Combination Immunotherapies: Melanoma

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Objectives

– Understand how combination immunotherapies are currently being used to treat patients with metastatic Melanoma

– Understand the clinical evidence supporting the use of combination immunotherapies to treat patients with metastatic Melanoma

– Be informed and updated on combination immunotherapies in development focusing on metastatic Melanoma
Immunotherapies are being used today to treat a number of different tumor types

- **Prostate Cancer**
  - e.g. Sipuleucel-T

- **Melanoma**
  - e.g. Ipilimumab, pembrolizumab, nivolumab, T-Vec

- **Non-Small Cell Lung Cancer**
  - e.g. Nivolumab, pembrolizumab

- **Renal Cell Carcinoma**
  - Nivolumab
Immunotherapy – Checkpoint Inhibitors

Tumors escape detection from the immune system by expressing “checkpoint” proteins on their cell surface; targeting and inhibiting these cell surface proteins enhances the immune response to the tumor.

**CTLA-4 Inhibition**

**INHIBITION**

**ACTIVATION**

**PD-1/PD-L1 Inhibition**

**INHIBITION**

**ACTIVATION**

- T-Cell
- CTLA-4
- CD28
- Ipilimumab
- B7
- APC (Antigen-Presenting Cell)
- Tumor Cell
- PD-L1
- PD-1 Receptor
- PD-1 Inhibitor
- PD-L1 Inhibitor

**Antigen-Presenting Cell**
Checkpoint inhibitors ipilimumab, nivolumab, and pembrolizumab are FDA approved to treat patients with metastatic melanoma

**Yervoy (ipilimumab)**

*Mechanism of Action*: human, monoclonal antibody that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cells

*Melanoma Indication*: the treatment of unresectable or metastatic melanoma

**Opdivo (nivolumab)**

*Mechanism of Action*: human, monoclonal antibody directed against the programmed death-1 (PD-1) receptor of the T cell

*Melanoma Indication*:
- Monotherapy: the treatment of patients with BRAF V600 wild-type or BRAF V600 mutation positive unresectable or metastatic melanoma
- Combination: in combination with ipilimumab for unresectable or metastatic melanoma

**Keytruda (pembrolizumab)**

*Mechanism of Action*: human, monoclonal antibody directed against the programmed death-1 (PD-1) receptor of the T cell

*Melanoma Indication*: the treatment of patients with unresectable or metastatic melanoma
**Combination immunotherapy is recommended for both 1\textsuperscript{st} line and 2\textsuperscript{nd} line/subsequent metastatic or unresectable melanoma**

<table>
<thead>
<tr>
<th>Metastatic or Unresectable Melanoma $\delta$</th>
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<tbody>
<tr>
<td><strong>1\textsuperscript{st} Line</strong></td>
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<tr>
<td>- Immunotherapy</td>
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<tr>
<td>- Anti PD-1 monotherapy</td>
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<tr>
<td>o Nivolumab</td>
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<tr>
<td>o Pembrolizumab</td>
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<td>- Combination immunotherapy</td>
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<td>o Nivolumab/ipilimumab</td>
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<td><strong>2\textsuperscript{nd} Line or subsequent</strong></td>
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<tr>
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<td>o Nivolumab/ipilimumab</td>
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<td>- Dabrafenib/trametinib</td>
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<tr>
<td>- Dabrafenib</td>
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<tr>
<td>- High-dose IL-2 or Biochemotherapy or cytotoxic agents or imatinib (patients with C-KIT mutations)</td>
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*(source: NCCN Clinical Practice Guidelines in Oncology, Melanoma, Version 2.2016)*

- Targeted therapy if BRAF mutated
- Additional systemic therapies not represented include the following cytotoxic regiments: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel; Biochemotherapy: dacarbazine or temozolomide, and cisplatin or carboplatin with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b; Biochemotherapy for adjuvant treatment of high risk disease: Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b; NCCN also recommends clinical trials for 1\textsuperscript{st} or 2\textsuperscript{nd} line/subsequent therapy
Melanoma - Nivolumab in combination with ipilimumab

Use of nivolumab in combination with ipilimumab is supported by clinical evidence from Phase II and Phase III, double-blind, randomized trials in patients with previously untreated, unresectable or metastatic melanoma

*CR = Complete Response; PR = Partial Response

Patients previously untreated, unresectable, or metastatic melanoma, wild type BRAF V600

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by single agent nivolumab (3 mg/kg) every 2 weeks (n=72)</th>
<th>Ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by placebo every 2 weeks (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>CR=17%; PR=43%</td>
<td>CR=0%; PR=11%</td>
</tr>
<tr>
<td>Median Progression-free Survival</td>
<td>8.9 months</td>
<td>4.7 months</td>
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</table>

Similar results were observed in patients with the BRAF mutation

(source: Hodi et al., 2015)
Melanoma - Nivolumab in combination with ipilimumab

Use of nivolumab in combination with ipilimumab is supported by clinical evidence from Phase II and Phase III, double-blind, randomized trials in patients with previously untreated, unresectable or metastatic melanoma

Phase III: Nivolumab in combination with ipilimumab vs. single agent nivolumab vs. ipilimumab in combination with placebo:

<table>
<thead>
<tr>
<th>Patients previously untreated, unresectable, or metastatic melanoma</th>
<th>Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by single agent nivolumab (3 mg/kg) every 2 weeks (n=314)</th>
<th>Nivolumab (3 mg/kg every 2 weeks (n=316)</th>
<th>Ipilimumab (3 mg/kg) every 3 weeks for 4 doses followed by placebo every 2 weeks (n=315)</th>
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<tbody>
<tr>
<td>Median Progression-free Survival (PFS)</td>
<td>11.5 months</td>
<td>6.9 months</td>
<td>2.9 months</td>
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<tr>
<td>Objective Response Rate (ORR)</td>
<td>CR = 8.9%; PR = 41%</td>
<td>CR = 8.5%; PR = 31%</td>
<td>CR = 1.9%; PR = 12%</td>
</tr>
<tr>
<td>Duration of Response: proportion ≥ months in duration</td>
<td>76%</td>
<td>74%</td>
<td>63%</td>
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(source: Opdivo (nivolumab) FDA approved label, Bristol-Myers Squibb; Larkin et al., 2015)
Adverse events – nivolumab in combination with ipilimumab

Phase III: Nivolumab in combination with ipilimumab vs. single agent nivolumab vs. ipilimumab in combination with placebo; previously untreated, unresectable or metastatic melanoma

<table>
<thead>
<tr>
<th>Treatment-related adverse events</th>
<th>Nivolumab + Ipilimumab (n=313)</th>
<th>Nivolumab (n=313)</th>
<th>Ipilimumab (n=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or 4</td>
<td>55.0%</td>
<td>16.3%</td>
<td>27.3%</td>
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<tr>
<th>Most Common Grade 3 or 4 treatment-related adverse events (&gt;5% Nivolumab + Ipilimumab arm)</th>
<th>Nivolumab + Ipilimumab (n=313)</th>
<th>Nivolumab (n=313)</th>
<th>Ipilimumab (n=311)</th>
</tr>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>9.3%</td>
<td>2.2%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Increase in alanine aminotransferase level</td>
<td>8.3%</td>
<td>1.3%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase level</td>
<td>6.1%</td>
<td>1.0%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Colitis</td>
<td>7.7%</td>
<td>0.6%</td>
<td>8.7%</td>
</tr>
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- Treatment-related adverse events of any grade that led to discontinuation of therapy was 36.4% in the nivolumab + ipilimumab group, 7.7% in the nivolumab group, and 14.8% in the ipilimumab group
- One death was reported in the nivolumab group (neutropenia) and the ipilimumab group (cardiac arrest), but none in the nivolumab + ipilimumab group

According to investigators, “Adverse events were manageable with established treatment guidelines, and most select adverse events resolved with the use of immune-modulatory agents.”

(source: Larkin et al., 2015)
In addition to melanoma, nivolumab in combination with ipilimumab is being studied in a number of tumor types:

- Melanoma
- Lung Cancer
- Myelodysplastic Syndromes
- Lymphoma
- Multiple Myeloma
- Sarcomas
- Renal Cell Carcinoma
- Pancreatic Cancer
- Gastric Cancer
- Bladder Cancer
- Ovarian Cancer
- Glioblastoma
- Colorectal Cancer
- Liver Cancer
- Breast Cancer
Case Report 1:
Metastatic Mucosal Melanoma

• 88-year-old white female
• Left-nasal bloody discharge and pain in March 2014
• Left ethmoid mass resection 3/23/14-musosal melanoma pT3N0M0, 13 mitoses/mm2
• Adjuvant XRT for close margins
• Re-resection 10/23/13 for in situ residual melanoma-followed by radiographic surveillance
Case Report 1: Metastatic Mucosal Melanoma

- Developed new pain in RUQ, April 2015
- Required 120 mg of long-acting morphine 3X daily
- ECOG performance status=2
- PET/CT scan 05/08/2015

LDH = 499 (normal <225)
WBC = 13.6, ANC=11.9,
HCT = 40, Plt = 554
Alk Phos = 225 (<110),
AST = 36, ALT = 19
PET/CT: bones, liver, lung, soft tissue, nasal cavity
Case Report 1:
Metastatic Mucosal Melanoma

- BRAF, c-kit, NRAS wt
- Ipilimumab 3 mg/kg+
  Nivolumab 1mg/kg (05/21/15)
- C2D1 06/15/15
- C3D1 held for grade 2 mucositis, arthralgias,
  AST 160 (grade 2), ALT 90
- Steroid taper 4 weeks, starting 1 mg/kg daily po, PPI bid, Bactrim DS TIW x 2 weeks
Case Report 1:
Metastatic Mucosal Melanoma

- Toxicity resolved in 2 weeks on steroids, finished taper
- PET/CT 08/19/2015-CR
- Started nivolumab 3 mg/kg (09/30/15)-now 11 more doses
- Continues with grade 1 mucositis, arthralgias, LFTs nl.
- PET/CT 11/23/15-CR
Conclusions:
Rapidly Progressing Metastatic Melanoma including Mucosal Melanoma

- Ipilimumab/Nivolumab combination may be as fast acting as targeted BRAF or c-kit targeted therapies
- Age should not play decisive role (biologic age may)
- Close surveillance for novel toxicities:
  - 2 recent cases at Vanderbilt of rapidly fatal myocarditis after 1 dose ipi/nivo (12 and 17 days), more cases being discovered of myocarditis, rhabdomyolysis
  - 1 patient survived with steroids and early infliximab therapy (Dr. Hamid, personal communication)
  - recommending weekly CPK, Troponin x 12 weeks of ipi/nivo (ECOG, BMS trials)
- Biomarkers in development (PDL-1, MHC Class II expression)
Talimogene laherparepvec, or T-Vec, was approved to treat patients with melanoma

**Imlygic (talimogene laherparepvec)**

**Mechanism of Action:**
- T-Vec, a modified herpes virus type 1 oncolytic, replicates within tumors and produces the immune stimulatory protein GM-CSF; T-Vec causes the tumor cell to lyse releasing tumor-derived antigens which, along with GM-CSF, promotes an anti-tumor immune response

**Melanoma Indication:**
- Monotherapy: local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
Proposed Mechanism of Action of T-VEC With PD-1 Inhibitor

TDA: tumour-derived antigen
T-VEC: talimogene laherparepvec
Exact MoA of T-VEC is not known
Melanoma - T-Vec in combination with ipilimumab

**Phase Ib, multicenter, open-label trial of T-Vec in combination with ipilimumab in patients with previously untreated, unresected stage IIIB-IV melanoma**

**Dose:** T-Vec administered intralesionally at ≤ 4 mL of $10^6$ PFU/mL at week 1, then $10^8$ Plaque Forming Units (PFU)/mL at week 4, and then once every two weeks; ipilimumab 3 mg/kg once every 3 weeks as 4 infusions starting week 6

<table>
<thead>
<tr>
<th>Patients previously untreated, unresected stage IIIB-IV melanoma</th>
<th>T-Vec in combination with ipilimumab (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate (ORR)</td>
<td>56% (CR = 33%)</td>
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<tr>
<td>Durable Response Rate (DRR)</td>
<td>44%</td>
</tr>
<tr>
<td>Median Progression-free Survival (PFS)</td>
<td>10.6 months</td>
</tr>
<tr>
<td>Median Overall Survival (OS)</td>
<td>Not reached</td>
</tr>
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</table>

- 12 month and 18 month survival were 72.2% and 67%, respectively
- Grade 3 or 4 treatment-emergent adverse events = 32%; Grade 3 or 4 immune-related adverse events occurred in 2 patients; no treatment-related deaths

(source: Puzanov et al., 2015)
Melanoma - T-Vec in combination with pembrolizumab

**Phase Ib trial of T-Vec in combination with pembrolizumab in patients with previously untreated, unresected stage IIIB-IV melanoma**

**Dose:** T-Vec injected into cutaneous, subcutaneous or nodal lesions at up to 4 mL of $10^6$ PFU/ml day 1, then at up to 4 mL of $10^8$ PFU/ml day 22 and once every 2 weeks (Q2W). Pembrolizumab is given at 200 mg IV Q2W from day 36

<table>
<thead>
<tr>
<th>Patients previously untreated, unresected stage IIIB-IV melanoma</th>
<th>T-Vec in combination with pembrolizumab (n=16 evaluable)</th>
</tr>
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<tbody>
<tr>
<td>Objective Response Rate (ORR)</td>
<td>56.3% (CR = 12.5%, PR = 43.8%)</td>
</tr>
<tr>
<td>Disease Control Rate (DCR)</td>
<td>68.8%</td>
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</table>

- All patients enrolled (n=21) had at least one adverse event
  - Adverse events occurring in at least 30% of patients of any grade: fatigue (52%), pyrexia (48%), chills (43%), rash (38%), headache (33%), and nausea (33%)
  - Grade 3 adverse events: headache (5%) and diarrhea (5%)
  - Treatment-related Grade 3 adverse events occurring in 5 patients: anemia, hyperglycemia, hypoglycemia, hypophosphatemia, headache, macular rash and generalized rash.

- No dose-limiting toxicities

Case Report 2: Metastatic Melanoma with Injectable Lesions

- 64-year-old white female
- Left-leg primary melanoma 06/15/12-superficial spreading melanoma pT3aN0M0, 3 mitoses/mm²
- Surveillance until
- Developed multiple in-transit metastases, lung and soft tissue distant metastases
- LDH 156 (<226)
- Stage IV, pT3aN2cM1b
T-VEC+Pembrolizumab

Stage IV  M1b: In-Transit Lt Leg

Response After 6 Weeks of Treatment
Response in Non-Injected Tumors

Baseline (Week -5)  Week 0  Week 12

Soft tissue

Lung lesion
Pathological Evaluation of a persistent injected lesion

Baseline
(Week -5)

Week 0

Week 24

Week 30 tumor resection
Conclusions:
Metastatic Melanoma with Injectable Lesions

- T-VEC+Ipilimumab or T-VEC+Pembrolizumab combination may be a good option for patients with injectable tumors
- Favorable toxicity profile
- Data from Phase Ib in 1st line patients
- Residual lesions may be scar tissue only
- Will need to add data or at least capture experience in pretreated patients as an addition upon progression on ipi/pembro
- Role of T-VEC injected into liver lesions currently explored for multiple tumor types (melanoma, HCC, breast, lung, gastric etc.)
Melanoma Combination Immunotherapies

Key Takeaways

• Because of their clinical effectiveness, immunotherapies are being developed in combination with each other for use in a number of tumor types

• Nivolumab in combination with ipilimumab is approved to treat patients with unresectable or metastatic melanoma

• T-Vec / ipilimumab and T-Vec / pembrolizumab are promising combination immunotherapies in development for the treatment of patients with previously untreated, unresected stage IIIB-IV melanoma
Questions?
Save-the-Date
ICLIO National Conference
September 30, 2016
Philadelphia
www.accc-icl.io.org
References

Hodi, F.S., et al. Clinical response, progression-free survival (PFS), and safety in patients (pts) with advanced melanoma (MEL) receiving nivolumab (NIVO) combined with ipilimumab (IPI) vs IPI monotherapy in CheckMate 069 study. *J Clin Oncol* 33, 2015 (suppl; abstr 9004)


Opdivo (nivolumab) FDA approved label, Bristol-Myers Squibb

Puzanov, I. et al. Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. *J Clin Oncol* 33, 2015 (suppl; abstr 9063)

Ribas, A. et al. A multicenter, open-label trial of talimogene laherparepvec (T-VEC) plus pembrolizumab vs pembrolizumab monotherapy in previously untreated, unresected, stage IIIB-IV melanoma. *J Clin Oncol* 33, 2015 (suppl; abstr TPS9081)