratitude
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side effects.
- Long term follow up.
Principles of Cancer Immunotherapy
Immune System

Natural killer
Kills stuff

Cytotoxic
Kills stuff

Memory
Remembers the thing that has been destroyed. Next time this gets into the body a much faster, better response occurs.

Suppressor
After invaders have been destroyed, these cells calm the immune response and make everyone rellllllax!

©SciencebyDave2015
T-Cell Response: Accelerate or Brake?

Activating Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

T-Cell Stimulation
T-Cell Inhibition

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

Priming Phase (Lymph Node)

Effector Phase (Peripheral Tissue)

T-Cell Migration

Ribas. NEJM. 2012;366:2517.
Checkpoint Blockade Inhibitors

Turning on T cells

T Cell

PD-1

PD-L1

Tumor Cell
Checkpoint Blockade Inhibitors
Turning on T cells

T Cell

PD-1

PD-L1

Tumor Cell

T Cell

Tumor Cell

OPDIVO (nivolumab)
KEYTRUDA (pembrolizumab) injection 100 mg
BAVENCIO avelumab Injection 20 mg/mL
YERVOY (ipilimumab)
Checkpoint Blockade Inhibitors

Turning on T cells

T Cell

PD-1

Tumor Cell

PD-L1

T Cell

Tumor Cell
T Cell tolerance

"Driving" an Immune Response

- TCR: antigen-MHC
  - Signal 1
- CD28: B7
  - Signal 2
- CTLA4: B7
  - Blockade of Signal 2
- PD-1: PD-L1
How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them

Immunotherapy drugs can block tumor cells from deactivating T-cells
Immune checkpoints inhibitors

The CTLA-4 checkpoint protein prevents dendritic cells from priming T cells to recognize tumours. Inhibitor drugs block the checkpoint.

CTLA-4 blockade (e.g. ipilimumab)

The PD-1 checkpoint protein prevents T cells from attacking cancer cells. The inhibitor drug allows T cells to act.

PD-(L)1 blockade (e.g. Nivolumab, pembrolizumab, Atezolizumab)

Ledford, Nature 508, 24-26, 2014
Down-regulation of antigen presentation leading to impaired recognition by T cells

Reduced expression of ligands for co-stimulatory molecules such as B7.1 and inducible co-stimulator ligand (ICOSL) on APCs leading to defective immune functions

Creation of an immunosuppressive microenvironment leading to recruitment of, or promotion of, suppressive immune cell differentiation or expansion

Expression of inhibitory receptors, e.g., PD-L1 and PD-L2, leading to T-cell inhibition

1. Topfer, et al. 2011
Molecular Determinants of Response to PD-1 and PD-L1 Blockade in Patients With Advanced NSCLC

- In patients with advanced NSCLC (N = 240):
  - TMB assessed by next-generation sequencing
  - Tumor PD-L1 expression assessed by IHC (n = 84)

![Bar chart showing TMB and PD-L1 expression categories and their clinical benefit durations.]

- TMB Low
  - PD-L1 High: 29.4% (5 of 17)
  - PD-L1 Low: 18.2% (4 of 22)

- TMB High
  - PD-L1 High: 50.0% (10 of 20)
  - PD-L1 Low: 35.3% (6 of 17)

Rivzi. JCO. 2018;36:633.
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side affects.
- Long term follow up.
Gratitude
Gratitude
Rise of Immunotherapy

- Long-term disease control against recalcitrant cancers
- Game-changing discoveries – more coming

- **2011**
  - Ipilimumab introduced for melanoma

- **2014**
  - Pembrolizumab, nivolumab approved for melanoma

- **2015-2016**
  - PD-1/L-1 drugs benefit even more of cancers

- **2016 ASCO**
  - Advance of the Year

- Head/Neck Cancer
- Melanoma
- Lung Cancer
- Kidney Cancer
- Bladder Cancer
- Hodgkin Lymphoma (Lymph Node Cancer)
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell Head &amp; Neck Cancer</td>
<td>1L/2L after platinum chemotherapy:</td>
</tr>
<tr>
<td></td>
<td>• nivolumab or pembrolizumab</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>Adjuvant ipilimumab, nivolumab, or pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>1L ipilimumab, nivolumab, or pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>1L combination nivolumab + ipilimumab</td>
</tr>
<tr>
<td>Merkel Cell Carcinoma</td>
<td>2L avelumab or pembrolizumab</td>
</tr>
<tr>
<td>Cutaneous Squamous Cell Carcinoma</td>
<td>1L cemiplimab</td>
</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
<td>2L nivolumab or pembrolizumab after sorafenib</td>
</tr>
<tr>
<td>Adv. Renal Cell Carcinoma</td>
<td>1L nivolumab plus ipilimumab</td>
</tr>
<tr>
<td></td>
<td>2L nivolumab after anti-angiogenic therapy</td>
</tr>
<tr>
<td>MSI-H or dMMR Cancers</td>
<td>2L nivolumab in CRC</td>
</tr>
<tr>
<td></td>
<td>2L nivolumab plus ipilimumab in CRC</td>
</tr>
<tr>
<td></td>
<td>2L pembrolizumab in any MSI-H/dMMR cancer</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>2L pembrolizumab CPS≥1</td>
</tr>
<tr>
<td>Small Cell Lung Cancer</td>
<td>3L nivolumab</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer</td>
<td>Maintenance durvalumab after chemoradiation</td>
</tr>
<tr>
<td></td>
<td>1L pembrolizumab TPS≥50%</td>
</tr>
<tr>
<td></td>
<td>1L non-squamous NSCLC</td>
</tr>
<tr>
<td></td>
<td>• pembrolizumab + pemetrexed &amp; platinum-salt</td>
</tr>
<tr>
<td></td>
<td>• atezolizumab + bevacizumab, paclitaxel &amp; carboplatin</td>
</tr>
<tr>
<td></td>
<td>1L squamous NSCLC</td>
</tr>
<tr>
<td></td>
<td>• pembrolizumab + carboplatin &amp; (nab-)paclitaxel in 2L</td>
</tr>
<tr>
<td></td>
<td>2L pembrolizumab TPS≥1</td>
</tr>
<tr>
<td></td>
<td>2L atezolizumab or nivolumab</td>
</tr>
<tr>
<td>Triple-Negative Breast Cancer</td>
<td>1L atezolizumab + paclitaxel protein-bound PD-L1≥1%</td>
</tr>
<tr>
<td>Gastric &amp; GEJ Carcinoma</td>
<td>3L pembrolizumab CPS≥1</td>
</tr>
<tr>
<td>Classical Hodkin Lymphoma</td>
<td>4L pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>3L/4L nivolumab after auto-HSCT and BV</td>
</tr>
<tr>
<td>PMBCL</td>
<td>3L pembrolizumab</td>
</tr>
<tr>
<td>Locally Adv. or Met. Urothelial Cancer</td>
<td>1L/2L pembrolizumab,</td>
</tr>
<tr>
<td></td>
<td>1L/2L after platinum salt:</td>
</tr>
<tr>
<td></td>
<td>• atezolizumab, avelumab, durvalumab, or nivolumab</td>
</tr>
</tbody>
</table>
Immune Checkpoint Inhibitors FDA Approved in Multiple Cancers as of April 2019

- Number of patients treated with ICIs is growing
  - ICIs now approved as monotherapy, in combination with other ICIs, and in combination with chemotherapy
  - ICIs historically used in later-line metastatic disease
    - Moving into earlier lines of therapy and earlier stages of disease (eg, adjuvant tx for melanoma; tx for stage III NSCLC)
    - Patients may receive ICI therapy for years, as optimal duration is unknown
      - Initial strategy was continuing ICI until progression/toxicity or to 2 years


Slide credit: clinicaloptions.com
# U.S. FDA Approved Immune-Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Target</th>
<th>Indications</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nivolumab (Opdivo®)</strong></td>
<td>Bristol-Myers Squibb</td>
<td>PD-1</td>
<td>• Adj./1L Inoperable or metastatic melanoma</td>
<td>• Single agent in BRAF-WT and BRAF-MU or in combination with ipilimumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Adj. treatment of melanoma</td>
<td>• Patients with lymph node involvement or metastatic disease, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2L metastatic NSCLC</td>
<td>• Underwent complete resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 3L metastatic SCLC</td>
<td>• Irrespective of PD-L1 expression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L advanced, intermediate or poor risk renal cell carcinoma</td>
<td>• Failure on platinum chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2L advanced renal cell carcinoma</td>
<td>• Failure on EGFR/ALK targeted agent (if indicated)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 3L/4L classical Hodgkin lymphoma</td>
<td>• Progression on at least two lines of prior treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L recurrent or metastatic head and neck squamous cell carcinoma</td>
<td>• Including: one line of platinum-based therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L/2L locally advanced or metastatic urothelial carcinoma</td>
<td>• In combination with ipilimumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MSI-H or dMMR metastatic colorectal cancer</td>
<td>• After prior treatment with anti-angiogenic drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2L heptocellular carcinoma</td>
<td>• Adult patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L inoperable or metastatic melanoma</td>
<td>• After prior auto-HSCT and (4L-only) brentuximab vedotin (BV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Adjuvant treatment of stage IIIa cutaneous melanoma</td>
<td>• Failure on prior platinum chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L advanced, intermediate or poor risk renal cell carcinoma</td>
<td>• PD&lt;12 months after (neo)adjuvant platinum chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MSI-H or dMMR metastatic colorectal cancer</td>
<td>• Single agent or in combination with ipilimumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2L heptocellular carcinoma</td>
<td>• Adult and paediatric patients (≥12 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• PD following fluoropyrimidine, oxaliplatin, and irinotecan</td>
<td>• PD following fluoropyrimidine, oxaliplatin, and irinotecan</td>
</tr>
<tr>
<td><strong>Ipilimumab (Yervoy®)</strong></td>
<td>Bristol-Myers Squibb</td>
<td>CTLA4</td>
<td>• 1L inoperable or metastatic melanoma</td>
<td>• Adult and paediatric patients (≥12 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Adjuvant treatment of stage IIIa cutaneous melanoma</td>
<td>• Single agent or in combination with nivolumab (see Opdivo® USPI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 1L advanced, intermediate or poor risk renal cell carcinoma</td>
<td>• Patients with pathological involvement of the regional lymph nodes &gt;1 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• MSI-H or dMMR metastatic colorectal cancer</td>
<td>• who underwent complete resection, including total lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• In combination with nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Single agent or in combination with nivolumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adult and paediatric patients (≥12 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PD following fluoropyrimidine, oxaliplatin, and irinotecan</td>
</tr>
</tbody>
</table>
## U.S. FDA Approved Immune-Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Target</th>
<th>Indications</th>
<th>Details</th>
</tr>
</thead>
</table>
| Pembrolizumab (Keytruda®) | Merck (MSD) | PD-1 | • Adj. treatment of melanoma | - Patients with lymph node involvement, and  
• Underwent complete resection |
|  |  |  | • 1L inoperable or metastatic melanoma | - Single agent |
|  |  |  | • 1L metastatic Merkel cell carcinoma | - Adult and paediatric patients |
|  |  |  | • 2L metastatic NSCLC with PD-L1 expression | - Failure on platinum-doublet chemotherapy  
- Failure on EGFR/ALK targeted agent (if indicated)  
- TPS≧1% |
|  |  |  | • 1L metastatic non-squamous NSCLC | - In combination with pemetrexed and a platinum chemotherapy |
|  |  |  | • 1L metastatic squamous NSCLC | - In combination with carboplatin and paclitaxel or nab-paclitaxel |
|  |  |  | • 1L metastatic NSCLC with high PD-L1 expression | - No known EGFR/ALK tumour-driver mutations  
- TPS≧50% |
|  |  |  | • 1L/2L recurrent or metastatic head and neck squamous cell carcinoma | - PD on or after (adjuvant) platinum chemotherapy |
|  |  |  | • 4L refractory classical Hodgkin lymphoma | - Adult and paediatric patients with disease relapse after 3 prior treatments |
|  |  |  | • 3L refractory PMBCL | - Adult and paediatric patients relapsed≧2 or more prior lines of therapy.  
**Limitation of use:** not recommended when PMBCL patient requires urgent cytoreductive therapy |
|  |  |  | • 1L/2L locally advanced or metastatic urothelial carcinoma | - Ineligible for cisplatin chemotherapy and a CPS≥1  
- Ineligible for platinum chemotherapy irrespective of PD-L1 expression  
- PD on prior platinum chemotherapy  
- PD<12 months after (neo)adjuvant platinum chemotherapy |
|  |  |  | • MSI-H or dMMR cancers | - Adult and paediatric patients  
- PD in solid tumours following prior treatment and no other, satisfactory alternative treatment options  
- Colorectal cancer progressed following FOLFOXIRI  
**Limitation of use:** safety and effectiveness not established in paediatric patients with MSI-H CNS cancers |
|  |  |  | • Recurrent locally advanced or metastatic gastric GEJ adenocarcinoma | - CPS≥1  
- Disease progression ≧2 prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy  
- PD following HER2-targeted therapy, if indicated |
|  |  |  | • Recurrent or metastatic cervical cancer | - CPS≥1 and PD on chemotherapy  
- Pretreated with sorafenib |
|  |  |  | • 2L hepatocellular carcinoma | - |
### U.S. FDA Approved Immune-Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Target</th>
<th>Indications</th>
<th>Details</th>
</tr>
</thead>
</table>
| Atezolizumab (Tecentriq®) | Roche & Genentech              | PD-L1  | • 1L/2L locally advanced or metastatic urothelial carcinoma                 | • Ineligible for cisplatin chemotherapy and PD-L1 expression (PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 5% of the tumor area)  
• Ineligible for platinum chemotherapy regardless of PD-L1 expression  
• Failure on prior platinum chemotherapy  
• PD<12 months after (neo)adjuvant platinum chemotherapy  
• 1/L metastatic non-squamous NSCLC  
• In combination with bevacizumab, paclitaxel, and carboplatin  
• No EGFR or ALK genomic tumour aberrations  
| Avelumab (Bavencio®)       | Merck Serono & Pfizer           | PD-L1  | • 1L metastatic Merkel cell carcinoma                                       | Adult and paediatric patients (≥12 years)  
| Durvalumab (Imfinzi®)      | AstraZeneca                     | PD-L1  | • 1L/2L locally advanced or metastatic urothelial carcinoma                 | Failure on prior platinum chemotherapy  
• PD<12 months after (neo)adjuvant platinum chemotherapy  
• Maintenance for unresectable, stage III NSCLC  
• No PD following concurrent platinum-based chemotherapy and radiation therapy  
| Cemiplimab (Libtayo®)      | Sanofi                          | PD-L1  | • 1L metastatic cutaneous squamous cell carcinoma (CSCC)                   | Not amenable for curative surgery or curative radiation  

Updated on 09-Mar-2019 - citations on last page - ©medi-paper.com
<table>
<thead>
<tr>
<th>REF</th>
<th>Study</th>
<th>Study details</th>
<th>Line</th>
<th>Drug</th>
<th>Biomarker/Subgroup</th>
<th>N</th>
<th>Primary endpoint</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Lung-MAP S1400I NCT02785952 (N=350)</td>
<td>Phase III, randomised Stage IV SQ-NSCLC</td>
<td>2nd</td>
<td>nivolumab+ipilimumab</td>
<td>PD-L1 ≥5</td>
<td>125</td>
<td>mOS</td>
<td>IA mPFS / ORR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1 &lt;5</td>
<td></td>
<td>10.0 mo NS</td>
<td>3.8 mo NS / 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB ≥10</td>
<td></td>
<td>14.1 mo NS</td>
<td>3.9 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB &lt;10</td>
<td></td>
<td>8.3 mo NS</td>
<td>4.4 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td></td>
<td>13.1 mo NS</td>
<td>4.2 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1 ≥5</td>
<td>127</td>
<td>7.6 mo NS</td>
<td>1.9 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1 &lt;5</td>
<td></td>
<td>11.0 mo NS</td>
<td>2.9 mo NS / 19%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB ≥10</td>
<td></td>
<td>12.0 mo NS</td>
<td>2.9 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB &lt;10</td>
<td></td>
<td>10.3 mo NS</td>
<td>3.6 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td></td>
<td>11.4 mo NS</td>
<td>3.4 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1 ≥5</td>
<td></td>
<td>10.0 mo NS</td>
<td>2.7 mo NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD-L1 &lt;5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB ≥10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMB &lt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>KEYNOTE-189 NCT02578680 (N=616)</td>
<td>Phase III, double-blind, randomised Stage IV NSQ-NSCLC</td>
<td>1st</td>
<td>pembrolizumab + pemetrexed + carboplatin or cisplatin</td>
<td>All</td>
<td>410</td>
<td>mOS: 22.0 mo</td>
<td>HR Arm A vs Arm B</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS ≥50%</td>
<td>206</td>
<td>mOS: 10.7 mo</td>
<td>PFS: 0.47 (0.33, 0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS 1%–49%</td>
<td>202</td>
<td>OS: 0.56 (0.45, 0.70)</td>
<td>PFS: 0.47 (0.33, 0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS &lt;1%</td>
<td>186</td>
<td>PFS: 0.48 (0.40, 0.58)</td>
<td>PFS: 0.45 (0.37, 0.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>410</td>
<td>HR Arm A vs Arm B</td>
<td>PFS: 0.59 (0.41, 0.86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment-naive</td>
<td>206</td>
<td>OS: 0.59 (0.39, 0.88)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS ≥50%</td>
<td>202</td>
<td>PFS: 0.36 (0.26, 0.51)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS 1%–49%</td>
<td>186</td>
<td>OS: 0.62 (0.42, 0.92)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS &lt;1%</td>
<td>190</td>
<td>PFS: 0.51 (0.36, 0.73)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>410</td>
<td>HR Arm A vs Arm B</td>
<td>PFS: 0.51 (0.36, 0.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment-naive</td>
<td>206</td>
<td>OS: 0.52 (0.36, 0.74)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS ≥50%</td>
<td>202</td>
<td>PFS: 0.64 (0.47, 0.89)</td>
<td>PFS: 0.46 (0.33, 0.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS 1%–49%</td>
<td>186</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS &lt;1%</td>
<td>190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>KEYNOTE-001 NCT01295827 (N=550)</td>
<td>Phase Ib, open-label, randomised laNSCLC or mNSCLC</td>
<td>1st</td>
<td>pembrolizumab</td>
<td>All</td>
<td>550</td>
<td>ORR / median DoR</td>
<td>mOS / OS-rate 36-60-mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment-naive</td>
<td>101</td>
<td>42% / 16.8 mo</td>
<td>22.3 mo / 37 &amp; / 23.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS ≥50%</td>
<td>27</td>
<td>27% / 36.8 mo</td>
<td>35.4 mo / 48.1% / 29.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS 1%–49%</td>
<td>52</td>
<td>23% / 38.9 mo</td>
<td>19.5 mo / 27.5% / 15.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prior treatment(s)</td>
<td>449</td>
<td>23% / 38.9 mo</td>
<td>10.5 mo / 20.9% / 15.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS ≥50%</td>
<td>138</td>
<td>23% / 38.9 mo</td>
<td>15.4 mo / 30.4% / 25.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS 1%–49%</td>
<td>168</td>
<td>23% / 38.9 mo</td>
<td>8.5 mo / 16.9% / 12.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TPS &lt;1%</td>
<td>90</td>
<td>23% / 38.9 mo</td>
<td>8.6 mo / 11.1% / 3.5%</td>
</tr>
</tbody>
</table>

Abbreviations and citations on final slide
Data based on public abstracts and clinicaltrials.gov information
### Abbreviations and Citations

#### Abbreviations
- 1L: first-line
- 2L: second-line
- 3L: third-line
- 4L: fourth-line
- Adv: advanced
- ALK: anaplastic lymphoma kinase
- auto-HSCT: autologous haematopoietic stem cell transplantation
- BV: brentuximab vedotin
- CNS: central nervous system
- CPS: combined proportion score
- dMMR: mismatch-repair deficient
- EGFR: epidermal growth factor receptor
- GEJ: gastroesophageal junction
- HER2: human epidermal growth factor receptor 2
- Met: metastatic
- MSI-H: microsatellite instability-high
- Mu: mutation
- NSCLC: non-small cell lung cancer
- PMBCL: primary mediastinal B-cell lymphoma
- PD: progression disease
- PD-1: programmed death 1
- PD-L1: programmed death ligand 1
- TPS: tumour proportion score
- WT: wild-type

#### Citations
- 1 Prescribing information pembrolizumab (Keytruda®), revised: 02/2019
- 2 Prescribing information nivolumab (Opdivo®), revised: 02/2019
- 3 Prescribing information ipilimumab (Yervoy®), revised: 07/2018
- 4 Prescribing information atezolizumab (Tecentriq®), revised: 03/2019
- 5 Prescribing information avelumab (Bavencio®), revised: 10/2018
- 6 Prescribing information durvalumab (Imfinzi®), revised: 02/2018
- 7 Prescribing information cemiplimab (Libtayo®), revised: 09/2018
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side affects
- Long term follow up
A New Spectrum of Adverse Events

- Hypophysitis
- Dry mouth
- Hypothyroidism
- Hepatitis
- Pancreatitis
- Autoimmune diabetes
- Rash and vitiligo
- Arthralgia
- Uveitis
- Orbital inflammation
- Pneumonitis
- Adrenal insufficiency
- Enterocolitis
Immune-Related AEs With Immunotherapy

**Skin**
- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

**Eye**
- Uveitis
- Iritis

**Endocrine**
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

**Pulmonary**
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

**Gastrointestinal**
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

**Renal**
- Nephritis
- Autoimmune
- Renal failure

**Hepatic**
- Hepatitis
  - Autoimmune

**Neurologic**
- Autoimmune neuropathy
- Demyelinating
- Polineuropathy
- Guillain-Barré
- Myasthenia gravis-like syndrome

If not vigilant, may result in more serious immune-related AEs
Selected Adverse Events

- Inflammatory processes affecting any organ system
- Distinct mechanism of action from traditional chemotherapy-related side effects
- Evaluation and management are unique to this class of drugs
- May be exacerbated by underlying autoimmune conditions/presence of autoantibodies
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side effects
- Long term follow up
Immune-Mediated Colitis: Symptom Surveillance

- Monitor for signs and symptoms
- **Median time to onset from first dose ~ 10 wks from first dose**
- Ask pts to report any bowel habit changes promptly
- Rule out other causes of diarrhea

*Clinical Pearl:* colitis can occur without diarrhea; important to take all GI-related symptoms seriously and evaluate!
# Immune-Mediated Colitis: Symptom Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| Mild/grade 1: ≤ 4 stools/day above baseline | • Manage symptomatically (bland diet, PPI, anti-diarrheal)  
• Consider delaying treatment until symptoms improve |
| Moderate/grade 2: increase of 4-6 stools/day above baseline (persistent) | • Colonoscopy and steroids  
• Low-dose steroids may be sufficient  
• Hold treatment |
| Severe/grade ≥ 3: ≥ 7 stools/day above baseline | • Initiate high-dose steroids  
• Discontinue treatment |
| Prevention | • No known methods |
Immune-Mediated Hepatitis: Symptom Surveillance

- Monitor LFTs at baseline and prior to each dose of treatment
- Pts with abnormal LFTs should be monitored more frequently
- Hepatotoxicity appears worse when ipilimumab combined other drugs

Immune-Mediated Hepatitis: Symptom Management

- Rule out other causes of LFT abnormalities
- Increase LFT monitoring
- Corticosteroid treatment with grade ≥ 2 LFTs (prolonged taper may be required)

- Mycophenolate may be useful
- LFT abnormalities appear to be dose dependent

<table>
<thead>
<tr>
<th>LFT</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&gt; ULN to 1.5 × ULN</td>
<td>&gt; 1.5 to 3.0 × ULN</td>
<td>&gt; 3.0 to 10.0 × ULN</td>
<td>&gt; 10.0 × ULN</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>&gt; ULN to 2.5 × ULN</td>
<td>&gt; 2.5 to 5.0 × ULN</td>
<td>&gt; 5.0 to 20.0 × ULN</td>
<td>&gt; 20.0 × ULN</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt; LLN to 3 g/dL</td>
<td>&lt; 3 to 2 g/dL</td>
<td>&lt; 2 g/dL</td>
<td>--</td>
</tr>
</tbody>
</table>
Immune-Mediated Dermatitis

- Reported in up to 40% of pts with anti–CTLA-4 and anti–PD-1 agents
- Occasionally severe rashes
- Onset within a few wks of starting or several wks/mos into therapy
- Severity driven by symptoms
- Rule out other etiologies
- Generally not infusion related
Dermatologic Reactions in Patients Treated With Immune Checkpoint Inhibitors

Grade 3 Maculopapular Rash

Dermatologic Reactions in Patients Treated With Immune Checkpoint Inhibitors

Bullous Pemphigoid Combining Maculopapular Rash and Blisters (Green Circles)

Vasculitis With Digit Necrosis and Apparent Livedo

## Immune-Mediated Dermatitis: Symptom Management

<table>
<thead>
<tr>
<th>Severity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate (rash/pruritus)</td>
<td>- Topical nonsteroidal cream, antihistamine, oatmeal baths</td>
</tr>
<tr>
<td></td>
<td>- Skin care, moisturize, sunscreen, avoid sun</td>
</tr>
<tr>
<td>Persistent (&gt; 1 wk) or interferes with ADLs</td>
<td>- Moderate-potency steroid creams or</td>
</tr>
<tr>
<td></td>
<td>- Moderate-dose parenteral steroids</td>
</tr>
<tr>
<td>Severe</td>
<td>- Discontinue treatment</td>
</tr>
<tr>
<td></td>
<td>- High-dose steroids</td>
</tr>
<tr>
<td></td>
<td>- Avoid rapid steroid taper</td>
</tr>
</tbody>
</table>
Immune-Mediated Endocrinopathies

- Can be serious or fatal if not managed correctly
- Hypophysitis, thyroid disease, and primary adrenal insufficiency have all been reported
- Mechanism of injury not fully understood
- Monitor pt for pituitary, thyroid, or adrenal disease
- Check TFTs at baseline and prior to each dose
- Time to onset may be much later; median 11 wks

Immune-Mediated Endocrinopathies: Symptom Management

- Hormone replacement, corticosteroids
- Possibly delay treatment
- Co-syntropin stimulation test
- Many endocrinopathies can be controlled and treatment continued

Does a preexisting thyroid disorder put pts at higher risk of developing additional endocrinopathies?

Not as far as we know.
Immune-Mediated Pneumonitis

• Fairly uncommon, but potentially serious
  • Deaths have been reported
  • Need to carefully monitor pts

• Pts at increased risk for pneumonitis
  • NSCLC in the setting of chronic lung inflammation
  • Heavily pretreated pts
  • Combination of CTLA-4 and PD-1 agents
  • Prior radiation to lung
  • History of COPD
Immune-Related Pneumonitis: Signs and Symptoms

- Shortness of breath
- Dry cough
- New or increasing oxygen requirements

- May be detected just on imaging
- Decreasing O2 sat on room air

11/15/2013: Pre-pneumonitis
1/21/14: Pneumonitis
2/21/14: Improved with steroids; taper completed 3/7/14
**Grade**

1. Asymptomatic, Radiologic changes only

2. Mild/moderate new symptoms

3-4. Severe/life-threatening new symptoms or worsening hypoxia

**Investigations**

- Radiologic imaging (High resolution CT chest)
- Microbial assessment where necessary
- Consider Pulmonary/Infectious Diseases Consults and Bronchoscopy

**Management**

- Continue immunotherapy
  - Monitor for symptoms every 3 days
- Hold immunotherapy
  - Monitor for symptoms daily
  - Oral prednisone 1mg/kg/day or equivalent
- Discontinue immunotherapy
  - Hospitalization
  - IV methylprednisolone 2-4mg/kg/day or equivalent
  - Prophylactic antibiotics

**Follow-up**

- Repeat CT every cycle
- If develops symptoms, treat as higher grade
- If improves to ≤Grade 1 within 3 days of supportive care, resume immunotherapy at next dose
- If persistent beyond 3 days, discontinue immunotherapy
- After symptoms improve, taper steroids over ≥1 month
- After symptoms improve to ≤Grade 1 or baseline, taper steroids over ≥6 weeks
- If worsens in 48 hours consider additional immunosuppression (infliximab, cyclophosphamide, methotrexate, mycophenolate mofetil)

Naidoo et al, Ann Oncol 2015
Time to Onset of Grade 3/4 Toxicities With Nivolumab + Ipilimumab in Advanced Melanoma

- Retrospective review of 448 patients with advanced melanoma treated with nivolumab 1 mg/kg + ipilimumab 3 mg/kg x 4
Most irAEs Are Reversible With Immunosuppression/Steroids

![Graph showing the time course of irAEs with immunosuppression/stereoids. The x-axis represents weeks (Wks), and the y-axis represents toxicity grade. The graph shows the following changes over time:
- **Rash, pruritus**: Peaks around week 6 and resolves by week 10.
- **Liver toxicity**: Peaks around week 4 and resolves by week 10.
- **Diarrhea, colitis**: Peaks around week 8 and resolves by week 14.
- **Hypophysitis**: Continues to increase and remains high throughout the weeks shown.]

Most Common irAEs in Patients With Cancer Presenting to Emergency Department

- Retrospective review of 628 patients receiving ICIs who visited ED at MD Anderson Cancer Center (March 2011 to February 2016)
  - Of 1026 visits, 257 (25.0%) related to irAEs, with 210 (81.7%) of irAE-related visits leading to admission

<table>
<thead>
<tr>
<th>irAE, %</th>
<th>Ipilimumab (n = 186)</th>
<th>Nivolumab (n = 154)</th>
<th>Pembrolizumab (n = 109)</th>
<th>&gt; 1 Agent (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>14.5</td>
<td>8.4</td>
<td>6.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Colitis</td>
<td>7.0</td>
<td>2.6</td>
<td>1.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3.2</td>
<td>7.1</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>4.3</td>
<td>4.5</td>
<td>4.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>4.3</td>
<td>0.6</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.1</td>
<td>6.1</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>1.6</td>
<td>0.6</td>
<td>0</td>
<td>5.0</td>
</tr>
<tr>
<td>Pancreatitus</td>
<td>1.1</td>
<td>1.9</td>
<td>0.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Adrenalitis</td>
<td>0.5</td>
<td>1.3</td>
<td>0</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Least common irAEs (all ≤ 1.1%): nephritis, hematologic effects, myocarditis, vasculitis, eye effects.
# Common irAEs: Typical Presentations

<table>
<thead>
<tr>
<th>irAE</th>
<th>Common Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic[1,2]</td>
<td>Maculopapular rash with pruritus, predominantly on trunk and to lesser extent the upper limbs, spreading to extremities; eczematous, lichenoid, psoriasiform manifestations; blistering skin reactions</td>
</tr>
<tr>
<td>Diarrhea/colitis[3]</td>
<td>Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting</td>
</tr>
<tr>
<td>Hepatic[3]</td>
<td>Often asymptomatic and diagnosed via routine blood tests</td>
</tr>
<tr>
<td>Pancreatic[1]</td>
<td>Asymptomatic elevation in amylase/lipase; CT, clinical findings of pancreatitis; severe abdominal pain, vomiting, and hemodynamically unstable</td>
</tr>
<tr>
<td>Endocrine[3]</td>
<td>Headaches, visual disturbances, fatigue, altered consciousness, deranged electrolytes (particularly hyponatremia), anorexia, mood changes</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
# Less Common irAEs: Typical Presentations

<table>
<thead>
<tr>
<th>Immune-Related AE</th>
<th>Common Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis[1]</td>
<td>Dyspnea, cough, fever, chest pain</td>
</tr>
<tr>
<td>Renal[2]</td>
<td>Elevated serum creatinine; azotemia; inability to maintain acid–base or electrolyte balance; urine output change</td>
</tr>
<tr>
<td>Ocular[2]</td>
<td>Vision changes; photophobia; tenderness/pain; eyelid swelling; proptosis; red/purple discoloration; eye redness</td>
</tr>
<tr>
<td>Neurologic[2]</td>
<td>Progressive or fluctuating muscle weakness, usually proximal to distal; absent/reduced deep tendon reflexes; sensory–motor deficit; headache, photophobia, neck stiffness with nausea/vomiting; confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality</td>
</tr>
<tr>
<td>Cardiovascular[3]</td>
<td>Generalized malaise and fatigue; dyspnea; edema; decreased ejection fraction on ECG</td>
</tr>
<tr>
<td>Musculoskeletal[2]</td>
<td>Joint pain, swelling; inflammatory symptoms; stiffness after inactivity; improvement with heat; myalgias; myositis</td>
</tr>
</tbody>
</table>

General Principles for Managing irAEs

- Consult promptly with relevant specialists for affected organ systems (e.g., gastroenterology, dermatology)

- Management generally based on severity of symptoms
  - Mild (grade 1): supportive care, consider holding drug
  - Moderate (grade 2): hold drug, redose if toxicity improves, consider low-dose steroids (prednisone 0.5-1 mg/kg/day)
  - Severe (grade 3): discontinue drug, monitor closely (likely inpatient), start high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper (≥ 1 mo)
    - If not improving in 1-3 days, increase immunosuppression

- Dose reduction is not a recommended strategy

- Avoid delays in recognition and intervention
Recurrent Toxicities With Resumption of Anti–PD-1

- On CTLA-4/PD-1
- Recurred with PD-1
- De novo with PD-1


Slide credit: clinicaloptions.com
Infusion Reactions

- Infusion reactions with checkpoint inhibitors are very rare
  - Reported in up to 10% of pts (often much fewer)
  - Usually mild: stop the infusion and restart at a lower rate
  - No steroids: premedications are not necessary
  - As with any infusion, monitor carefully and have emergency medications available
Objectives

- Impact of immunotherapy on cancer treatment.
- Mechanism of action.
- FDA approved indications of Immunotherapy.
- Toxicity associated with immunotherapy and how it differs from conventional chemotherapy.
- Management of immune related side affects
- Long term follow up
Key Questions to Ask Patients Presenting With Potential Immune-Related AEs

- Have you ever received an immune checkpoint inhibitor/immunotherapy?
  - irAEs can occur after discontinuation of ICIs\(^1\)

- Do you have an immunotherapy wallet card?
  - Wallet cards list the type of immunotherapy, key symptoms, and how to notify HCPs\(^2\)

- Do you have an autoimmune condition?
  - ICIs may exacerbate preexisting autoimmune conditions\(^3,4\)

Keys to Optimal Pt Management

• Education of healthcare team, pts, and caregivers
• Rapid and timely intervention
  • Corticosteroids for some intolerable grade 2 irAEs and any grade 3/4 irAEs
  • SLOW taper of glucocorticoids
• Reinitiation of treatment may be possible

This goal is attainable through communication between all members of the healthcare team and pts
Take home messages

- Immune system is the key player in defeating cancer
- Immunotherapy is changing the landscape in Cancer Field
- Different Mechanism of action with different toxicity profile
- Physicians, Pharmacists & **PATIENTS** should be well educated about Immunotherapy **DATA, MOA & TOXICITY**
Conclusions 1

- More patients are being treated with ICIs as indications expand to new malignancies, earlier lines of therapy, and earlier stages of disease
- ICIs can cause irAEs by activating immune cells in nontumor tissues
  - irAEs can occur after discontinuing ICI
- irAEs most commonly presenting to emergency department are diarrhea, colitis, dermatitis, pneumonitis, hypophysitis
Conclusions 2

- When a patient with cancer history presents to clinic:
  - Ask about immunotherapy treatment, wallet card, autoimmune conditions
  - Consult promptly with specialists for affected organ systems
  - Manage based on severity of symptoms by providing supportive care, holding/discontinuing immunotherapy, and administering corticosteroids, as appropriate
  - Make use of resources on identification and management of irAEs, including NCCN Guidelines, ASCO guidelines, and free online CCO/NCCN Decision Support Tool
Gratitude