Melanoma Diagnosis and Management Considerations

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Objectives

1. Describe the epidemiology, pathophysiology, and risk factors associated with melanoma.
2. Discuss the screening, diagnosis, and staging of melanoma.
3. Outline treatment considerations and the mechanism of action of chemotherapy and supportive therapies.
4. Describe the side effect and monitoring parameters associated with therapies managed through specialty pharmacy.
5. Discuss counseling strategies to maximize compliance and adherence.
Epidemiology

• Estimations for 2016
  – 76,380 new cases of melanoma
  – 10,130 deaths
• 5th most frequent malignancy diagnosed in men and 7th most frequently diagnosed in women
• Roughly 85% cases diagnosed locally


Survival Curve: Stage of Disease

http://www.mmmp.org/MMMP/import.mmmp?page=tnm_staging.mmmp
Pathophysiology

- Melanomagensis
  - Alter cell proliferation, differentiation, and death
  - Impact susceptibility to the carcinogenic effects of ultraviolet radiation
- Sun-protect skin
  - High nevus count
  - Intermittent UV radiation
  - BRAF mutations
- Sun-exposed skin
  - Low nevus count
  - Chronic sun exposure
  - KIT mutations


Risk Factors

- Fair skin, light hair and eyes
- Close relatives with a history of melanoma
- Exposure to cancerous causing chemicals such as arsenic, coal tar, and creosote
- Presence of multiple birthmarks
- Weakened immune system from AIDS, leukemia, organ transplant, certain medications
- Tanning beds
- UVA and UVB exposure
- Previous melanoma

 Screening

• Without a history of family history
  – No studies completed
  – Periodic skin examinations

• Consider screening if:
  – Family history in two or more blood relatives
  – Presence of multiple atypical moles
  – Presence of numerous actinic keratosis

https://www.mskcc.org/cancer-care/types/skin/screening-guidelines-skin

 ABCDEs of Melanoma

A - Asymmetry
B - Border
C - Color
D - Diameter
E - Evolving

https://www.melanoma.org/understand-melanoma/diagnosing-melanoma/detection-screening/abcde-melanoma
Types of Melanoma

- Superficial spreading melanoma
- Nodular melanoma
- Lentigo Maligna melanoma
- Acral Lentiginous melanoma
- Melanoma of the eye

Superficial Spreading Melanoma

Nodular Melanoma

http://www.healthline.com/health/skin-cancer/nodular-melanoma

Lentigo Maligna Melanoma

http://www.regionalderm.com/Regional_Derm/Lfiles/lentigo_maligna.html
Diagnosis

• Biopsy
  – Shave vs. Punch
    • Shave biopsies should never be used to diagnose melanoma
  – Incisional vs. Excisional biopsy
    • Full thickness with margins

• Pathology
  – Type of melanoma
  – Degree invasion


Staging: Diagnostic Tests

• FNA
• Sentinel lymph node
• Chest XR
• CT scan
• PET
• MRI

Diagnosis

• Clark Level
  – How deep the tumor has penetrated base histology
  – Directly related to risk of metastasis to nodes
  – Level I-V
    • Level I is restricted to epidermis (in situ)
    • Level V is metastatic

Breslow’s Thickness

– I 0.75 mm or less
– II 0.76 mm to 1.49 mm
– III 1.50 mm to 2.49 mm
– IV 2.50 mm to 3.99 mm
– V 4.0 mm or greater

NCCN Guidelines, Version 1.2017
Staging: American Joint Committee on Cancer

- **Stage I**
  - A: < 1mm thick, no ulceration, Clark II-III
  - B: < 1 mm thick with ulceration, Clark IV-V

- **Stage II**
  - > 1 mm thick with any characteristic

- **Stage III**
  - Regional node involvement
  - Transit metastases

- **Stage IV**
  - Distant metastases


Treatment
Stage I & Stage II

- **Stage 0** (in situ)
  - Wide excision of primary tumor

- **Stage 1A**
  - Wide excision of primary tumor
  - If ≤ 1mm with poor disease characteristics consider sentinel lymph node mapping

- **Stage IB, Stage II**
  - Wide excision with or without sentinel lymph node mapping
    - Node positive → see stage III
    - Node negative → see next slide

Treatment
Stage IB & Stage II: Node negative

• If ≤ 1mm thick with ulceration
  – Observation or clinical trial
• If 1-4mm thick
  – Observation or clinical trial
• If > 4mm thick
  – Observation or clinical trial or interferon

Treatment
Stage III: Node positive

• Wide excision of tumor + complete lymph node dissection
  – Observation
  – Clinical trial
  – Radiation therapy to nodal basin
  – Systemic therapy
    • Interferon Alfa
    • Ipilimumab
• Additional therapy options for patient with in-transit metastasis
  – Intrallesional injection
  – Local ablation therapy
  – Topic imiquimod for superficial dermal lesions
  – Isolated limb infusion/perfusion with melphalan
Treatment
Stage IV: Distant metastasis

- Limited disease
  - Resection or observation or clinical trial or systemic therapy
- Disseminated disease
  - Systemic therapy
  - Clinical trial
  - Best supportive care
- Disseminated disease with brain metastasis
  - Resection/XRT then systemic therapy or clinical trial or best supportive care


Treatment of Stage IV Disease

- Systemic treatment options
  - BRAF Mutant
    - BRAF/MEK combination\(^a\)
      - Dabrafenib + Trafemitinib
      - Cobimetinib + Vemurafenib
    - BRAF inhibitors
      - Vemurafenib
      - Dabrafenib
    - MEK inhibitors
      - Trafemitinib
  - BRAF Wild Type
    - Ipilimumab
    - Pembrolizumab\(^a\)
    - Nivolumab\(^a\)
    - Nivolumab+Ipilimumab\(^a\)
- All patients
  - Chemotherapy
  - Interleukin 2

\(^a\) Indicated preferred treatment by NCCN

Systemic Treatment Options

- Single agents
  - Dacarbazine
  - Temozolomide
  - Cisplatin
  - Vinca alkaloids
  - Taxanes
  - Carmustine

- Combination chemotherapy agents
  - Chemotherapy
  - Chemotherapy + Biotherapy
  - Immune therapy
    - Interleukin
    - Ipilimumab
    - Pembrolizumab
    - Nivolumab
  - Targeted therapy
    - Vemurafenib
    - Dabrafenib
    - Trametinib
    - Cometinib
  - Combination targeted therapy
  - Combination immune therapy

Chemotherapy

- Dacarbazine (DTIC)
  - Only chemotherapy agent FDA approved for metastatic melanoma
  - Low response rate (10% to 15%)
  - Responses mostly partial and transient
  - No increase in overall survival (OS)
  - Combination with other chemotherapy agents has not shown improved outcomes

- Temozolomide
  - No superiority to dacarbazine
High dose Interleukin-2

- Immunotherapy; stimulates T-cell proliferation and function, natural killer cell proliferation and cytotoxic activity
  - Low response rate: 6 to 10%
  - Complete response: 0 to 4%

- Toxic side effects:
  - Leaky capillary syndrome, hypotension, renal insufficiency
  - Multi-organ failure

High dose Interleukin-2

- Biochemotherapy:
  - Combination of chemotherapy and IL-2
  - No difference in overall survival
  - Higher rates of adverse effects, poorer quality of life
High-dose Interferon-α2b

- Mechanism of action
  - Suppression of cell proliferation
  - Enhanced phagocytic activity of macrophages
  - Augmented cytotoxicity of natural killer cells
  - Increased antibody-dependent cellular cytotoxicity of polymorphonuclear leukocytes
- Dosing
  - 20 μg/m² IV days 1-5 x 4 weeks then 10 μg/m² SC TIW x 48 weeks
- Clinical data
  - 10% improvement in relapse-free survival
  - 3% improvement in overall survival


Interferon-α2b: Adverse Effects

- Constitutional
  - Chills
  - Fever
  - Malaise
  - Fatigue
- Arthralgias
- Myalgias
- Headache
- Depression
  - SSRI treatment
- Elevated LFT’s
- Thrombocytopenia
TARGETED THERAPY

Importance of Mutational Analysis

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Incidence (%)</th>
<th>Type of Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>40-50</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>NRAS</td>
<td>15-30</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>c-KIT</td>
<td>5-10</td>
<td>Acral and mucosal</td>
</tr>
<tr>
<td>GNAQ and GNA11</td>
<td>80</td>
<td>Uveal</td>
</tr>
</tbody>
</table>

BRAF Mutation

• Gene that encodes for serine/threonine kinase protein kinase B-raf (BRAF)
• Occurs in 40%-50% of metastatic melanomas
• 90% lead to substitution of valine for glutamate at the 600 amino acid (V600E)
• Activation of the mitogen-activated protein kinase pathway (MAPK)
• ↑ cellular proliferation, ↑ oncogenic activity

Finn BMJ Med (2012)

Vemurafenib

• Approved for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation
• Mechanism of action
  – Inhibition of V600 mutated BRAF
• 960mg PO BID with or without food
• Drug interactions
  – Avoid with CYP3A4

Vemurafenib Package Insert
Vemurafenib

- Phase 3 BRIM-3 Study:
  - Vemurafenib vs dacarbazine
  - Median PFS: 5.3 vs 1.6 months
  - OS at 6 months: 84% vs 64%

- Adverse reactions:
  - Cutaneous squamous cell carcinomas (cuSCCs) and rash
  - cuSCCs and keratoacanthomas in about 20% in first 2-3 months


Vemurafenib: Adverse Effects

- Arthralgias
- Rash
  - Can be severe
- Alopecia
- Fatigue
- Photosensitivity
- QTc prolongation
- Ocular
  - Uveitis
- Squamous cell carcinomas and keratoacanthomas
  - Skin check every 2 months and for 6 months after treatment
  - Require excision

Vemurafenib Package Insert
Dabrafenib

- Approved for the treatment of unresectable or metastatic melanoma with BRAF V600E mutation
- Phase 3 BREAK-3 Study:
  - Dabrafenib vs dacarbazine
  - PFS: 5.1 months vs 2.7 months; HR=0.30 (P<0.001)
- Vemurafenib and dabrafenib display similar efficacy
- Varying rates of cuSCC/keratoacanthoma:
  - 18%-25% in vemurafenib trials vs 6%-11% in dabrafenib trials

Dabrafenib

- Mechanism of action
  - Blocks BRAF to inhibit cell growth
- Dosing
  - 150mg PO BID
  - Needs to be taken without food
- Glucose-6-phosphate dehydrogenase deficiency (G6PD)
- Drug interactions
  - Inducer of CYP3A4
  - Drugs that increase gastric pH (PPI’s and H2 blockers) may decrease concentrations
Dabrafenib: Adverse Effects

- Alopecia
- Hand-foot syndrome
- Headache
- Myalgias
- VTE
- QTc prolongation
- SCC of skin
- Ocular
  - Uveitis and Iritis
- Labs
  - Hyperglycemia
  - Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency
  - ↓ Phos, sodium
  - ↑ Glucose, alk-phos
- Severe
  - Serious febrile drug reactions 3.7% (Hold drug for temps >101.3)

Trametinib

- Selective MEK1/2 inhibitor
- Phase 3 METRIC Study:
  - Trametinib vs chemotherapy (decarbazine or paclitaxel)
  - PFS: 4.8 vs 1.5 months; HR=0.45 (P<0.001)
  - OS at 6 months: 81% vs 67%; HR=0.54 (P=0.01)
  - AE: Papulopustular rash in 87%
  - Dose-limiting effect: acneiform dermatitis
- Failed to induce response in those previously treated with BRAF inhibitors
- Lower response rates compared to BRAF inhibitors (22% vs 48-50%)

Trametinib

- Approved for first-line treatment of patients with unresectable metastatic melanoma with BRAF V600E/K mutation
- Mechanism of action
  - Reversible inhibitor of MEK1 and MEK2, which are upstream regulators of the ERK pathway involved in cell survival
- Dosing
  - 2 mg orally once daily
  - Take ≥ 1 hour before or 2 hours after a meal
  - Pills must be refrigerated

Trametinib: Adverse Effects

- Acneiform dermatitis
- Diarrhea
- Stomatitis
- Hypertension
- Cardiomyopathy
- Ocular
  - Retinal pigment epithelial detachment
  - Retinal vein occlusion (RVO)
    - 0.2% of patients experienced RVO
    - Discontinue trametinib
- Interstitial lung disease (ILD)
  - 2% of patients
- Serious skin toxicity
  - Almost 90% experienced some degree of skin toxicity
- Labs
  - ↑ AST, ALT, Alk-phos
  - ↓ Albumin
BRAF Inhibitor Dermatologic Effects


Vemurafenib Resistance

BRAF Resistance

• Resistance ultimately occurs
  – Within 6 to 7 months about 50% show resistance
  – Even in those with tumor regression

• Mechanisms that reactivate the MAPK pathway or other pathways

• Combination therapy to block downstream or alternate pathways

Combination Therapy

• Dabrafenib + trametinib

• Unresectable or metastatic melanoma with BRAF V600E or V600K mutation

• Phase I/II study:
  – Dabrafenib/trametinib versus dabrafenib
  – ORR: 76% vs 54% (P=0.03)
  – PFS: 9.4 months vs 5.8 months; HR= 0.39 (P=<0.001)
  – Alive and progression-free at 1 year: 41% vs 9% (P<0.001)
  – Fewer cutaneous AEs, increasing incidence of pyrexia (71% vs 26%)
Combination Therapy

• Phase III study:
  – Dabrafenib/trametinib vs dabrafenib
  – PFS: 9.3 months vs 8.8 months; HR=0.75 (P=0.03)
  – ORR: 67% vs 51% (P= 0.002)
  – Survival at 6 months: 93% vs 85% (P=0.02)
  – Similar AEs as previous study

• COMBI-v phase III study:
  – Dabrafenib/trametinib vs vemurafenib
  – Survival at 12 months: 72% vs 65%
  – PFS: 11.4 vs 7.3 months; HR=0.56 (P< 0.001)
  – ORR: 64% vs 51% (P<0.001)
  – Duration of response: 13.8 months and 7.5 months
Ipilimumab

- Fully human monoclonal antibody
- Binds to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is a negative regulator of T-cell activation
- Net effect is an increase in T-cell activation and proliferation
- Approved for malignant melanoma, unresectable or metastatic
- First drug to show improvement in overall survival in metastatic melanoma

**Ipilimumab Efficacy**

<table>
<thead>
<tr>
<th>Ipilimumab Phase 3 Trials</th>
<th>Patients</th>
<th>RR% (CR/PR)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Number (patients)</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3 Hodi et al.</td>
<td>Ipilimumab plus gp 100 versus Ipilimumab alone versus gp 100 alone Previously treated metastatic melanoma</td>
<td>5.7 versus 10.9 versus 1.5</td>
<td>2.76 versus 2.86 versus 2.76</td>
<td>10.0 versus 10.1 versus 6.4</td>
<td>676</td>
<td>Ipilimumab with significant improvement in OS versus gp-100</td>
</tr>
<tr>
<td>Phase 3 Robert et al.</td>
<td>Ipilimumab plus dacarbazine versus Dacarbazine in untreated metastatic melanoma</td>
<td>15.2 versus 10.3</td>
<td>2.8 versus 2.6</td>
<td>11.2 versus 9.1</td>
<td>502</td>
<td>Ipilimumab plus dacarbazine with significant improvement in OS over dacarbazine</td>
</tr>
</tbody>
</table>
Survival Rates

- **Ipilimumab alone vs vaccine:**
  - 1 year: 45.6% vs 25.3%
  - 2 years: 23.5% vs 13.7%
- **DTIC and ipilimumab combo vs DTIC alone:**
  - 1 year: 47.3% vs 36.3%
  - 2 years: 28.5% vs 17.9%
  - 3 years: 20.8% vs 12.2%

Immune-related Adverse Effects (irAEs)

- Less common: hematologic, cardiovascular, ocular, renal

irAEs Timeline


irAEs Management

- Provide counseling for prompt identification of moderate or severe irAEs
- Rapid initiation of immunosuppression leads to favorable outcomes
  - Withhold treatment and do not resume until toxicity returns to grade ≤ 1
  - irAEs management options Initiate corticosteroids
    - 0.5 to 2 mg/kg/day of prednisone equivalent
      - Infliximab
      - Mycophenolate mofetil (MMF)
      - Cyclophosphamide
- Supportive care and symptom management

irAEs Monitoring

- Reduction in tumor growth
- Liver function tests
- Serum creatinine
- Thyroid function tests
- S/S pneumonitis
- S/S colitis


PD-1 Inhibitors

- Pembrolizumab and Nivolumab

  - Indication:
    - Malignant melanoma, unresectable or metastatic disease with progression following ipilimumab or a BRAF inhibitor (if BRAF V600 mutation-positive)

  - Mechanism of action:
    - Monoclonal antibody that binds to PD-1 receptors, blocking interaction with PD-L1 and PD-L2 (negative immune regulators)

PD-1 and PD-L1 Inhibitors

- **PD-1: checkpoint protein on T-cells**
  - Normally acts as “off switch” to help keep T-cells from attacking other cells in body
  - Does this when it attaches to PD-L1 protein on some normal and cancer cells
  - When PD-1 binds to PD-L1, this tells T-cells to leave other cells alone
  - Some cancer cells have large amounts of PD-L1 which helps them evade immune attack

- **Boost immune response against cancer cells**

Pembrolizumab

- **KEYNOTE-001:**
  - Phase 1b clinical trial
  - 173 patients total
  - Dose-comparing cohort (2 mg/kg vs 10 mg/kg)
  - ORR=26% at both doses
  - 21 of 81 patients in the 2 mg/kg group and 20 of 76 in the 10 mg/kg group (difference 0%, P=0.96)
Nivolumab

- Checkmate 037 phase III study:
  - Nivolumab versus dacarbazine or carboplatin plus paclitaxel
  - 32% (38/120) overall response rate (ORR) compared to 11% (5/47)
  - 95% (36/38) with response maintained response at 6 months
  - 82% of patients treated with nivolumab had ≥ 50% reduction in target lesion burden versus 60% with chemotherapy (11%; n=5)
  - Grade 3-4 drug-related adverse events
    - 9% of patients treated with nivolumab and 31% with chemotherapy


Ipilimumab + Nivolumab

- Randomized (2:1) placebo controlled trial
  - BRAF V600 wild-type, unresectable or metastatic melanoma
    - Nivolumab + ipilimumab (n=95): Nivolumab 1 mg/kg + ipilimumab 3 mg/kg IV Q3W X 4 doses, then nivolumab 3 mg/kg Q2W until disease progression or unacceptable toxicity
    - Ipilimumab arm + placebo (n=47): Ipilimumab 3 mg/kg and nivolumab-matched placebo IV Q3W weeks X 4 doses followed by placebo
  - Study endpoints
    - Objective response rate (ORR) and progression-free survival (PFS)

Larkin et al. Combined Nivolumab or Monotherapy in Untreated Melanoma. NEJM 2015; 373:23-34.
Ipilimumab + Nivolumab

- Results
  - The ORR statistically significant with 60% in the nivolumab plus ipilimumab group and 11% in the ipilimumab group
  - PFS for nivolumab and ipilimumab compared to the ipilimumab group was 8.9 vs. 4.7 months (P>0.002)
  - Duration of response was longer in the combination arm

- Safety
  - The most common adverse reactions reported were rash, pruritus, headache, vomiting, and colitis
  - There was a significant increase in grade 3/4 adverse effects with the combination
  - There is a higher incidence of autoimmune adverse effects in the combination

Talimogene Laherparepvec (TVEC)

- A genetically-modified oncolytic viral therapy
  - Mechanism of action
    - Attenuated HSV-1 to selectively replicate within the tumor environment causing death
    - Secretion of GM-CSF to attract dendritic cells to the site to start the process of antigen presentation and T cells activation. Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
Talimogene Laherparepvec (TVEC)

- Multicenter study patients with metastatic melanoma that could not be surgically removed (N=436)
  - GM-CSF or talimogene laherparepvec was administered as a direct injection into the lesion
  - 16.3% of patients who received talimogene laherparepvec had a decrease in size of their skin and lymph node lesions, compared to 2.1 percent of the study participants receiving GM-CSF
  - Adverse effects
    - Fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain
- Not to be used for patients with any visceral, bone or brain metastasis

Andtbacka et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. JCO 2015; 38:3377.

PATIENT ADHERENCE
Patient Adherence

• Adherence: the degree to which a patient follows the given instructions for timing,

Factors Affecting Adherence

- Socioeconomic
- Treatment
- Disease/malignancy
- Patient
- Health-system and healthcare

## Assessing Adherence

<table>
<thead>
<tr>
<th>Method</th>
<th>Pro</th>
<th>Con</th>
</tr>
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<tbody>
<tr>
<td>Self-reporting</td>
<td>Simple; inexpensive; often used in clinical setting</td>
<td>Overestimated and subject to patient bias</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Objective; quantitative; easy to perform; inexpensive</td>
<td>Easily altered by patient; does not account for schedule adherence</td>
</tr>
<tr>
<td>Prescription refill history</td>
<td>Objective; easy to obtain from home pharmacy</td>
<td>Does not account for schedule adherence</td>
</tr>
<tr>
<td>Microelectronic monitoring</td>
<td>Precise; quantitative</td>
<td>Expensive; limited to clinical trials; does not track medication ingestion</td>
</tr>
<tr>
<td>Pharmacokinetic monitoring</td>
<td>Objective; high level of accuracy</td>
<td>Not applicable to all meds; does not account for genetic variability; expensive</td>
</tr>
</tbody>
</table>


## Addressing Poor Adherence

- Patient interview to determine potential causes of non-adherence
  - Changes in co-morbidities/other medications
  - Difficulty in filling medication
    - Include cost or timing of refills
  - Understanding of how to take
    - Include when to take, drug/food interactions, storage, how to handle missed doses
  - Understanding of expected efficacy/adverse effects
    - What is normal vs. abnormal?
    - When to call clinic?
  - Changes in support or assistance at home
- Match intervention to patient cause
Improving Adherence

• Medication reminder aids
  – Medication calendars and checklists
  – Blister packs/pill boxes
  – Cell phone/text reminders
  – Electronic pill bottles/boxes

Addressing Cost

• Talk to patients about the cost of medication
• Try to address the copay/prior authorization prior to arrival at pharmacy
• Review medication list with patient looking for other cost saving opportunities
• Utilize patient assistance programs
  – General patient assistance programs (typically from non-profit organizations)
    • www.patientassistance.com
    • www.needymeds.com
  – Pharmaceutical company sponsored programs
  – Discount pharmacy programs
  – Oncology Nursing Society (ONS) oral adherence toolkit
Improving Adherence

• Enhanced education
  – Consistently shown to improve adherence rates in cancer patients
  – Includes several types of educational methods
    • Written handouts
    • Follow-up phone calls
    • Frequent check-ins (often timed with refills)
    • Standardized/guided teaching method
      – Multinational Association of Supportive Care in Cancer (MASCC) Teaching Tool for Patients Receiving Oral Agents for Cancer (MOATT)
      – SIMPLE method for addressing adherence
      – Motivational interviewing


Summary

• New advances in the treatment of metastatic melanoma has made older therapies less favorable
• Treatment of BRAF mutation positive disease responds best with combination therapy
• BRAF mutation negative disease first line treatment is ipilimumab, although PD-1 inhibitors may be better options
• New trials ongoing to target other steps in MAPK pathway
References


References

- Robert C, Karaszewska B, Schachter J, et al. COMBI-v: A randomised, open-label, phase III study comparing the combination of dabrafenib (D) and trametinib (T) to vemurafenib (V) as first-line therapy in patients (pts) with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma [abstract]. Ann Oncol 2014; 25 (4): Abstract LBA4.
- Abstract LBA3_PR - A phase 3 randomized, open-label study of nivolumab (anti-PD-1; BMS-936558, ONO-4538) versus investigator’s choice chemotherapy (ICC) in patients with advanced melanoma after prior anti-CTLA4 therapy.
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