Learning Objectives:

1. Describe the epidemiology and pathophysiology of melanoma
2. Review the fundamentals of immunotherapy
3. Discuss current pharmacotherapy options for the treatment of metastatic melanoma
4. Evaluate the immunotherapeutic agents for metastatic melanoma
5. Recommend the appropriate sequence and dosing of the new immunotherapeutic agents
I. Epidemiology
   A. Types of skin cancer
      i. Basal cell carcinoma
      ii. Squamous cell carcinoma
      iii. Kaposi’s sarcoma – Rare cancer of cells lining blood vessels
      iv. Melanoma – Neoplasm of pigment (melanin) producing cells
   B. Incidence
      i. Average age at diagnosis is 62 years
      ii. Melanoma is the fifth leading cancer in men and seventh in women
      iii. Melanoma accounts for less than two percent of skin cancers, though it is responsible for the vast majority of deaths from skin cancers
      iv. Melanoma is more than 20 times more common in fair skinned individuals
      v. Incidence is rising dramatically
         a. Fastest growing cancer incidence rates in the United States – Incidence has doubled 1982-2011
         b. Lifetime probability of developing melanoma in the United States (from 2004-2006)
            1) 1 in 37 men
            2) 1 in 56 women
   C. Geographical representation
      i. Australia and New Zealand have the highest incidence and mortality rates of melanoma in the world
         a. High rates of predominantly fair skinned population
         b. High levels of ambient ultraviolet (UV) radiation
   D. Survival
      i. Melanoma survival rates depend on stage of diagnosis
         a. Metastatic melanoma has a five-year survival rate at about 15% to 20%. The 10-year survival is about 10% to 15%
         b. Comparison of other stages of melanoma (Figure 1)

![Figure 1: Survival comparison between melanoma cancer stages](image)
E. Risk factors

   i. UV-radiation exposure
      a. UVB Radiation > UVA Radiation
      b. History, timing, and pattern of sun exposure (intense, intermittent exposure)
      c. Tanning beds
      d. Skin and hair color – fair and pale skinned individuals pose a higher risk

   ii. Family history of melanoma

   iii. History of non-melanoma skin cancer

   iv. Immunosuppression
      a. HIV patients
      b. Organ transplant recipients

II. Pathophysiology

A. The sequence of events (melanomagenesis) is poorly understood

B. Likely arises from the epidermal melanocytes of the skin through a multistep process involving both (Figure 2)

   i. UV radiation exposure
      a. Can directly affect mutagenesis
      b. Promote growth factor secretion – leads to cell proliferation
         1) FGF – (Fibroblast growth factor)
         2) TGF-α – (Transforming growth factor – alpha)

   ii. Genetic susceptibility – mutations altering cell proliferation, differentiation, and death
      a. Mutations take place in
         1) Specific oncoproteins responsible in regulating cell survival, growth, and differentiation
            • BRAF – (v-raf murine sarcoma viral oncogene homolog B) common mutation found in 40-60% of patients – inhibitors on the market
            • MEK – (mitogen activated protein kinase) – inhibitors on the market
            • NRAS – (neuroblastoma RAS viral [v-ras] oncogene homolog)
         2) Tumor suppressor genes
            • CDKN2A – (cyclin-dependent kinase inhibitor 2A)

Figure 2: Mechanisms involved in melanoma carcinogenesis
C. Melanocytes synthesize melanin to protect various tissues, such as the skin, from UV radiation-induced damage

D. In adults, most melanocytes are located in two main areas
   i. Epidermal – dermal junction of skin
   ii. Choroid of the eye

E. Primary melanoma can arise in any area of the body with melanocytes and has low tendency to metastasize

F. Vertical growth of melanoma and high nevus count (moles) have a very high potential for metastasis

G. Melanocytes require growth factors for proliferation
   i. They secrete growth autocrine and paracrine factors that can also facilitate growth
   ii. The PI3K-AKT pathway is often over-active

H. Tumor progression by the Clark Model
   i. Starts with benign nevus and can eventually spread vertically to surrounding tissue (Figure 3)
   ii. In situ and locally invasive melanomas are typically curable by surgery, advanced disease is difficult to treat and often lethal

![Figure 3: Tumor progression by the Clark Model](image-url)

III. Prevention and Screening
    A. “ABCD” – acronym used when screening for tumors
       i. A – Asymmetry
       ii. B – irregular Borders
       iii. C – Color of lesions
       iv. D – Diameter (>6 mm)
       v. E – Evolving
IV. Signs and symptoms

A. Local disease – usually asymptomatic
   i. Pruritus
   ii. Bleeding
   iii. Pain

B. Metastatic disease – symptoms based on location of tumor spread
   i. Common metastatic sites – lungs, liver, brain, bone
   ii. Rare sites – adrenal glands, spleen, gastrointestinal tract

V. Diagnosis and staging

A. Diagnosis is based on excisional biopsy
   i. Requires one to three mm margins of normal skin and part of subcutaneous fat
   ii. Complete history
   iii. Positron Emission Tomography (PET)/Computed Tomography (CT) scan if suspicion of stage III or higher
   iv. Mutation analysis – helps guide treatment decision
      a. Specifically BRAF V600
      b. Pharmacologic agents available for this specific mutation

B. Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Node</th>
<th>Metastases</th>
<th>Key Description of Lesion</th>
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<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>Non-invasive tumor</td>
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<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>≤1mm in thickness – no ulceration</td>
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<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>≤1mm in thickness – w/ ulceration OR 1.01-2.0 mm – no ulceration</td>
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<tr>
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<td></td>
<td></td>
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<tr>
<td>IIA</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td>1.01-2.0 mm – w/ ulceration OR 2.01-4.0 mm – no ulceration</td>
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<tr>
<td></td>
<td>T3a</td>
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<tr>
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<td>M0</td>
<td>2.01-4.0 mm – w/ ulceration &gt;4.0 mm – no ulceration</td>
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<td></td>
<td>T4a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
<td>&gt;4.0 mm – w/ulceration</td>
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<td>≥N1</td>
<td>M0</td>
<td>Node positive disease</td>
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<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Metastatic disease</td>
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</table>

Table 1: Melanoma staging criteria

TREATMENT

I. Immunology Review

A. Human immune system is broken down into two categories
   i. Innate immune system
      a. Non-specific defense mechanism that responds within hours of antigen exposure
      b. First line of defense after pathogen has entered systemic circulation that requires
         1. Inflammatory response
         2. Phagocytes (also called antigen presenting cells – APCs) – can ingest and digest foreign pathogens into its protein components
            • Neutrophils – fast and abundant cells that respond first
            • Macrophages
            • Dendritic cells (DCs) – cells that are most involved in activating adaptive immune system
      c. Rapid response
ii. Adaptive immune system
   a. Divided into humoral and cell-mediated immunity (Figure 4)
   
   ![Diagram of Humoral vs. Cellular Immunity]

   **Figure 4: Humoral vs. cellular immunity**

   b. Creates defense against specific invaders
   c. Involves antigen-specific immune responses consisting of lymphocytes
      1. B-lymphocytes (B-cells)
         - Produced in the bone marrow
         - Involved in the humoral response – production of antibodies to ‘tag’ foreign pathogens for phagocytosis or pathogen dysfunction
      2. T-lymphocytes (T-cells)
         - Produced in bone marrow but mature in the thymus
         - Consist of helper T-cells and cytotoxic T-lymphocytes (CTLs)
         - Involved in cell-mediated response
   
   d. Much slower response
   e. Eliminating cancer cells require activation of CTL
      1. Antigen bound to Major Histocompatibility Complex I (MHC-I) interacts with the T-cell Receptor (TCR) of CTL
      2. B7 protein binds to CD28 receptor on CTL to provide a costimulatory signal that maintains CTL activation
      3. Activated CTLs travel to site of cancer cell
      4. CTLs target specific antigen on cancer cell surface
      5. Causes apoptosis of cancer cell
      6. Intricate balance of checkpoints that accelerate or dampen immune responses
   f. Helper T-cells provide support by secreting cytokines to keep CTLs activated
II. Melanoma Immunotherapy
A. Historical perspective
   i. Over 100 years of research and development
      a. 1890’s – Dr. William Coley found success in injecting bacteria directly into tumors
         1. Caused complete remission in a 21 year old man with malignant sarcoma
         2. Results were unpredictable
      b. 1900-1957 – Immuno-surveillance was a theory formulated suggesting that lymphocytes act as ‘sentinels’ in recognizing and eliminating continuously arising, nascent, transformed cells
         1. Surveillance provides important host protection
         2. Decreases cancer rates by inhibiting carcinogenesis and maintaining regular cell homeostasis
      c. 1976 – Dacarbazine became the first approved alkylating agent for use in metastatic melanoma
         1. Use was limited due to low response rates of 10-15% (Appendix I)
         2. Median survival 6-9 months
         3. Five year overall survival – 6%
         4. Toxicities of myelosuppression, nausea/vomiting, flu-like symptoms
         5. Other chemotherapy agents approved
      d. 1986-1992 – Interferon-α (IFN-α) and high dose interleukin-2 (IL-2) introduced as therapeutic options for melanoma
      e. Late 2000’s – Development of novel effective agents
B. Four general approaches to immunotherapy in cancer
   i. Non-specific immune stimulation (applying the gas)
      a. Creates generalized activation of immune system in-vivo
      b. APCs can be activated using pharmacological cytokines
         1. IFN-α
            • Historically used as adjuvant therapy in those with high risk of relapse after surgery
            • Many intolerable toxicities – fevers, chills, malaise, arthralgias, weight loss, and depression
         2. IL-2
            • 15-25% response rates with 2-5% achieving complete response
            • 5-10% of patients can last for decades
            • Many toxicities – capillary leak syndrome, bone marrow suppression, hepatotoxic, renal toxic, nausea/vomiting
      c. T-cells become activated to kill tumor cells
      d. Disadvantage
         1. Many adverse effects due to non-specific activation of immune system
         2. Subsequent treatments not well-tolerated
   ii. Vaccines (eliciting an immune response to cancer antigens)
      a. Intended to specifically initiate or amplify a host response against evolving tumors
         1. Glycoprotein 100 (gp100) – studied in Phase II trials with IL-2
            • Minimal response rates: ~16%
         2. Melanoma-associated antigen 3 (MAGE-3) – protein expressed on around 70% of melanoma cells
            • Study vaccine was associated with significantly prolonged times to treatment failure
      b. Two important limitations
         1. Lack of understanding of how to immunize patients to achieve potent cytotoxic T-cell responses
2. Presence of inhibitor signaling in the tumor microenvironment may decrease or disable antitumor immune responses before clinically relevant tumor killing can take place
   c. Overall, vaccines have failed to induce significant objective tumor shrinkage and more research is needed

iii. Adoptive cell transfer (engineered CTLs)
   a. Extract immune cells from patient
   b. Activates the extracted cells outside the body
   c. Engineered to specifically target cancer tissue
   d. Preliminary results are promising
   e. Disadvantages
      1. More research needed
      2. Therapy likely to be very costly

iv. Immune-checkpoint blockade (removing the brakes)
   a. Receptor upregulation on tumor cells and APCs that dampen immune response
   b. Normal function is to prevent collateral damage to healthy tissue
   c. Blocking interaction allows for immune system to continue fighting

C. The cancer-immunity cycle<sup>13</sup>
   i. Model of stepwise events required for an appropriate immune response to killing cancer cells

   ![Figure 5: Cancer immunity cycle]

   ii. Cycle steps
      a. Step 1 – Neoantigens created by oncogenesis are released and captured by DCs for processing
      b. Step 2 – DCs present the captured antigen on MHCI & MHC II to T-cells
         1. DCs having antigen bound to MHCI presents to CTL
         2. DCs having antigen bound to MHCII present to helper T-cells
      c. Step 3 – Priming and activation of effector T-cell responses against cancer specific antigens that are viewed as foreign
1. Helper T-cells become activated through interaction of co-stimulatory interactions
2. Activation causes produce cytokines to active other CTL
d. Step 4 - Activated effector T-cells traffic to tumor site
e. Step 5 – Activated effector T-cells infiltrate the tumor bed
f. Step 6 – Recognition of cancer cells by T-cells through interaction between T-cell receptors (TCRs) and cognate antigen bound to MHCI
g. Step 7 – Killing of targeted cancer cells
h. Return to Step 1 – Killing of the cancer cells releases additional tumor-associated antigens that will cause the cycle to repeat again

iii. Problems
   a. In melanoma, the immunity cycle does not work optimally
   b. Tumor antigens may not be detected
   c. DCs and T-cells may treat antigens as self rather than foreign
      1. PD-L1 on tumor binding to PD-1 on CTL plays a role
      2. Suppresses CTL ability to recognize foreign cancer cells

iv. Goals of cancer immunotherapy
   a. Initiate or re-initiate a self-sustaining cycle of cancer immunity
   b. Enabling the immunity to amplify and propagate
   c. Have appropriate restraints to prevent autoimmune inflammatory responses
   d. Modulation of the immune system may allow for better host response to clearing tumors

D. Immune checkpoints – function to restrain or dampen over-exuberant responses\textsuperscript{14, 25-27}
   i. CTLA-4 inhibitors (cytotoxic T-lymphocyte-associated antigen 4)
      a. Ipilimumab is the only approved agent
      b. Site of action – Priming phase of T-cells (Step 3)
      c. Mechanism of action: blocks the interaction CTLA-4 found on CTL with B7 protein on dendritic cells (See Figure 6)
      d. CTLA-4 receptors are upregulated during T-cell activation
      e. CTLA-4 bound to B7 normally prevents helper T-cell activation
      f. This interaction binds with higher affinity than the stimulatory interaction of CD28 with B7
      g. Blockade may be more non-specific
      h. Reported toxicities
         1. Common: Fatigue, diarrhea, pruritus, colitis
         2. Many are immune-mediated adverse events that may require supportive care
   ii. Approval of CTLA-4 inhibitors – ipilimumab
      a. Efficacy first shown in two large Phase III trials\textsuperscript{15-17}
### Table 2: CTLA-4 inhibitor approval trial summary

#### iii. PD-1 inhibitors (Programmed-Death 1)
- **a.** Two FDA approved agents
  1. Pembrolizumab
  2. Nivolumab
- **b.** Site of action: priming and effector phases (Steps 3 and 6 respectively)
- **c.** Mechanism of action: inhibits interaction of PD-L1 and PD-L2 found on tumors cells/antigen presenting cells with PD-1 found on CTLs (See Figure 6)
- **d.** PD-L1 is naturally upregulated on host cells like B-cells and macrophages
- **e.** Tumor cells can express the PD-L1 protein and are thought to ‘escape’ killing by binding to the PD-1 protein on an activated CTL
- **f.** Blocking this interaction can allow lysis to continue
- **g.** May be more specific therapy than CTLA-4 inhibitors
- **h.** Reported toxicities
  1. Fatigue, peripheral edema, chills, constipation, pruritus, diarrhea
  2. Immune mediated adverse effects: pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hypo/hyperthyroidism

#### iv. Approval of PD-1 inhibitors\(^{18,19}\)

### Table 2: CTLA-4 inhibitor approval trial summary

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#### iv. Approval of PD-1 inhibitors\(^{18,19}\)
CHECKMATE-066 trial
418 previously untreated patients with metastatic melanoma without BRAF mutation

Nivolumab
- 3 mg/kg Q 2 weeks vs.
Dacarbazine
- 1000 mg/m² Q 3 weeks

1 year OS
Nivolumab 72.9%
Dacarbazine 42.1%

And
PFS
Nivolumab 5.1 months
Dacarbazine 2.2 months

And
ORR
Nivolumab 40%
Dacarbazine 13.9%

Table 3: PD-1 inhibitor approval trial summary

v. Pembrolizumab is currently approved as second-line option in ipilimumab refractory patients
vi. Nivolumab approved as first line option in metastatic melanoma

Figure 6: Immune checkpoint blockade of PD-1 and CTLA-4

E. Combination checkpoint inhibition
   i. Preliminary evidence from phase 1 and phase 2 clinical trials have shown the combination to be effective

<table>
<thead>
<tr>
<th>Population</th>
<th>Interventions</th>
<th>Primary Endpoint</th>
<th>Results</th>
</tr>
</thead>
</table>
| Phase I Trial
86 patients with stage III or IV melanoma with no previous T-cell modulating antibody therapy (except ipilimumab for patients in sequenced-regimen cohorts). | Various dosing regimens involving ipilimumab and nivolumab | ORR | Depending upon the dose cohort, ORR ranged from 21-53%
Nivolumab 1 mg/kg + ipilimumab 3 mg/kg yielded the most substantial ORR
Supported the utilization of those doses in Phase II trial |
**Phase II Trial**

142 patients with Stage III or IV melanoma

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Nivolumab 1 mg/kg Q 3 weeks x 4 doses</th>
<th>Ipilimumab 3 mg/kg Q 3 weeks x 4 doses</th>
<th>Nivolumab + ipilimumab ORR 61% (95% CI: 49-72)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td>Ipilimumab 3 mg/kg Q 3 weeks x 4 doses</td>
<td><strong>VS</strong></td>
<td>Ipilimumab 11% (95% CI: 3-25).</td>
</tr>
</tbody>
</table>

**Table 5: Combination immune checkpoint inhibitor trial summary**

**III. Current Treatment Guideline Recommendations for Metastatic Melanoma**

i. National Comprehensive Cancer Network – NCCN

```
First Line Therapy

Unresectable or metastatic melanoma BRAF V600 wild type

Nivolumab (Category 1)
Ipilimumab (Category 1)
Pembrolizumab
High-dose IL-2
```

**Figure 7: NCCN Melanoma treatment recommendations for metastatic melanoma**

ii. Current guidance provides no preference for any checkpoint inhibitor agent over another

**IV. Clinical Question**

A. Which checkpoint inhibitor/combinations should be used initially in first-line treatment of metastatic melanoma? What evidence if any supports this?

B. Of the PD-1 inhibitors, which agent is preferred?

C. Are the toxicities of combination treatment manageable?

**LITERATURE REVIEW**


**Objective**

To compare PD-1 inhibition with CTLA-4 blockade involving patients with advanced melanoma

**Study Design**

Randomized, controlled, phase III study

**Population**

- **Inclusion**
  - Patients 18 years of age or older
  - Histologically confirmed, unresectable Stage III or IV melanoma
  - No previous systemic therapy for advanced disease
  - Known BRAF V600 mutation status required
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2)

- **Exclusion**
  - Previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors
| Primary Outcome | Patient characteristics:  
| Patient characteristics: | o Patients with ocular melanoma  
| o Active brain metastases  
| o History of serious autoimmune disease |
| PFS – defined as time from randomization to documented disease progression  
| OS – defined as time from randomization to death from any cause |
| Secondary Outcomes | Outcome definitions:  
| Outcome definitions: | o ORR – defined as percentage of patients with complete or partial response  
| o Duration of response – defined as the time from the first documented response to radiologic progression  
| o Safety as assessed in as-treated population  
| o Efficacy in intent-to-treat population |
| Methods | Study design:  
| Study design: | o Patients randomly assigned in a 1:1:1 ratio to receive  
| Study design: | o Pembrolizumab 10 mg/kg of body weight either:  
| Study design: |  - Every 2 weeks  
| Study design: |  - Every 3 weeks  
| Study design: | o Ipilimumab –3 mg/kg every 3 weeks (4 cycles)  
| Study design: | o Pembrolizumab administered IV during 30 min infusion and continued until either  
| Study design: |  - Disease progression  
| Study design: |  - Onset of unacceptable side effects  
| Study design: |  - Investigators decision to discontinue treatment  
| Study design: |  - Maximum of 24 months of therapy  
| Study design: | Patients with confirmed complete response (CR) who received 6 months of pembrolizumab could discontinue therapy – with two more additional doses beyond CR  
| Study design: | Ipilimumab administered during a 90-minute period and continued for the same reasons as pembrolizumab  
| Study design: | Response measured at week 12 and every 6 weeks thereafter  
| Study design: | Survival assessed every 3 months after discontinuation of study drug |
| Statistics | Statistical methods:  
| Statistical methods: | o Kaplan-Meier method to calculate estimates of PFS and OS  
| Statistical methods: | o Hazard ratios (HR) and associated 95% confidence intervals (CI) assessed with Cox-proportional-hazards model  
| Statistical methods: | o Response rates studied using Miettinen and Nurminen method |
| Enrollment | Patient enrollment:  
| Patient enrollment: | o Pembrolizumab every 2 week arm - 279 patients  
| Patient enrollment: | o Pembrolizumab every 3 week arm – 277 patients  
| Patient enrollment: | o Ipilimumab every 3 weeks arm – 278 patients |
| Baseline | Baseline characteristics:  
| Baseline characteristics: | o Well matched between groups  
| Baseline characteristics: | o Among enrolled patients, 68.7% had no previous treatment for advanced melanoma  
| Baseline characteristics: | o 68.7% had an ECOG performance status of 0  
| Baseline characteristics: | o BRAF V600 mutation was observed in 36.2% of patients (with ~50% receiving previous BRAF inhibitor treatment)  
| Baseline characteristics: | o 80.5% of patients had PD-L1-positive tissue samples |
| Results | Study results:  
| Study results: | o Estimated 6 month PFS rates |
• Median estimates of PFS:
  o Pembrolizumab every 2 weeks: 5.5 months (95% CI 3.4-6.9 months)
  o Pembrolizumab every 3 weeks: 4.1 months (95% CI 2.9-6.9 months)
  o Ipilimumab: 2.8 (95% CI 2.8-2.9 months)
• HR for disease progression for both pembrolizumab groups vs. ipilimumab: 0.58 (95% CI 0.46-0.72) – p<0.001
• Benefit for pembrolizumab over ipilimumab seen in both PD-L1-positive and PD-L1 negative subgroups (PD-L1 negative subgroup not statistically significant)
• OS
  o Pembrolizumab every 2 weeks and 3 weeks longer than ipilimumab
  o 1 year OS: ~70% pembrolizumab vs. 58.2% ipilimumab
• RR
  o ~33% for pembrolizumab groups and 11.9% in ipilimumab group (p<0.0001)
• Adverse Events
  o Grade 3-5 toxicities attributed to study drugs pembrolizumab every 2 weeks, every 3 weeks, and ipilimumab: 13.3%, 10.1%, and 19.9% respectively
    ☀ Hypo/hyperthyroidism was more frequent in the pembrolizumab groups
    ☀ Colitis and hypophysitis were more frequent in the ipilimumab group

Conclusions
• Pembrolizumab prolonged progression free survival and overall survival compared to ipilimumab

Discussion

Strengths
• Trial design – Phase 3, randomized, controlled
• Multi-centered – 16 countries
• Efficacy determined in intent-to-treat population
• Safety assessed in as-treated (per-protocol) population
• First trial comparing head-to-head immune checkpoint inhibitors

Limitations
• Pembrolizumab did not show statistical benefit in overall survival for
  o Female population
  o PD-L1 negative patients
  o **BRAF** mutant gene with or without previous therapy
• Long-term duration of benefit not known for pembrolizumab
• Median overall-survival benefit data not reached
• 10 mg/kg dose is 5 times the dose used in the approval of drug. Potentially much more costly

Take Home Points
• Pembrolizumab is superior to ipilimumab in specific patient populations for frontline treatment of patients with metastatic melanoma
• First study to give insight that PD-1 inhibitors can be used first line
• Dose of pembrolizumab every 3 weeks = better patient convience
• 10 mg/kg dose is not currently FDA approved and confers more patient costs

<table>
<thead>
<tr>
<th>Percent</th>
<th>Pembrolizumab Q 2</th>
<th>Pembrolizumab Q 3</th>
<th>Ipilimumab Q 3</th>
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*Estimated 6 month PFS*
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<th>Objective</th>
<th>To determine the efficacy of combination therapy of ipilimumab plus nivolumab compared to ipilimumab</th>
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</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Double blind, randomized, placebo-controlled, Phase III trial</td>
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</table>
| Population | - Inclusion  
  - Patients 18 years of age or older  
  - Histologically confirmed, unresectable Stage III or IV melanoma  
  - No previous systemic therapy for advanced disease  
  - Known *BRAF* V600 mutation status required  
  - Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1  
  - Exclusion  
  - ECOG performance status of 2 or higher  
  - Previous therapy with CTLA-4, PD-1, or PD-L1 inhibitors  
  - Patients with ocular melanoma  
  - Active brain metastases  
  - History of serious autoimmune disease |
| Primary Outcome | - PFS – defined as the time between date of randomization and date of documented progression or death  
  - OS – defined as time from randomization to death from any cause |
| Secondary Outcomes | - ORR  
  - PD-L1 expression as a predictable biomarker for efficacy outcomes  
  - Safety |
| Methods | - Patients randomly assigned in 1:1:1 ratio to receive one of the following  
  - Nivolumab 3mg/kg every 2 weeks (plus ipilimumab matched placebo)  
  - Nivolumab 1mg/kg every 3 weeks plus 3 mg of ipilimumab every 3 weeks for 4 doses  
  - followed by nivolumab 3mg/kg for cycle 3 and beyond  
  - Ipilimumab 3mg/kg IV every 3 weeks for 4 doses (plus nivolumab-matched placebo)  
  - Randomization was stratified according to  
  - PD-L1 status  
  - *BRAF* mutation status  
  - Cancer stage  
  - Assessment of tumor response at 12 weeks, then every 6 weeks for 49 weeks  
  - Then assessed every 12 weeks until progression or treatment discontinuation |
| Statistics | - PFS calculated by – Two-sided log rank test with stratification  
  - Hazard ratios (HR) and two sided 99.5% CI calculated using Cox proportional-hazard model  
  - Kaplan-Meier method used to measure PFS |
| Enrollment | - 945 patients randomized 1:1:1  
  - Patients balanced on age and gender  
  - Majority of patients were male (~64%) and <65 years old  
  - Most patients (~65%) were PD-L1 negative with no *BRAF* mutation (~68%) |
| Results | - Most frequent reason for discontinuation in nivolumab and ipilimumab group was disease progression (49.2% and 65% respectively)  
  - Most frequent reason for discontinuation of nivolumab plus ipilimumab group was toxicity (38.3%)  
  - 61% of patients had measurable tumor shrinkage  
  - Only ~14% of patients did not respond  
  - PFS |
HR of combination compared to ipilimumab – 0.42 (99.5% CI 0.31-0.57)
HR of nivolumab compared to ipilimumab – 0.57 (99.5% CI 0.43-0.76)
HR of combination compared to nivolumab – 0.74 (95% CI 0.60-0.92) – study not designed for formal comparison

Secondary Endpoints
• ORR – Combination (57.6%), nivolumab (43.7%), ipilimumab (19.0%)
• Complete response (CR) – Combination (11.5%), nivolumab (8.9%), ipilimumab (2.2%)
• PFS in pre-specified subgroups showed consistently longer survival with nivolumab or combination therapy for
  ▪ PD-L1 status
    ▪ Positive
  ▪ Negative

• BRAF mutation status – positive or wild type – median PFS 11.2-11.7 months
• PD-L1 negative status showed difference in PFS for nivolumab compared to PD-L1 positive status
• Adverse events
  ▪ Treatment of adverse events of any grade occurred in 95.5% of those in the combination group
  ▪ Most common adverse event in the combination – diarrhea, fatigue, pruritis
  ▪ Incidence of treatment-related adverse events of grade 3 or 4 higher in combination group, 55%, compared to 16.3% in nivolumab and 27.3% in ipilimumab
Conclusions

- In previously untreated advanced melanoma, longer PFS and higher rates of ORR with nivolumab alone and with combination of nivolumab and ipilimumab compared to ipilimumab alone

Discussion

Strengths

- Results of PD-L1 positive/negative results provide insight as to who would benefit from combination therapy the most
- Relatively large sample size
- Multi-centered trial (137 centers)
- Study design – Phase III, randomized, controlled
- Confirmation of superiority of PD-1 inhibitor class over CTLA-4 class

Limitations

- Overall survival results are still pending
- Toxicities of combination therapy may limit first line use
- Majority of patients <65 years old – benefit in elderly may be questionable
- Majority of patients male gender
  - No breakdown in efficacy between genders
- Majority of patients were ECOG 0-1

Take Home Points

- Combination therapy with nivolumab plus ipilimumab and nivolumab alone in metastatic melanoma produced far better response rate compared to ipilimumab alone
- Results are too early to be standard of care due to no overall survival data
- PD-1 inhibitor class is superior to CTLA-4 and should be category 1 recommendation
- This combination therapy comes at the price of more toxicities and tremendous cost of therapy

Costs & Considerations

I. Cost Effective Analysis (CEA) with Checkpoint Inhibitors
   A. No analysis has been performed to date
   B. Wholesale Acquisition Cost (WAC) Comparison
      i. Nivolumab vs. pembrolizumab
      ii. Cost of ipilimumab ~$160,000 for 3 months of therapy
      iii. Combination therapy would be very costly for patients

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
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<tbody>
<tr>
<td><em><em>Cost for 3 months of therapy (WAC</em>)</em>*</td>
<td></td>
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<tr>
<td>$41,437</td>
<td>$41,434</td>
</tr>
<tr>
<td><strong>Frequency of Administration</strong></td>
<td></td>
</tr>
<tr>
<td>Every 2 weeks</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td><strong>Infusion Time</strong></td>
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<tr>
<td>1 hour</td>
<td>30 minutes</td>
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<tr>
<td><strong>Efficacy (no official comparison between agents)</strong></td>
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<tr>
<td>Median OS at 12 months: 63%</td>
<td>OS at 12 months: 66%</td>
</tr>
<tr>
<td>Median OS at 24 months: 48%</td>
<td>OS at 24 months: 49%</td>
</tr>
<tr>
<td></td>
<td>Median PFS: 4.4 months</td>
</tr>
<tr>
<td></td>
<td>Progression free at 12 months: 35%</td>
</tr>
</tbody>
</table>

* WAC – Wholesale Acquisition Cost
^ Acquisition cost is based on the average wholesale price (AWP) for the most common or FDA-approved dosage and a patient weighing 80 kg, and it does not include the cost of supportive care for immune-related toxicity.
CONCLUSIONS

I. Optimal first-line sequence of therapy in unresectable metastatic melanoma
   A. PD-1 inhibitor \(\rightarrow\) Ipilimumab
   B. Combination therapy (PD-1 inhibitor + CTLA-4) offers greater response rates than either agent alone
      i. Results are very exciting
      ii. No OS data to support first-lint use
      iii. Although generally tolerable, patients are subjected to many more toxicities
      iv. Very high cost combining two very expensive therapies
      v. Wait until more data is available to try this option in most patients
         i. May consider if patient’s ECOG is 0-1
         ii. May be an option in PD-L1 negative patients
         iii. No significant co-morbidities
         iv. If patient is able to afford therapy
   C. Pembrolizumab vs. Nivolumab?
      i. Costs are virtually comparable
      ii. Patient convenience favors pembrolizumab due to dosing frequency and infusion time
      iii. Nivolumab may have better market advantage right now due to fixed dosing recommendation in other types of malignancies
      iv. Pembrolizumab likely preferred in metastatic melanoma due to slightly longer market experience, ease of administration, and patient convenience
   D. Toxicities
      i. PD-1 inhibitors – have shown to be rare and manageable
      ii. CTLA-4 inhibitors – much more prevalent in terms of immune mediated reactions

II. Expect NCCN guideline update for metastatic melanoma soon
III. Proposed Algorithm

![Figure 8: Proposed NCCN treatment algorithm for metastatic melanoma](image-url)
*Considerations for nivolumab plus ipilimumab

- Excellent performance status
- No co-morbidities
- Possible PD-L1 negative status
- Affordability of high cost of dual therapy

IV. The future is bright for immunotherapy and is now the standard of care over chemotherapy in metastatic melanoma

A. Immune checkpoint inhibitors are being studied in many different cancers
   i. Non-small cell lung cancer (nivolumab already approved)
   ii. Renal cell carcinoma
   iii. Many hematologic malignancies

REFERENCES

I. Glossary of terms used in oncology studies

A. **Objective response (OR) or Overall response rate (ORR):** Objective response means either a partial or complete response (In the literature, frequently see “CR+PR” which means the same thing).

B. **Complete response (CR):** All detectable tumor has disappeared.

C. **Partial response (PR):** This roughly corresponds to at least a 50% decrease in the total tumor volume but with evidence of some residual disease still remaining.

D. **Progression free survival (PFS):** Measures the length of time that a patient is both alive and without worsening of their cancer.

E. **Overall survival (OS):** Time from randomization until death from any cause.

II. Eastern Cooperative Oncology Group (ECOG) Performance Status

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ECOG PERFORMANCE STATUS</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
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