CUTANEOUS MELANOMA and NON-MELANOMA SKIN CANCERS

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LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Design an appropriate patient-specific treatment, supportive care, and monitoring plan taking into consideration efficacy and safety outcomes from clinical trials and current treatment guidelines for patients with melanoma or non-melanoma skin cancer.
2. Discuss short- and long-term goals, including post-therapy and survivorship, with a patient with melanoma or non-melanoma skin cancer and his or her caregiver.
3. Select relevant information and guidance for the public regarding melanoma and non-melanoma skin cancer-related issues (e.g., risk factors, prevention, screening).
4. Develop an appropriate plan for preventing, monitoring, and treating adverse reactions associated with the treatment of melanoma and non-melanoma skin cancers, including thyroid level monitoring for chemotherapy agents, immune-mediated toxicities, and toxicity from BRAF inhibitors.

MELANOMA

I. Etiology and Risk Factors[1]

A. Melanoma can occur regardless of ethnicity and in areas that are not associated with exposure to substantial sunlight; however, skin type, history of atypical moles, dysplastic nevi or a prior melanoma can increase the risk in addition to the following:

1. Light skin with fair hair (red or blond) and light-colored eyes (blue or green)
2. Latitude nearer the equator with high intensity of solar exposure
3. Experiencing blistering sunburns (especially during youth)
4. Immunocompromised conditions

B. Intermittent, intense sun exposure is more closely correlated with melanoma than chronic, occupational exposure.[2]

C. Exposure to sunbeds or sunlamps increases the risk of cutaneous melanoma, especially when exposed as a young adult [3]

D. Family history including certain genetic mutations

II. Pathophysiology[4, 5]

A. Histologic subtypes of melanoma

1. Superficial spreading melanoma
    a. Most common morphologic type of cutaneous melanoma (70% of all melanoma) and usually evolves from a preexisting nevus
    b. Early in the lesion development the melanoma is flat, but as the lesion develops the surface becomes irregular and asymmetrical
    c. Common pathogenic mutations include BRAF V600E/K in 41%, NRAS in 22%, and TP53 in 17%[6]
2. Nodular melanoma
    a. Second most common melanoma (15% to 30% of cutaneous melanoma)
    b. Nodular melanoma is a “pure” vertical growth-phase disease and is more aggressive, and develop more rapidly than superficial spreading melanoma
    c. Typically, lesions are dark blue-black and often uniform in color, although about 5% are amelanotic and have a fleshy appearance. They typically occur on the trunk, head and neck.
    d. Common pathogenic mutations are similar to superficial spreading melanoma including mutations in BRAF (29%) and NRAS (27%). [7]
3. Lentigo maligna melanoma
    a. Rare form of melanoma that is unique from other histologic subtypes because it does not have the same propensity to metastasize.
    b. Most commonly seen in elderly patients with sun-exposed or damaged skin.

4. Acral lentiginous melanoma

    a. Characteristically seen on the palms of the hands, soles of the feet, and beneath the nailbeds.

    b. Most common type of melanoma in Blacks, Asians, and Hispanics

    c. Pathogenic alterations in KIT are seen in 11% of acral melanomas along with mutations in NRAS (24%) and BRAF V600E/K (19%)[6]

5. Mucosal melanoma

    a. 1% of all melanomas

    b. Arises from the melanocytes located in mucous membranes and is most commonly seen in the head and neck region with the gastrointestinal and genital tracks also being possible sources.

    c. Common pathogenic mutations include mutations in NRAS (21%), KIT (16%), TP53 (9%), and BRAF V600E/K (7%).[6]

6. Uveal melanoma is the most common primary intraocular malignancy seen in adults, but only accounts for about 3% of all melanomas (NCCN now has a separate guideline focused on the management of uveal melanoma and it will not be discussed in detail as part of this module)[8]

    a. Uveal melanoma arises from the melanocytes of the choroid plexus, ciliary body, and iris.

    b. The liver is the most common site of uveal melanoma metastases

    c. Common pathogenic mutations

        1) Unlike cutaneous melanoma, uveal melanoma is not typically BRAF mutated

        2) GNA11 were seen in 32% of primary uveal melanomas and 57% of metastatic lesions.

        3) GNAQ mutations were seen in 45% of primary and 22% of metastatic lesions.

        4) Occurrence of alterations in these genes was mutually exclusive and most commonly occur at Q209 in both genes.[9]

        5) GNA11 and GNAQ are G-protein-coupled receptors and mutations in uveal melanoma have been shown to activate downstream signaling targets including MAPK, PI3K, and others though the optimal method of targeting is less clear with clinical trials assessing inhibitors of MEK and protein kinase C.

III. Prevention/Screening [10-12]

A. Prevention is aimed at minimizing exposure to UV radiation. The American Cancer Society (ACS) and Centers for Disease Control and Prevention (CDC) recommend the following measures to minimize sun exposure:

1. Avoid direct exposure to the sun between the hours of 10 a.m. to 4 p.m. (Daylight Savings Time), when UV rays are the most intense.

2. Wear hats with a brim wide enough to shade face, ears, and neck, as well as clothing that covers as much as possible of the arms, legs, and torso.

    a. Covering up does not block all UV rays and in general, if you can see light through a fabric, UV rays can also get through it

b. Clothing with UV protection factor (UPF) can also provide protection from UV radiation. The UPF indicates the level of protection the clothing provides from the sun on a scale of 15 to 50+

3. Avoid tanning beds and sun lamps, which provide an additional source of UV radiation.

   a. Based on a meta-analysis of 27 studies, using tanning beds before the age of 35 can increase the risk of developing melanoma by 59% with increasing usage correlated with increased risk. There was a 1.8% increased risk of melanoma for each additional session of tanning bed use per year. [13]

   b. Women who are younger than 30 are 6 times more likely to develop melanoma if they tan indoors.[14]

4. The CDC recommends covering exposed skin with a sunscreen lotion with a Sun Protection Factor **(SPF) of 15** or higher even on cloudy and cool days.[11]

   a. SPF indicates the level of protection against UVB rays, which are the main cause of sunburn. "Broad spectrum" sunscreen has been tested and shown to prevent exposure to both UVB and UVA rays.

   b. SPF 15 filters out about 93% of UVB rays, SPF 30 filters out about 97% and SPF 50 filters out about 98%. Only broad spectrum sunscreen with SPF of $\geq$ 15 can state it helps to protect against skin cancer and early skin aging if used as directed. SPF < 15 must include a warning indicating that it has been shown to help only with sunburn and not skin cancer or early skin aging.

   c. Counseling about the appropriate use of sunscreens to optimize benefits including use of about 1 ounce of sunscreen (about a shotglass or palmful) with reapplication every 2 hours (more frequently after swimming or sweating)

   d. Sun protection beyond sunscreen may be beneficial for those individuals in the sun for prolonged periods of time or who are at high risk of burning

   e. Sunscreen without an expiration date will have a shelf life of no more than 3 years and will be less if stored in high temperatures.

B. Screening

1. The clinical features used to describe or evaluate a questionable lesion are called the ABCDEs of melanoma – approximately 50% of melanomas evolve from pre-existing nevi, while the remaining are new lesions.[10]

   a. **A**symmetric

   b. Irregular **B**orders

   c. **C**olor of melanoma lesions are often variegated, ranging in color from tan to blue-black, and at times the lesion is intermingled with colors of red, purple, and white.

   d. **D**iameter of a melanoma lesion is frequently 6 mm or greater

   e. **E**volving characteristics of a lesion

2. A similar 7 point check list (3 major, 4 minor) was designed in England for early detection[15]

   a. Major criteria: Change in **size**, **color**, **shape**

b. Minor features: **Inflammation**, **bleeding/crusting**, **sensory change**, **diameter** greater than 6 mm

3. The American Academy of Dermatology recommends monthly self-examination of skin to serve as a mechanism of recognizing moles or marks on the skin that may be melanoma (derived from publications of the American Academy of Dermatology).[16]

C. Suspicious lesions should be excised or biopsied by a professional

Patient Case #1:

LB is a 42-year-old female with newly diagnosed stage IIC melanoma involving her upper back. LB underwent a complete wide excision and next generation sequencing which confirmed the presence of a BRAF V600E mutation. After discussion, LB wishes to pursue adjuvant therapy.

Which of the following is the most appropriate adjuvant treatment for LB at this time?

A. ipilimumab
B. nivolumab
C. encorafenib and binimetinib
D. pembrolizumab

IV. Treatment[1]

A. The treatment and management of a patient with cutaneous melanoma is based on the stage of disease.

B. Surgery

1. Complete surgical excision provides best chance for cure. May be used as single modality in localized and regional disease.

2. Defining a clear surgical margin around lesion depends on the thickness but is generally 1-2 cm

a. Margins may need to accommodate anatomical or cosmetic considerations (i.e., Moh's surgery)

3. Sentinel lymph node (SLN) mapping and evaluation:

a. Consider for patients with clinical stage IB, T1b disease (Breslow depth < 0.8 mm with ulceration or 0.8-1 mm with or without ulceration) or T1a with Breslow depth < 0.8 mm but with other adverse features (very high mitotic index especially with young age and/or lymphovascular invasion).

b. SLN biopsy should be offered to patients with stage IB melanoma or greater. If the sentinel node is found to have micrometastatic melanoma, regional dissection of the involved nodal basin can be considered.[1]

C. Radiation therapy

1. Limited role in melanoma

2. Adjuvant therapy for prevention of nodal relapse in high-risk patients.

3. More commonly confined to palliation of metastatic disease sites that are unresectable

4. Stereotactic radio surgery can be useful for isolated brain metastasis

D. Adjuvant therapy[1]

1. Treatment by extent of tumor

    a. For patients with node negative early stage (stage I - IIA), observation is recommended unless a clinical trial is being considered.

    b. For patients with stage IIB - IIID, adjuvant treatment options following wide excision of the primary tumor and sentinal lymph node (SLN) dissection include:

        1) Observation

            a) This a consideration for patients with very low risk stage IIIA disease (non-ulcerated primary, ≤ 2mm in thickness, SLN metastasis < 1 mm)

            b) The toxicity of therapy should be weighed against the patient's risk of relapse

        2) Pembrolizumab (NCCN Guidelines® category 1 option for patients with AJCC 7th Edition stage IIB/C – IIIC disease (IIIA-IIIC with SLN metastasis > 1 mm)[1]

        3) Nivolumab (NCCN Guidelines® category 1 option for patients with AJCC 7th Edition stage IIIB-IIIC disease)[1]

        4) Dabrafenib/trametinib for tumors found to harbor a BRAF V600E/K mutation

            5) NCCN Guidelines® category 1 option for patients with AJCC 7th Edition stage IIIA with SLN metastasis > 1 mm or stage IIIB/C disease[1]

            6) Other BRAF/MEK inhibitor combinations may be considered in the context of unacceptable toxicities to dabrafenib/trametinib

    c. For stage III melanoma not completely resected with satellite (visible cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma) or in-transit lesions (regional cutaneous and/or subcutaneous metastatases at a distance > 2 cm from the primary melanoma):

        1) Talimogene laherparepvec (T-VEC) (NCCN Guidelines® category 1 recommendation)[1]

        2) NCCN Guidelines category 2B recommendations include BCG, interferon, interleukin-2, local ablation therapy or topical imiquimod.[1]

        3) Regional therapy with isolated limb infusion/perfusion with melphalan (NCCN Guidelines category 2A)[1]

2. Treatment options in the adjuvant setting

    a. Nivolumab

        1) CheckMate 238 was a randomized, double-blind, phase III trial comparing nivolumab to ipilimumab in 906 patients who underwent complete resection of stage IIIB, IIIC or IV melanoma[17, 18]

        b) Nivolumab was dosed at 3 mg/kg every 2 weeks for up to one year. Ipilimumab was dosed at 10 mg/kg every 3 weeks x 4 doses then every 12 weeks for up to one year.

        c) The primary endpoint was recurrence-free survival (RFS) which after 4 years was 51.7% in the nivolumab patients and 41.2% in the ipilimumab patients (HR 0.71; 95% CI 0.60-0.86; p = 0.0003). 4-year OS was 77.9% in the nivolumab patients and 76.6% in the ipilimumab patients (p=0.31)[18]

d) Adverse events were higher in the ipilimumab-treated patients compared with those who received nivolumab

i. Grade 3 or 4 adverse effects were seen in 14.4% of nivolumab patients and 45.9% of ipilimumab patients

ii. Treatment discontinuation due to adverse effects occurred in 9.7% and 42.6% of patients receiving nivolumab or ipilimumab, respectively

2) Based on the results of this trial, nivolumab is now an NCCN Guidelines® category 1 option for patients with AJCC 7th Edition stage IIIB/C melanoma following complete resection.[1]

b. Pembrolizumab

1) EORTC 1325/KEYNOTE-054 was a randomized, double-blind, phase III trial comparing pembrolizumab with placebo in 1019 patients with completely resected stage III melanoma.[19, 20]

a) Pembrolizumab was dosed at 200 mg IV every 3 weeks for a total of 18 doses (1 year) or until disease progression.

b) The primary endpoints were RFS in both the intent-to-treat (ITT) population and subgroup who were PD-L1 positive

i. For the ITT patients: 1-year RFS was 75.4% in the pembrolizumab patients and 61% in those receiving placebo (HR 0.57; 98.4% CI 0.43-0.74; p<0.0001). After 3.5-years, RFS was 59.8% in the pembrolizumab patients and 41.1% in those receiving placebo (HR 0.59; 95% CI 0.0.49-0.70).

ii. PD-L1 positive patients (n=853): 1-year RFS was 77.1% in the pembrolizumab patients and 62.6% in those receiving placebo (HR 0.54; 95% CI 0.42-0.69; p<0.0001). After 3.5-years, RFS was 61.4% in the pembrolizumab patients and 44.1% in those receiving placebo (HR 0.59; 95% CI 0.49-0.73).

iii. This benefit was seen across subtypes including patients with BRAF-mutated melanoma

c) Grade $\geq$ 3 adverse effects were seen in 14.7% of pembrolizumab patients and 3.4% of those who received placebo. There was one death in the pembrolizumab group due to myositis.

2) KEYNOTE-716 was a randomized, double-blind, phase III trial comparing pembrolizumab with placebo in 976 patients (>/= 12 years old) with completely resected stage IIB or IIC melanoma[21]

a) Pembrolizumab was dosed at 200 mg IV every 3 weeks for a total of 17 doses (1 year) or until disease progression.

b) The primary endpoint was RFS in the ITT population

i. For the ITT population: 1-year RFS was 90% in the pembrolizumab patients and 83% in the those receiving placebo

ii. Longer follow-up needed to evaluate impact on overall survival.

3) Based on the results of these trials, pembrolizumab is now an NCCN Guidelines® category 1 option for patients with AJCC 7th Edition stage III disease following complete resection and a listed option for stage IIB/C disease.[1]

Patient Case #1, Discussion:

Pembrolizumab (answer D): Pembrolizumab is now approved for adjuvant therapy in resected stage IIB to IIID melanoma. Nivolumab is approved for adjuvant treatment in stage IIIB to IIID. Encorafenib and binimetinib are only approved in BRAF mutated metastatic melanoma. Ipilimumab is no longer recommended for adjuvant treatment in melanoma.

Patient Case #2

HB is a 57-year-old man with recently diagnosed stage IIIC BRAF wild-type melanoma involving his scalp. He underwent a wide excision with negative margins and his treatment plan is for adjuvant pembrolizumab. You are asked to provide patient education to HB prior to starting therapy.

Which of the following immune-related toxicities is most likely to occur during the first 4 weeks of treatment with pembrolizumab?

A. Skin rash
B. Hypothyroidism
C. Flu-like symptoms
D. Elevated liver enzymes

c. Anti-CTLA4 and anti-PD1 Toxicity: [22-24]

1) The American Society of Clinical Oncology (**ASCO**) and **NCCN Guidelines®** published a joint guideline focused on the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors initially in June 2018 with subsequent updates by NCCN. These guidelines provide recommendations for the management of toxicities associated with these treatments.

a) The importance of patient education is emphasized including mechanism of action of the treatment and the clinical profile of the possible adverse effects prior to starting treatment, throughout treatment, and survivorship.

b) When a new side effect occurs, there should be a high suspicion for it being treatment-related

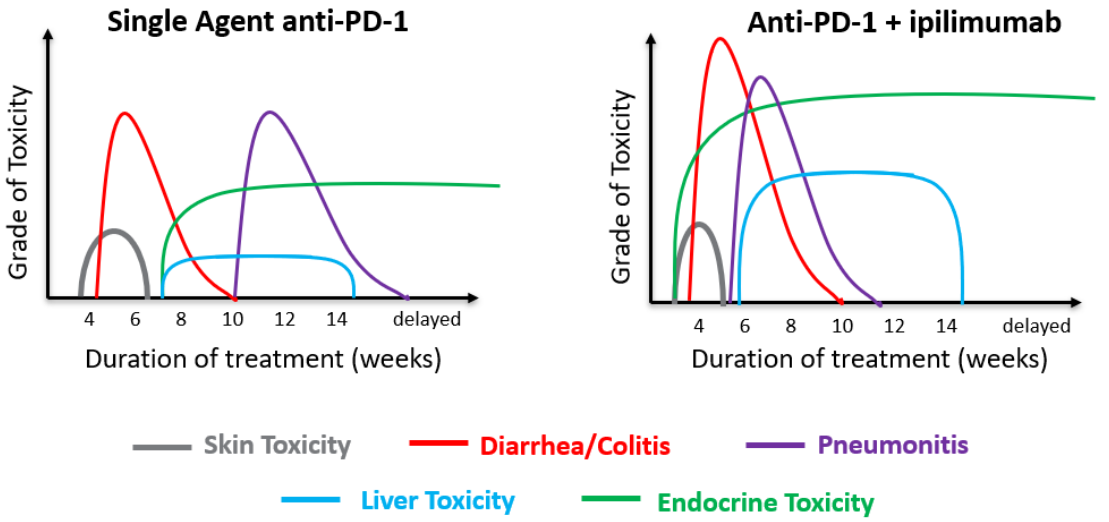
c) Though treatment interruption may be needed for some toxicities depending on severity, dose adjustments are not recommended after restarting therapy following toxicity

2) Most common immune-related adverse events are seen in the skin and GI tract (similar to graft-versus-host-disease), which are treated with steroids and have a median time to resolution of about 2 weeks with treatment.

a) Systemic steroids should be initiated for higher grade toxicity and persistence of low grade toxicity.

b) Oral steroids are preferred; however, in cases where absorption may be compromised (i.e. colitis), IV methylprednisolone or equivalent should be used

Timeline of anti-PD-1 and anti-PD-L1 Immune Related Toxicities[25]



General Management of Immune-Related Adverse Effects[24]

Grade (G)	Management
G1	• Continue ICPi therapy with close monitoring • Exceptions: neurologic, hematologic, and cardiac toxicities
G2	• Hold ICPi for most toxicities, resume when resolved to ≤ grade 1 • Prednisone 0.5-1 mg/kg/day or equivalent may be administered
G3	• Hold ICPi • Start prednisone 1-2 mg/kg/day or methylprednisolone IV 1-2 mg/kg/day with taper over ≥ 4-6 weeks • If no improvement after 48-72 hours, then consider alternative immunosuppression
G4	• Generally warrant permanent ICPi discontinuation (except for endocrine therapy controlled by hormonal replacement)

ICPi: Immune checkpoint inhibitor

3) Skin

a) One of the most common immune-related adverse effects seen in about 45% of ipilimumab patients and 34% of patients receiving PD-1 inhibitors. Skin effects commonly occur within the first few weeks after starting therapy.

b) Common presentations include rash and pruritis. Vitiligo has also been reported in about 8% of melanoma patients receiving either anti-PD-1 therapy alone or in combination with ipilimumab and was positively associated with clinical response.

Management of Rash and Inflammatory Dermatitis Immune-Related Adverse Effects[24]

Grading	Management
G1: Rash covering < 10 % BSA, which may or may not be associated with symptoms of pruritis or tenderness	• Continue ICPi • Topical emollients and/or mild/moderate topical corticosteroids • Avoid irritants and sun exposure
G2: Rash covering 10-30% BSA with/without symptoms; limiting instrumental ADL; rash covering >30% with/without mild symptoms	• Consider holding ICPi, monitor weekly for improvement. If not improved after 4 weeks, regrade as grade 3 • Treat with Topical emollients, oral antihistamines, and moderate/high topical corticosteroids • Consider prednisone 0.5-1 mg/kg, taper over at least 4 weeks. In patients with pruritis without rash, topical anti-itch remedies
G3: Rash covering >30% BSA with moderate or severe symptoms; limiting self-care ADL	• Hold ICPi and consult dermatology • Treat with Topical emollients, oral antihistamines, and high potency topical corticosteroids. May consider phototherapy for severe pruritis • Oral prednisone or equivalent (1 mg/kg/day) tapering over at least 4 weeks • Once downgraded to ≤ G1 and prednisone <10 mg/day, may resume ICPi with close monitoring and follow up with dermatology • In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, dupilumab
G4: Severe consequences requiring hospitalization/urgent intervention or life-threatening consequences	• Hold ICPi, consult dermatology, admit patient • Methylprednisolone 1-2 mg/kg, slow taper when toxicity resolves • Monitor closely for progression • Consider alternative future therapy or restart ICPi when resolved to G1 with close follow-up

4) Gastrointestinal[26,27]

a) Diarrhea is more common with ipilimumab compared with the PD-1 inhibitors with the more severe colitis being seen in around 8-22% of ipilimumab-treated patients.

b) One of the most common grade 3 or higher toxicities seen with ipilimumab and is often the first immune-related toxicity that leads to treatment discontinuation.

Management of Colitis Immune-Related Adverse Effects[24]

Grading	Management
G1: Increase of < 4 stools /day or mild increase in ostomy output	• May continue ICPi or hold until < G1 • Monitor dehydration, rule out infection, may include loperamide
G2: Increase in 4-6 stools/day, moderate increase in ostomy output	• Hold ICPi until ≤ G1 (may permanently d/c CLTA-4 inhibitors) • Consult with gastroenterology, consider EGD/colonoscopy to stratify for infliximab or vedolizumab • Initiate prednisone 1 mg/kg/day, taper over 4-6 weeks when ≤ G1
G3: Increase in ≥ 7 stools/day, incontinence, severe ostomy output, hospitalization indicated; limiting self-care ADL	• As above for G3, with hospitalization for electrolyte replacement initiate prednisone 1-2 mg/kg/day, consider methylprednisolone • If symptoms ≥ 3 days or recur after improvement, consider infliximab or vedolizumab • Consider permanent discontinue of CTLA-4 agent
G4: Life threatening consequences	• Follow G2-G3 recommendations • Permanently discontinue ICPi • Methylprednisolone 1-2 mg/kg/day • Infliximab or vedolizumab if inadequate response to steroids

5) Hepatic[24]

a) Typically occurs in about 5-10% of patients receiving either single agent ipilimumab or PD-1 inhibitors with less than 2% of cases being grade 3 or higher. Combination therapy results in about 15% grade 3 hepatitis.

b) Liver enzymes (LFT) and bilirubin should be assessed prior to each cycle of immunotherapy

c) Therapy should be withheld for grade 2 elevations and systemic corticosteroids (e.g. prednisone 1-2 mg/kg/day) should be started for persistent grade 2 or more severe toxicity.

d) If grade 3 or 4, LFT monitoring should be done daily or every other day. For LFT and/or bilirubin elevations, immunotherapy should be permanently discontinued and systemic corticosteroids started. If no response after 2-3 days, then mycophenolate mofetil or azathioprine can be added. Infliximab not recommended due to risk of hepatitis.

6) Endocrine

a) Typically appear later in therapy and are the last to reverse, though in some cases may not be completely reversible.

b) Monitoring of ACTH, thyroid function (TSH and T4), blood glucose, testosterone and other endocrine markers as appropriate at baseline and during the course of therapy is recommended.

c) Treatment includes correcting the endocrine abnormality with steroids and/or hormonal replacement (i.e. levothyroxine, testosterone, etc.)

d) A meta-analysis comparing incidence of endocrine dysfunction across the different immunotherapies assessed 7551 patients who received either a PD-1 inhibitor, CTLA-4 inhibitor, or the combination of the two.[28]

i. Patients receiving combination therapy had the higher rates of hypothyroidism (OR 3.81; p<0.01) and hyperthyroidism (OR 4.27; p=0.001) compared to ipilimumab monotherapy.

ii. Patients receiving PD-1 inhibitor monotherapy had a higher rate of hypothyroidism (OR 1.89; p=0.03) though were less likely to experience hypophysitis (OR 0.29; p<0.001) compared with ipilimumab monotherapy

Management of Hypothyroid Immune-Related Adverse Effects[24]

Grading	Management
G1: TSH > 4.5 and < 10 mIU/L and asymptomatic	• Continue ICPi with monitoring of TSH (option for free T4) every 4-6 weeks as part of routine care
G2: Moderate symptoms, TSH persistently > 10 mIU/L	• May continue or hold ICPi until symptoms resolve to baseline • Consider endocrine consult • Thyroid supplementation in symptomatic patients with TSH levels > 10 mIU/L, monitor every 6-8 weeks while titrating
G3-4: Severe symptoms, life threatening consequences	• Hold ICPi until symptoms resolve to baseline with appropriate supplementation • Endocrine consultation • May admit for IV therapy such as steroids if bradycardia and/or hyperthermia is present, depending on the underlying endocrinopathy • All the above from G2

7) Lung toxicity

a) Reported incidence is variable from 0% to 10%. In a combined analysis of 915 patients treated with anti-PD-1/PD-L1 therapy, pneumonitis developed in 5% of patients with a time of onset ranging from 9 days to 19.2 months.[29] Earlier occurrences have been reported with combination therapy compared with single agent.

b) The incidence appears higher in patients receiving combined anti-PD-1 and anti-CTLA-4 therapy than monotherapy. Patients treated with single agent ipilimumab appear to have lower rates of pneumonitis than patients receiving single agent anti-PD-1 inhibitors.

c) It is unclear whether tumor type is associated with occurrence of pneumonitis with some studies showing higher rates in patients with lung and renal cell cancer compared with melanoma but this has not been consistent.

Management of Lung Immune-Related Adverse Effects [24]

Grading	Management
G1: Asymptomatic, confined to one lung lobe or < 25% of lung parenchyma	• Hold ICPi with radiographic evidence of pneumonitis progression • May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, treat as a grade 2. • Monitor weekly
G2: Symptomatic, involves more than one lung lobe or 25-50% of lung parenchyma, medical intervention indicated	• Hold ICPi until resolution to ≤ grade 1 • Prednisone 1-2 mg/kg/day with taper by 5-10 mg/week over 4-6 weeks • Consider empirical antibiotics • Monitor every 3 days, if no improvement after 48-72 hours of prednisone, treat as grade 3.
G3: Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, oxygen indicated **G4:** Life threatening respiratory compromise, urgent intervention (intubation) required	• Permanently discontinue ICPi • Empirical antibiotics and methylprednisolone IV 1-2 mg/kg/day, if no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil or IVIG for 5 days or cyclophosphamide. Steroids should be tapered over 4-6 weeks • Pulmonary and infectious disease consults if necessary • Hospitalize for further management

8) Less common immune-related toxicities:

   a) These include musculoskeletal, renal, nervous system, hematologic, cardiovascular and ocular.

   b) Detailed guidelines regarding management are available in the ASCO Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors document[24] and the NCCN Guidelines® on Management of Immunotherapy -Related Toxicities.[30]

9) Immunosuppression considerations:[24]

   a) Some patients may require longer steroid tapers of > 4 weeks and even up to 6-8 weeks or longer, especially for pneumonitis and hepatitis

   b) Prophylaxis considerations:

      i) Herpes zoster prophylaxis may be considered in patients with prior zoster infection.

      ii) For patients with a higher risk of gastritis, proton pump inhibitors or H2 blockers can be considered

      iii) Patients receiving prednisone 20 mg (or equivalent) daily **for ≥ 4 weeks** or >30 mg **for 3 weeks or more** may require pneumocystis jirovecii pneumonia (**PJP**) prophylaxis

      iv) Patients receiving prednisone 20 mg (or equivalent) daily **for > 12 weeks** may require **antifungal** prophylaxis

   c) Vitamin D and calcium should be used to prevent osteoporosis

d) Inactivated vaccines may be used during immunotherapy but live vaccines should be avoided due to lack of data currently

10) Immunotherapy should be used with caution in patients with pre-existing autoimmune disorders, organ transplantation or prior stem cell transplantation though successful use has been reported.[31]

11) An observational, cross-sectional pharmacovigilance cohort study assessed the rate of recurrence of irAE after rechallenge with an immune checkpoint inhibitor using the WHO VigiBase database[32]

a) A total of 24,079 irAE cases were identified with 452 of 6,123 irAEs being associated with immune checkpoint rechallenge and included for analysis

b) The recurrence rate of the initial irAE was 28.8% with colitis, hepatitis and pneumonitis having the highest rates of recurrence following re-challenge with immune checkpoint inhibitor therapy.

Patient Case #2, Discussion:
Skin rash (answer A) is usually seen after 2-3 weeks of immunotherapy treatment with an agent like pembrolizumab. Gastrointestinal side effects, including diarrhea and colitis, as well as elevations in liver enzymes generally occur after 6-7 weeks. Endocrine toxicity, including hypophysitis and hypothyroidism, are typically seen after several doses, around 9 weeks or later but can be prolonged. Pembrolizumab does not typically cause flu-like symptoms like those seen traditionally with interferon.

d. Dabrafenib and Trametinib[33]

1) The combination of the BRAF-inhibitor dabrafenib and MEK-inhibitor trametinib was assessed in a double-blind, placebo controlled trial of 870 patients with completely resected, stage III melanoma with either a BRAF V600E or V600K mutation.

i. Patients were randomized 1:1 to receive either dabrafenib 150 mg PO BID and trametinib 2 mg PO daily or matched placebo for a duration of 12 months

ii. The primary endpoint was RFS and the estimated 3-year RFS rate was 58% in the combination therapy arm and 39% in the placebo arm (HR 0.47; 95% CI 0.39-0.58; p<0.001).

iii. The 3-year OS rate was 86% and 77% in the combination and placebo arms, respectively (HR 0.57; p=0.0006)

iv. An updated 5-year analysis showed a RFS of 52% in patients treated with dabrafenib and trametinib and 36% in patients treated with placebo (HR 0.51; 95% 0.42-0.61)[34]

v. The most common toxicities in the combination arm were pyrexia, fatigue and nausea, (see additional details in the metastatic treatment setting below). In this trial, 26% of combination-treated patients discontinued therapy due to toxicity and 38% of patients required a dose reduction.

2) The combination of dabrafenib and trametinib is a NCCN Guidelines® category 1 option for patients with AJCC 8th Edition stage IIIA with sentinel lymph node metastasis > 1 mm or stage IIIB/C disease[1]

3) It remains unclear whether patients with BRAF mutations derive the most benefit from adjuvant BRAF/MEK inhibitors or immunotherapy. This is the focus of ongoing clinical trials.

4) See additional information the section below on the use of this combination in the metastatic setting

e. Intralesional vaccine therapy: Talimogene laherparepvec (T-VEC)

1) First therapeutic vaccine for melanoma, approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.[35]

a) T-VEC is an HSV-1 derived oncolytic virus that exerts its mechanism of action by selectively replicating in tumor cells, which results in cell lysis. The virus is modified through deletion of ICP34.5 to decrease viral pathogenicity and increase tumor-selective replication and deletion of ICP47 to decrease virally mediated antigen presentation suppression and increase HSV US11 gene expression[36]

b) It is also engineered to express granulocyte-macrophage colony stimulating factor (GM-CSF) to further enhance cancer immunity.[36]

2) NCCN Guidelines® list it as a category 1 recommendation for patients with unresectable stage III melanoma with in-transit or satellite lesions[1].

3) Dosing is based on the size of the lesion with a max of 4 mL total given intralesionally across all treated lesions.[37]

4) Approval was based on a randomized, open-label, phase III trial of 436 patients with unresected stage IIIB or IV melanoma suitable for direct or ultrasound-guided injection of at least 1 cutaneous, subcutaneous, or nodal lesion or aggregation of lesions $\geq$ 10 mm in diameter. [35]

a) Patients were randomized 2:1 to either T-VEC administered at 10^6 plaque forming units(pfu)/mL to seroconvert HSV-seronegative patients followed 3 weeks later by treatment doses of 10^8 pfu/mL every 2 weeks or GM-CSF 125 mcg/m^2 once daily for 14 days of every 28 day cycle.

b) The primary endpoint was durable response rate (DRR), defined as an objective response lasting continuously for at least 6 months by independent review. The DRR was 19% with T-VEC and 1.4% with GM-CSF ($p<0.0001$). The overall RR was 31.5% in those treated with T-VEC with a 16.9% complete response rate compared with 1.4% and less than 0.7% in the GM-CSF group, respectively. Among the patients who achieved a CR, 88.5% were alive at 5 years [38]

c) The final updated analysis showed a median OS of 23.3 months with T-VEC and 18.9 months with GM-CSF (unstratified HR 0.79; $p=0.0494$)[38]

d) T-VEC was well tolerated with the most common adverse effects being fatigue, chills, and pyrexia. No premedication was required. The only grade 3 or higher toxicity was cellulitis, seen in 2.1% of patients.

e) The greatest response benefits were seen in treatment-naive patients and those with stage IIIB, IIIC and IV M1a disease. Responses were seen in both injected and uninjected lesions[35]

f) Viral shedding occurs at the injection site and can pass through the dressing placed following injection[37].

g) Blood should be considered infectious and viral DNA was found in the urine on the day of the injection but cleared afterwards.

h) Acyclovir and other antiherpetic viral agents should be avoided as they may interfere with the effectiveness of T-VEC

i) Patient recommendations include educating the importance of avoiding direct contact with treatment sites, dressings or body fluids. Gloves should be worn when dressings are changed and the injection site should be covered for at least 1 week following the injection. All used dressings and cleaning materials should be disposed of in a sealed plastic bag before disposing in the garbage.[37]

Patient Case #3:

KL is a 48-year-old woman with newly diagnosed cutaneous melanoma of her right upper arm. Additional imaging shows 2 suspicious lesions in her lung which are biopsied and consistent with metastatic melanoma. Next generation sequencing is performed on the lung specimen and is negative for any pathogenic BRAF alterations. She is asymptomatic with no significant past medical history and has extensive family support. She wishes to be as aggressive as possible treatment.

Which of the following treatment options is most appropriate for KL at this time?

A. Pembrolizumab
B. Vemurafenib, cobimetinib and atezolizumab
C. Ipilimumab and nivolumab
D. Pembrolizumab and low-dose ipilimumab

E. Metastatic disease

1. First line systemic therapy options:[1]

a. Nivolumab (NCCN Guidelines category 1, preferred)

b. Pembrolizumab (NCCN Guidelines category 1, preferred)

c. Combination nivolumab plus ipilimumab (NCCN Guidelines category 1, preferred)

1) Useful in certain circumstances with relative indications for combination therapy over single agent including the patient's willingness to take on the high risk of treatment-related toxicities, the absence of comorbidities or autoimmune processes that would elevate the risk of irAE, presence of social support and anticipated compliance with medical team to handle toxicities and/or the absence/low tissue PD-L1.

d. Nivolumab/Relatlimab (NCCN Guidelines category 2A, preferred)

e. Pembrolizumab and low-dose ipilimumab (NCCN Guidelines category 2B, other recommended regimen)

f. For patients with BRAF V600-activating mutations (all doublet combinations are NCCN Guidelines category 1. They are preferred over immune checkpoint inhibitor therapy if clinically needed for an early response):

1) Dabrafenib and trametinib (preferred)

2) Vemurafenib and cobimetinib (preferred)

3) Encorafenib and binimetinib (preferred)

4) Combination of vemurafenib, cobimetinib and atezolizumab is a NCCN category 2A, other recommended regimen

2. Second or Subsequent Systemic Therapy Options for Metastatic Melanoma[1]

a. For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and if from a different class.

b. For patients who progressed on single-agent anti-PD-1 checkpoint immunotherapy, nivolumab/ipilimumab combination therapy or ipilimumab monotherapy is a reasonable treatment option.

c. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered

Second or Subsequent Systemic Therapy Options for Metastatic Melanoma[1]

Preferred Regimens	Useful in Certain Circumstances
Nivolumab	Ipilimumab and intralesional T-VEC (category 2B)
Pembrolizumab	Imatinib (for tumors with KIT-activating mutations)
Nivolumab and ipilimumab	Binimetinib for NRAS-mutated tumors after progression on prior immune checkpoint inhibitor therapy (category 2B)
Nivolumab/Relatlimab	
Pembrolizumab and low-dose ipilimumab (following progression on prior anti-PD-1 therapy)	Larotrectinib or entrectinib for activating NTRK gene fusions
Dabrafenib and trametinib (BRAF-mutated)	Cytotoxic agents*
Vemurafenib and cobimetinib (BRAF-mutated)	Pembrolizumab/lenvatinib (Category 2B) for patients who have progressed after treatment with anti-PD-1/PD-L1 therapy including with ipilimumab for ≥ 2 doses
Encorafenib and binimetinib (BRAF-mutated)	
Other Regimens	
Ipilimumab	
High-dose interleukin-2: should not be used for patients with inadequate organ reserve, poor performance status or untreated or active brain metastases. Therapy should be restricted to an institution with medical staff experienced in the administration of the drug.	

* Case-by-case basis for patients who are unable to receive immunotherapy and/or targeted therapy, which are preferred options. Cytotoxic agents that have been used alone or in combination include (but are not limited to): dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel, and cisplatin/vinblastine/dacarbazine (CVD) (category 2B for CVD)

****All recommendations are category 2A unless otherwise indicated**

Patient Case #3, Discussion:

Answer C: Ipilimumab and nivolumab

Ipilimumab and nivolumab is most appropriate. All of the answers are options for first-line metastatic melanoma; however, she is young, healthy with strong family support and can likely tolerate the combination of ipilimumab and nivolumab. This combination is most useful over single agent when the patient is willing to take on the high risk of treatment-related toxicities, the absence of comorbidities or autoimmune processes that would elevate the risk of irAE, and the presence of social support. This would make it preferred over single agent pembrolizumab and the combination with low-dose ipilimumab (category 2A). She does not have a BRAF V600 mutation and so BRAF/MEK therapy is not indicated.

KL starts on combined ipilimumab and nivolumab x 4 doses and then continues on single agent nivolumab. Three months following the start of therapy, KL is tolerating therapy well but having low grade fatigue. Her disease is responding to therapy. While at a routine monitoring visit, her TSH level is 12 mIU/L

Based on this finding, what is the most appropriate management strategy at this time?

A. Continue nivolumab and monitor TSH
B. Hold nivolumab until TSH normalizes
C. Continue nivolumab and start levothyroxine
D. Continue nivolumab and start levothyroxine and prednisone 1 mg/kg

3. BRAF V600 should be assessed in all stage III and metastatic melanomas.[1, 5]

    a. BRAF V600 mutations are found in 40-50% of cutaneous melanomas. The V600E mutation is the most common, representing about 80-90% of the BRAF mutations while 5-12% are V600K. In V600E or V600K mutated tumors, the initial selection between BRAF inhibitors and immunotherapy is commonly done based on the aggressive nature of the tumor. While patients with BRAF V600K mutations still benefit from BRAF +/- MEK inhibitor therapy, responses may be slightly lower.

    b. BRAF non-V600 mutations near V600E such as BRAF L597 and K601 have derived some clinical benefit to inhibitors of BRAF and MEK while mutations in other codons like exon 11 or exon 15 have not shown responses.[39]

    c. Rapidly growing tumors that are symptomatic are preferentially treated with BRAF-directed therapy because it generates a higher response rate and quicker response, while asymptomatic or more indolent tumors may be treated with immunotherapy.

    d. Effects on the biology or best sequence from a large randomized trial are unclear but trials are underway to better assess.[1]

4. Surgery: metastasectomy of isolated lesions may result in prolonged survival in patients where resection is anatomically possible[1]

5. Immunotherapy (anti-PD1 and anti-CTLA4 therapy) in the metastatic setting

    a. Patient responses have been described to fall into 1 of four categories: [40]

        1) **A**: response in baseline lesions

        2) **B**: "stable disease" with slow, steady decline in total tumor volume

        3) **C**: response after initial increase in total tumor volume

        4) **D**: reduction in total tumor burden after the appearance of new lesions.

        5) Both C and D above are traditionally considered progression of disease, but this is not necessarily the case with immunotherapy. Consequently, there has been discussion and proposed response criteria developed for immunotherapy (immune related Response Criteria; irRC).[40]

    ii. Pseudoprogression[1]

        1) Describes when there is radiographic or clinically evident increase in tumor size early in the treatment course followed by regression

        2) Average time to response can vary between 6 to 12 weeks

        3) NCCN Guidelines recommend continuing immune checkpoint inhibitor therapy for an additional 6 to 10 weeks even in the presence of tumor growth

        4) Continued growth at 16 weeks after starting therapy can be considered true progression

Comparison of Response Criteria for Immunotherapy [40]

	WHO	irRC
New, measurable lesions (i.e., ≥5× 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR (complete response)	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR (partial response)	≥ 50% decrease in all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥ 50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD (stable disease)	50% decrease in the sum of the product of the diameters (SPD) compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD (progressive disease)	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Patient Case #3, Continued:

Answer C:

KL has grade 2 hypothyroidism as evidenced by increasing low grade fatigue and TSH 12mIU/L. Thyroid supplementation is recommended in symptomatic patients with TSH > 10 mIU/L with monitoring every 6-8 weeks while the dose is titrated. Nivolumab can be held, but this is clinical judgment based on the severity of side effects. This patient is only having low grade fatigue; therefore, immunotherapy can be continued. Steroids are not typically utilized for immune-related hypothyroid like other immune-related toxicities.

Patient Case #4

MT is a 51-year-old man with newly diagnosed metastatic melanoma involving the scalp, liver, lungs and numerous lymph nodes. Biopsy of the liver confirms the diagnosis and next generation sequencing performed on the specimen shows a BRAF V600E mutation. He has moderate to severe shortness of breath requiring oxygen and moderate abdominal pain requiring daily opioids for management.

Which of the following options is most appropriate first-line therapy for MT at this time?

A. Talimogene laherparepvec (T-VEC)
B. Pembrolizumab + low-dose ipilimumab
C. Vemurafenib
D. Encorafenib and binimetinib

iii. Pembrolizumab.[41-43]

1) First line therapy: The KEYNOTE-006 trial[42] compared 2 dosing regimens of pembrolizumab with ipilimumab in 834 patients with unresectable, stage III or IV melanoma who had received no more than 1 previous therapy for advanced disease. Approximately 66% of patients were untreated and >95% had metastatic disease.

a) It is important to note that this dose of pembrolizumab in this study (10 mg/kg) is different than the 200mg every 3 week dose that is currently FDA-approved for metastatic melanoma.

b) For the long-term outcome analysis, the 2 pembrolizumab groups were combined due to similarity in results

5-Year Outcomes from KEYNOTE-006[43]

	Pembrolizumab 10 mg/kg q 2 or 3 weeks*	Ipilimumab 3 mg/kg q 3 weeks x 4 doses	
Median PFS	8.4 months	3.4 months	HR 0.55, 95% CI 0.48-0.67, p < 0.0001
Median OS	32.7 months	15.9 months	HR 0.73, 95% CI 0.61-0.88, p < 0.00049

*Pembrolizumab was continued until disease progression in each arm while ipilimumab was only give for a total of 4 doses.

c) The estimated 24-month PFS in patients with complete and partial responses was 85.4% and 82.3%, supporting the durable nature of these responses.[43]

d) Treatment toxicities were lower in the pembrolizumab arms with grade ≥ 3 toxicities in 17% of the combined pembrolizumab-treated patients compared to 20% of the ipilimumab-treated patients. The most common treatment-related effects were colitis, diarrhea and fatigue.[43]

e) Single agent pembrolizumab is a NCCN category 1 preferred regimen option for first line therapy[1]

2) Pembrolizumab and low-dose ipilimumab[44, 45]

a) KEYNOTE-029 assessed the combination of pembrolizumab (initially 2 mg/kg amended to 200 mg) every 3 weeks plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by pembrolizumab alone for up to 2 years in 153 patients with advanced melanoma who had not received prior immune checkpoint inhibitor therapy

b) Safety was the primary endpoint with secondary endpoints of ORR, PFS and OS (median follow-up of 36.8 months)

i. ORR was 62.1% with 27.5% complete responses and 34.6% partial responses

ii. Median PFS and OS were not reached

iii. 36-month PFS was 59.1% and OS was 73.4%

c) This combination is an NCCN category 2B option for first line therapy

3) Second line therapy[41, 46]

a) 70 patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody therapy were enrolled with the median length of prior treatment being 4.8 months

i. Treatment was pembrolizumab 200 mg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses followed by pembrolizumab monotherapy

ii. Primary endpoint was response rate by irRECIST: 29% with 5 complete and 15 partial responses

iii. Median PFS was 5 months

iv. Median OS was 24.7 months

v. Response was not associated with median time on prior anti-PD-1/L1 antibody therapy or time to starting pembrolizumab/ipilimumab

This combination is an NCCN category 2A option (along with other options) for second line therapy

4) Pembrolizumab and Lenvatinib

a) LEAP-004: 103 patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody therapy or combination immunotherapy[47]

i. Treatment was pembrolizumab 200 mg every 3 weeks with lenvatinib 20 mg once daily

ii. Primary endpoint was overall response rate: 21.4 % with 3 complete and 19 partial responses

iii. Median PFS was 4.2 months

iv. Median OS was 14 months

v. Grade 3-5 treatment related AEs: 45.6 %, most commonly hypertension (21.4%), with one death from decreased platelet count

iv. Nivolumab +/- ipilimumab

1) First-line therapy: CheckMate 067[48] study compared single agent nivolumab with single agent ipilimumab or the combination of nivolumab and ipilimumab in this placebo-controlled trial of 945 patients with previously untreated, unresectable stage III or IV melanoma.

6.5-Year Outcomes from CheckMate 067[49,50]

	Nivolumab 3 mg/kg q 2 weeks*	Ipilimumab 3 mg/kg q 3 weeks x 4 doses	Nivolumab and Ipilimumab**	P value
Median PFS	6.9 months	2.9 months	11.5 months	<0.001 for both nivolumab and the combination vs. ipilimumab
Median OS	36.9 months	19.9 months	72.1 months	<0.001 for both nivolumab and the combination vs. ipilimumab

*Nivolumab was continued until disease progression in each arm while ipilimumab was only give for a total of 4 doses

** Nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond until toxicity or progression. Note that the FDA approved dosing recommends the flat dose of nivolumab 240 mg every 2 weeks after the initial 4 doses of ipilimumab.

a) Notably, the median OS and PFS in patients who discontinued ipilimumab and nivolumab due to treatment-related toxicities were similar to patients who did not discontinue due to toxicity

b) Patients with PD-L1 positive tumors had similar benefits from the 2 nivolumab arms with a median PFS of about 14 months for single agents and combination. The PD-L1 negative patients had a higher median PFS with the combination (11.2 months) compared with nivolumab alone (5.3 months).

c) Grade 3 or higher treatment-related toxicities were highest in the combination group (55%) compared with the single agent nivolumab (16.3%) or ipilimumab (27.3%) patients. Drug discontinuation due to toxicity occurred in 36.4% of the patients treated in the combination group compared to 7.7% with nivolumab monotherapy and 14.8% of ipilimumab monotherapy arms[48]

d) Both **single agent nivolumab** and the combination of **ipilimumab and nivolumab** are NCCN Category 1 preferred options for first line therapy[1]

Combination therapy is associated with higher clinical response rates, PFS and OS but needs to be balanced with the increase risk of toxicity so may be preferred in patients with good performance status who have appropriate supportive resources

CheckMate 067: Toxicity comparison between nivolumab, ipilimumab and the combination[48]

Toxicity (%)	Nivolumab		Ipilimumab		Nivolumab and Ipilimumab	
	All grade	Grade 3 - 4	All grade	Grade 3 - 4	All grade	Grade 3 - 4
Diarrhea	19.2	2.2	33.1	6.1	44.1	9.3
Fatigue	34.2	1.3	28	1	35	4.2
Rash	25.9	0.6	32.8	1.9	40.3	4.8
Increased ALT	3.8	1.3	3.9	1.6	17.6	8.3
Increased AST	3.8	1.0	3.5	0.6	15.3	6.1
Hypothyroidism	8.6	0	4.2	0	15	0.3
Colitis	1.3	0.6	11.6	8.7	11.8	7.7
Arthralgia	7.7	0	6.1	0	10.5	0.3
Dyspnea	4.5	0.3	4.2	0	10.2	0.6

2) Nivolumab/Relatlimab-rmbw[51]

   a) Mechanism of action: Combination of nivolumab (PD-1 inhibitor) and relatlimab-rmbw (LAG-3 inhibitor)

      i. Lymphocyte-activation gene-3 (LAG-3) inhibitor blocks the interaction between LAG-3 and its ligands (including MHC II) to reduce LAG-3 pathway-mediated immune response inhibition. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

   b) RELATIVITY-047 evaluated the combination versus nivolumab alone in 714 patients with previously untreated metastatic or unresectable melanoma. [51]

   c) Nivolumab 480 mg/relatlimab-rmbw 160 mg every 4 weeks versus nivolumab 480 mg every 4 weeks until disease recurrence

   d) Primary endpoint was progression-free survival

      i. Median PFS 10.1 months versus 4.6 months

      ii. 12-month PFS: 47.7% versus 36%

   e) Grade 3 or 4 irAEs: 18.9% versus 9.7%

Toxicity (%)	Nivolumab		Nivolumab/relatlimab-rmbw	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Puritis	15.9	0.6	23.4	0
Fatigue	12.8	0.3	23.1	1.1
Rash	12	0.6	15.5	0.8
Arthralgia	7.2	0.3	14.4	0.8
Hypothyroidism	12	0	14.4	0
Diarrhea	9.2	0.6	13.5	0.8
Vitiligo	9.7	0	10.4	0
Hepatitis	**2.5**	**1.1**	**5.6**	**3.9**

f) This combination is a NCCN preferred, category 2A option for first line therapy

3) Second line therapy[52]

a) Patients with advanced melanoma who had received at least one prior line of therapy, including prior immunotherapy, were treated with escalating doses of nivolumab every 2 weeks until disease progression or toxicity.

i. Median OS was 16.8 months with 1-year and 2-year survival of 62% and 43%, respectively.

ii. Most common toxicities of any grade were fatigue (32%), rash (23%) and diarrhea (18%).

Patient Case #4, Continued:

Answer D: Encorafenib and binimetinib

MT has symptomatic BRAF V600E mutated metastatic melanoma. Other first line therapy options include inhibitors of BRAF (including dabrafenib and vemurafenib) and MEK (including trametinib and cobimetinib.) The combination of a BRAF and MEK inhibitor has resulted in improved outcomes compared with the BRAF inhibitor alone and BRAF-targeted therapy is preferred over immunotherapy when patients are symptomatic and/or have rapidly growing tumors. T-VEC is currently only approved for unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (not metastatic disease).

MT is beginning treatment with encorafenib and binimetinib. What baseline labs or other monitoring should be ordered?

A. Mg, Phos
B. CBC, CMP, CPK, EKG, echocardiogram, routine eye exams
C. PFTs, Chest x-ray, CMP
D. INR, PT/PTT

4. BRAF / MEK targeted therapies in the metastatic setting

    a. Dabrafenib, encorafenib and vemurafenib are all BRAF inhibitors. Trametinib, binimetinib and cobimetinib are all MEK inhibitors.[53-56]

    b. BRAF and MEK inhibitor toxicities:[53, 54]

        1) The most common BRAF inhibitor all grade toxicities include: rash, photosensitivity, hair loss, and joint pain though the incidence differs slightly between the 3 agents.

        2) Grade 3 toxicities included dermatologic effects (rash, keratoacanthoma and cutaneous squamous cell cancer), gastrointestinal, fatigue, and joint pain.

        3) Cutaneous squamous cell cancers and keratoacanthomas are the result of compensatory RAF signaling and are decreased with the addition of a MEK inhibitor.

            i. In the phase III trial with vemurafenib alone, the rate of grade 3 cutaneous squamous cell cancer was 12% but was higher in the phase I and II trials at 26%.

            ii. These cancers are typically localized and easily treated with surgical excision or topical fluorouracil cream.

            iii. Regular skin assessments should be done throughout therapy with BRAF inhibitors.[54]

        4) Pyrexia (defined as a temperature of $\geq$ 38.5 C) is seen in about 55% of patients receiving BRAF and MEK inhibitor combination therapy[53, 54]

            i. Usual onset of 2-4 weeks following the start of therapy and lasting a median duration of 9 days.

            ii. Holding the BRAF and MEK inhibitor therapy at the onset of pyrexia will typically lead to resolution and therapy can be restarted at full dose upon cessation.

            iii. For prolonged or severe pyrexia that does not resolve with holding of therapy, prednisone 10 mg PO daily can be used

            iv. Patients should be educated to use antipyretics and increase fluid intake

        5) It is recommended to hold BRAF and/or MEK inhibitors 1 day before and after stereotactic radiosurgery (SRS) and at least 3 days before and after fractionated radiation therapy

    c. Though initially evaluated as single agents, combination therapy is now the recommended treatment regimen. This is secondary to the development of resistance to the single agent BRAF inhibitors typically after 6-7 months. Combination therapy with both BRAF and MEK inhibitors may suppress the downstream resistance mechanism.

        1) The combination of vemurafenib and cobimetinib was compared with vemurafenib and placebo in 495 patients with previously untreated, unresectable, advanced melanoma that was BRAF V600-positive (coBRIM trial).[56, 57]

            a) After median follow-up of 14.2 months, the primary endpoint of PFS was 12.3 months in the combination group and 7.2 months in the vemurafenib and placebo group (HR 0.58, 95% CI 0.46 – 0.72, p<0.001).

            b) Median OS was 22.3 months in the combination group and 17.4 months in the vemurafenib and placebo group (HR 0.70, 95% CI 0.55-0.90; p<0.005)

c) Though the combination was associated with a higher incidence of grade 3 or higher toxicities, the discontinuation rate was 14% and 7% in the combination and single arm groups, respectively. Toxicities were more common in the combination group including gastrointestinal effects, central serous retinopathy, photosensitivity, renal and hepatic effects.[56]

2) The combination of dabrafenib and trametinib was compared with dabrafenib alone in the phase III COMBI-d trial. Dabrafenib 150 mg PO BID was alone or in combination with trametinib 2 mg PO daily. The trial included 423 previously untreated patients with unresectable stage IIIC or IV melanoma that had either a BRAF V600E or V600K mutation.[58, 59]

   a) Median PFS was 11 months in the combination arm compared with 8.8 months in the monotherapy arm (HR 0.67, 95% CI 0.53-0.84; p=0.0004.

   b) Median OS was 25.1 months in the combination arm compared with 18.7 months in the monotherapy arm (HR 0.71; 95% CI 0.55-0.92; p=0.0107)

   c) Toxicity was similar between the two arms with except for more pyrexia (51% v 28%) and less cutaneous toxicity including squamous cell carcinomas (2% v 9%) seen in the combination arm. Discontinuation due to toxicity occurred in 11% of the combination and 7% of the monotherapy groups.[59]

3) The combination of dabrafenib and trametinib was also compared with single agent vemurafenib in an open-label phase III trial. Dabrafenib and trametinib were dosed as above and compared with vemurafenib 960 mg PO BID in 704 advanced melanoma patients with either a BRAF V600E or V600K mutation. [60]

   a) OS at 12 months was longer in the combination arm (72% v 65%, 95% CI 0.53-0.89, p = 0.005).

   b) Median PFS was 11.4 months in the combination arm compared with 7.3 months in the vemurafenib arm (HR 0.56 (95% CI 0.46-0.69), p < 0.001)

   c) Toxicity was similar between the two arms with less cutaneous squamous cell carcinomas and keratoacanthomas seen in the combination group (1% v 18%).

   d) Long-term follow-up of dabrafenib and trametinib treated patients showed a median overall survival (mOS) of more than 2 years with about 20% of patients remaining free of disease progression at 3 years.[60]

Comparison of toxicity between single agent vemurafenib compared with dabrafenib and trametinib[61]

Toxicity	Vemurafenib		Dabrafenib + Trametinib	
	All grade	Grade 3 and 4	All grade	Grade 3 and 4
Pyrexia	21%	1%	53%	4%
Rash	43%	9%	22%	1%
Diarrhea	38%	< 1%	32%	1%
Hand Foot Syndrome	25%	< 1%	4%	0%
Hyperkeratosis	25%	1%	4%	0%
Cutaneous Squamous cell carcinoma (SqCC)	18%	17%	1%	1%
Decreased ejection fraction	0%	0%	8%	4%

4) The BRAF inhibitor encorafenib and MEK inhibitor binimetinib were compared with encorafenib alone and with vemurafenib alone in the COLUMBUS trial (n=577 patients). **Encorafenib was dosed at 300 mg PO daily which is lower than the FDA approved dose of 450 mg PO daily**. This was due to subsequent studies that showed the maximum tolerated dose of encorafenib was higher when it was dosed with binimetinib compared to when it was dosed alone. Binimetinib was dosed at the FDA approved 45 mg PO BID dose.[62, 63]

    a) The primary endpoint was median PFS by blinded independent review and was higher for the combination at 14.9 months compared to 7.3 months with vemurafenib [HR 0.54 (95% CI 0.41-0.71), two sided p<0.0001].

    b) Median OS was also higher with the combination at 33.6 months compared to 16.9 months with vemurafenib [HR 0.61 (95% CI 0.47 – 0.79), two sided p<0.0001].

    c) The combination arm had a higher median PFS compared to single agent encorafenib (14.9 months vs 9.6 months, HR 0.75 (95% CI 0.56-1.00) though the p value was 0.051. Median OS was also improved with the combination with a 33.6 month mOS with encorafenib and binimetinib compared with 16.9 months with vemurafenib alone (HR 0.61, 95% CI 0.47-0.79; p<0.001) and 23.5 months with encorafenib alone (HR 0.76, 95% VI 0.58-0.98; two sided p=0.033)

    d) The toxicity associated with encorafenib and binimetinib had some differences compared with other approved BRAF and MEK inhibitors including less pyrexia (seen with dabrafenib and trametinib) and photosensitivity (seen with vemurafenib and cobimetinib).

    e) Grade 3 or 4 toxicities reported included increased gamma-glutamyltransferase (9%), increased creatinine phosphokinase (7%), and hypertension (6%). Rates of discontinuation due to toxicity were similar, being seen in 15% of patients in the encorafenib and binimetinib group compared with 16% in the encorafenib alone group[63]

5) The combination of vemurafenib, cobimetinib and atezolizumab became the first BRAF/MEK targeted therapy combined with an immune checkpoint inhibitor to be approved for advanced BRAF V600-mutated melanoma

a) The IMSPIRE150 trial was a phase 3 trial that randomized 514 patients 1:1 with unresectable stage IIIC-IV BRAF V600-mutated melanoma to receive either the combination of vemurafenib, cobimetinib and atezolizumab (atezolizumab group) or vemurafenib, cobimetinib and placebo (placebo group)[64]

i. The primary endpoint of median PFS assessed by study investigator was 15.1 vs. 10.6 months in the atezolizumab and placebo groups, respectively (HR 0.78; 95% CI 0.63-0.97; p=0.025)

ii. The most common toxicities reported in more than 30% of patients in the atezolizumab group were increased creatinine phosphokinase, diarrhea, rash, arthralgia, pyrexia, AST and lipase increases.

b) The NCCN Guidelines include this triplet combination as another first-line recommended regimen for BRAF V600-mutated metastatic or unresectable melanoma with a category 2A. It is noted that currently it is not preferred over the double combinations as mature overall survival data has not yet been reported.[1]

5. Management of brain metastases[1]

a. Treatment modalities include surgery, radiation and systemic therapies and depend on the burden of intracranial disease and associated symptoms.

1) Higher volume intracranial disease associated with symptoms will often require local brain-directed therapies like radiation

2) Lower volume, asymptomatic brain metastases and/or patients with a high burden of extracranial disease may benefit most from systemic therapy

3) Patients commonly require both brain-directed and systemic therapies

b. Systemic therapy[1]

1) Sole systemic therapy as the initial treatment option may be considered in patients with < 3 cm asymptomatic brain metastases who do not require corticosteroids and who have not received prior systemic therapy

2) Ipilimumab and nivolumab[65]

a) Assessed in 94 patients with metastatic melanoma and at least one measurable, nonirradiated brain metastasis (0.5 to 3 cm in diameter) and no neurologic symptoms

b) Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks until progression

c) Primary endpoint: 57% of patients had stable disease for $\geq$ 6 months including 26% with complete response and 30% with partial response

d) Safety was similar to patients with melanoma who did not have brain metastases

3) In patients for whom ipilimumab and nivolumab is not preferred, single agent anti-PD-1 therapy has had more limited benefits and is not preferred as the initial treatment options. Brain-directed therapy should be considered as first line therapy, if appropriate.

4) For BRAF V600-mutated patients, BRAF/MEK inhibitor combination therapy can be considered for select symptomatic patients who have not received prior BRAF/MEK therapy. PFS is typically shorter that reported for extracranial disease.

c. Corticosteriods are often required for symptom management. The lowest dose possible to control symptoms is recommended with plan for taper if intracranial disease responds to therapy.

d. Patients who undergo brain metastases resection can be considered for adjuvant radiation and, in the event of no evidence of disease, can be considered for systemic adjuvant therapy

Patient Case #2, continued:

Answer B: CBC, CMP, CK, EKG, echocardiogram, routine eye exams

Baseline and routine labs should include a CBC, CMP, and CPK level. While rare, BRAF/MEK inhibitor combinations can cause anemia, thrombocytopenia, and leukopenia. Monitoring of LFTs and renal function are also recommended due to potential elevations of LFTs and changes in renal function. Binimetinib can cause increases in creatinine phosphokinase. BRAF/MEK inhibitor combinations have warnings for QTc prolongation. Baseline EKG is recommended and routine monitoring should be done as well. Baseline echocardiogram is also recommended and repeated regularly in patients with a history of low ejection fraction or show signs of cardiac dysfunction while on therapy. BRAF/MEK inhibitor combinations can cause visual impairment, eye irritation, and more severe toxicities such as retinal detachment and macular edema.

6. Aldesleukin (IL-2)

a. Clinical trials report response rates from 15% to 25% with 2% to 5% of patients achieving complete responses. Durable responses can be seen in 5-10% of patients and can last for decades. [66]

b. The doses used in the initial clinical trials and recommended in the labeling of the drug are associated with significant toxicities and may limit the practicality of therapy for individual patients. Treatment-related mortality was as high as 2.2% in clinical trials.[67] The high dose (600,000 international units (IU)/kg/dose q8h x 14 doses) is FDA-approved for treatment of metastatic melanoma.

c. Administration of high-dose IL-2 requires careful attention to management of toxicities, adherence to patient-eligibility criteria and well-trained staff.[68] Toxicities include:

1) Cytokine-induced capillary leak syndrome (hypotension sometimes requiring vasopressor support, visceral edema sometimes requiring diuresis, dyspnea sometimes requiring artificial ventilator support, tachycardia, and arrhythmia)

2) Visceral edema can result in pulmonary congestion, pleural effusions, and edema

3) Constitutional symptoms

4) Pruritis

5) Eosinophilia

6) Bone marrow suppression

7) Increase in liver function test

8) Renal insufficiency/failure

9) Nausea/vomiting

d. Majority of toxicities will reverse following discontinuation

e. Should not be used in patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases

7. Chemotherapy now has a limited role in the treatment of metastatic melanoma. The benefits of novel immunotherapy agents have moved chemotherapy agents to the salvage setting. None of the chemotherapy agents/regimens have been shown to improve OS in a randomized phase III setting.

a. Dacarbazine (DTIC)[1]

1) DTIC is the only FDA-approved chemotherapeutic agent for the treatment of metastatic melanoma in the United States. The optimal dose and schedule has never been determined.

2) Response rates: 20% to 25% with an average duration of response of 5 to 7 months, complete responses are uncommon[1]

b. Temozolomide was developed as a potential alternative to dacarbazine and can be administered orally.

1) Temozolomide appears to cross into the central nervous system (CNS) and therefore may be beneficial for patients with CNS metastases

2) One phase III randomized trial demonstrated equivalent efficacy vs. dacarbazine[69]

c. Taxanes – paclitaxel is listed as an option in the NCCN Guidelines®; however, the response rates to paclitaxel and docetaxel are relatively low (6-18%).[1]

d. Combination Chemotherapy

Paclitaxel/carboplatin – although suggested as an alternative in the NCCN Guidelines®, when compared to weekly paclitaxel monotherapy, the combination only increases toxicity, with no improvement in response or OS. Some evidence of benefit as second line therapy after temozolomide or dacarbazine.[70]

II. Survivorship and Long-Term Follow-up[1]

A. Scheduled screening in addition to routine surgical follow-up is required for any patient with a history of melanoma. The frequency and duration recommended is dependent on the stage of melanoma and the pre-existing risk factors of the patient. The optimal duration of follow-up is controversial; however, the period of greatest risk is the first 2 years after initial diagnosis. Guidelines for follow-up are present in the NCCN Guidelines®[1]

B. All melanoma patients should have a skin examination and surveillance at least once per year for the rest of their life, regardless of stage at diagnosis

C. Patients should also be educated about self skin and lymph node checks

D. Continued use of sunscreen and skin care is also recommended

NON-MELANOMA SKIN CANCERS (NMSC)
BASAL CELL CARCINOMA (BCC), SQUAMOUS CELL CANCER (SCC) AND MERKEL CELL CARCINOMA (MCC)

I. Risk Factors (within a common ancestry – cumulative sun exposure [UV light] and age are most important)[71-73]

A. UV light exposure – additional risk in individuals with a susceptibility for sunburn

1. Fair complexion including those with skin freckling
2. Skin freckling
3. Individuals treated with psoralens and PUVA for psoriasis
4. Inhabitants of areas closer to the equator
5. Total skin exposure (prolonged sun exposure appears to be most closely linked to SCC)
    a. Correlation with age
6. BCC closely correlates with tendency to sunburn and intermittent childhood & adolescent exposure
7. MCC that is Merkel cell polyomavirus negative is more likely to have a UV genetic signature which is associated with a high tumor mutation burden

B. Approximately 60% of SCC lesions came from actinic keratosis. Sun avoidance and sunscreen can decrease incidence of actinic keratosis.

1. Treatment depends on size, number of lesions, and location. Therapy ranges from liquid nitrogen, surgical excision, topical fluorouracil, topical diclofenac, topical imiquimod, topical retinoids, dermabrasion, chemical peels, and photodynamic therapy.

C. Ionizing radiation – 3-5 fold increase with therapeutic radiation

D. Chronic immunosuppression

1. Immunosuppressive diseases (HIV infection, chronic lymphocytic leukemia, severe combined immunodeficiency (SCID)) significantly increase the risk of skin cancer (basal cell, melanoma, and especially SCC).
2. Solid organ transplant patients on long-term immunosuppression are also at an increased risk of skin cancer, particularly SCC. The type of transplant also seems to differentiate risk; highest with heart transplant, followed by renal, then liver. Immunosuppression with tacrolimus, mycophenolate, or rapamycin seems to convey a lower risk than cyclosporine, glucocorticoids, or azathioprine in organ transplant.

E. Viruses

1. Human papilloma virus (HPV) infection types 16 and 18 increase risk of anogenital SCC
2. Merkel cell polyomavirus (MCPyV) is found in 43-100% of MCC[73]

F. Chronic arsenic exposure

G. Chronic skin inflammation

H. Genetic conditions affecting skin pigmentation only account for a relatively small portion of skin cancers, but at an individual level predict a very high risk. They include: xeroderma pigmentosum, epidermolysis bullosa, albinism, epidermodysplasia verruciformis

I. Risk factors for **recurrence**

1. Increased size
2. Poorly defined borders
3. Recurrent disease
4. Site of prior radiotherapy (RT)
5. Immunosuppression
6. Aggressive growth pattern
7. Perineural involvement

II. Prevention[71, 72]

A. Minimize UV radiation exposure

B. Use of sunscreen decreases incidence of SCC, but not BCC

C. Actinic keratosis (premalignant SCC lesion) can be treated with retinoids to prevent SCC formation

D. Nicotinamide may help reduce development of SCC

III. Screening: see melanoma section for details

Patient Case #3:
TC is a 78-year-old male with a 2 cm lesion on his scalp that he has noticed is bleeding more frequently and does not appear to be healing. His PMH is significant for multiple severe sunburns during his childhood. He has had several small BCCs removed from his face, arms and back. An excisional biopsy of the lesion reveals a sclerosing BCC. TC is treated with Moh's surgery and then radiation for extensive positive margins. Eight months following local therapy, he develops a recurrence with numerous satellite lesions.

What is the most appropriate systemic therapy for TC's recurrent BCC?

A. Fluorouracil
B. Cisplatin
C. Ipilimumab
D. Vismodigib

IV. Treatment[71, 72]

A. The goal of primary treatment in non-melanoma skin cancer is cure and maximal preservation of function.

B. Surgery:

1. Moh's micrographic surgery
2. Curettage and electrodesiccation

3. Surgical excision

C. Radiation (RT)

1. Radiation is used for lesions that are not surgically resectable
2. Radiation is fractionated to maximize cosmesis
3. Contraindicated in patients with genetic conditions predisposing to skin cancer and in connective tissue diseases (SLE, XP)
4. Adjuvant RT may be considered in non-melanoma skin cancers with significant perineural involvement
5. Adverse effects:
    a. Erythema
    b. Radiation to eyelids: loss of eyelashes
    c. RT to nose: mucositis
    d. Long-term complications: radiation dermatitis

D. Photodynamic therapy (PDT): involves application of a photosensitizing agent (such as methyl aminolevulinate or 5-aminolevulinic acid) to the skin followed by irradiation.

Local Management Options

Management of BCC and SCC	
Low risk BCC	Curettage and electrodesiccation *or* Excision with postoperative margin assessment *or* Radiation
High risk BCC	Excision with postoperative margin assessment *or* Moh's or resection with complete circumferential peripheral and deep margin assessment with frozen or permanent section *or* Radiation
Low risk SCC	Curettage and electrodesiccation *or* Excision with postoperative margin assessment *or* Radiation
High risk SCC	Excision with postoperative margin assessment *or* Moh's or resection with complete circumferential peripheral and deep margin assessment with frozen or permanent section *or* Radiation
SCC with palpable LN	Biopsy – if LN is positive regional LN dissection

E. Chemotherapy is not routinely used for BCC or SCC

1. Topical imiquimod or fluorouracil (5-FU) for select patients when surgery or radiation are not appropriate.
2. For MCC, adjuvant therapy with cisplatin or carboplatin with or without etoposide may be considered in select cases, however no survival benefit has been reported with the use of adjuvant therapy..[73]
3. For locally advanced SCC in patients who are not surgical candidates, concurrent chemoradiation may be a consideration after multidisciplinary discussion for select patients. If indicated, cisplatin is the preferred agent.[72]

F. Targeted therapy and immune checkpoint inhibition for BCC[71]:

1. Considered for locally advanced or metastatic BCC when topical therapy, surgery or radiation is unlikely to be curative.

2. Side effects with vismodegib and sonidegib can be intolerable. Based on this, drug holidays or alternatives to daily dosing can be used to improve adherence, reduce toxicity and improve quality of life.

3. Vismodegib[74, 75]

   a. Approved for the treatment of adults with metastatic or locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation (NCCN Guideline® Category 2A for this indication).[71]

   b. The registry trial evaluated 96 patients (33 with metastatic disease, 63 with locally advanced disease)[75, 76].

      1) After 9 months, ORR of 30% in those with metastatic disease and 43% in locally advanced disease; 21% and 22% had a complete remission, respectively.

      2) After 39 months, the final efficacy results showed investigator assessed ORR of 48.5% in those with metastatic disease (all partial responses) and 60.3% in those with locally advanced disease (including 20 complete responses). Median OS was 33.4 months and not reached, respectively.[76]

      3) Toxicity: grade 3 toxicities in > 1% of patients included weight loss, fatigue, muscle spasms, and decreased appetite. Adverse reactions occurred in more than 10% of patients: muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, diarrhea, decreased appetite, constipation, arthralgias, vomiting, and ageusia[75]

4. Sonidegib

   a. This is the second hedgehog pathway inhibitor to gain FDA approval and is approved for the treatment of adults with locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation (NCCN Guideline® Category 2A for locally advanced disease and Category 2B for metastatic disease).[71]

   b. The approval was based on the BOLT trial that enrolled 230 patients with locally advanced or metastatic basal cell carcinoma not amenable to curative surgery or radiation. This 2 arm trial randomized patients in a 1:2 ratio to either 200 mg (FDA approved dose) or 800 mg of sonidegib daily.[77]

      1) The primary endpoint was objective response rate (ORR). After a follow-up of 13.9 months, ORR was seen in 36% of patients receiving 200 mg and 39% receiving 800 mg.[77]

      2) After 30 months, the centrally assessed ORR was 56.1% in those with locally advanced disease and 7.7% in those with metastatic disease receiving 200 mg daily. Median duration of response was 26.1 months and 24 months, respectively with median OS not reached in either population.[78]

      3) The most common grade 3 or higher toxicities were increased creatinine kinase and lipase concentration. The most common adverse effects of any grade were muscle spasms, dysgeusia, alopecia, nausea, increase creatinine kinase, decreased weight and fatigue which were less common in the 200 mg group.[77]

Patient Case #3: continued

Answer D: Vismodegib

Hedgehog inhibitors are the most active against BCC so vismodigib is recommended in this setting. Chemotherapy has shown limited response and ipilimumab is not currently recommended for the treatment of BCC.

Which of the following toxicities with vismodigib is most appropriate to discussed with TC prior to starting therapy?

A. Changes in taste
B. Secondary skin cancers
C. Hypothyroidism
D. Weight gain

5. Cemiplimab-rwlc

    a. FDA approved for patients with locally advanced basal cell carcinoma followed treatment with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. It is also an NCCN Guideline® Category 2A recommendation for this indication.

    b. The approval was based on a phase 2 trial of patients with either metastatic or locally advanced BCC who had progressed on prior or were intolerant to previous hedgehog inhibitor therapy. The primary analysis was only reported for the 84 locally advanced patients as the metastatic patient analysis was still ongoing.[79]

        1) The ORR by independent review was 31% with best ORR of 5 complete responses and 21 partial responses.

        2) The most common grade 3 or higher toxicities were hypertension and colitis.

Patient Case #3: continued

Answer A: Changes in taste

Vismodigib is associated with taste changes (dysgeusia) in about 55% of patients; making it one of the most common all grade toxicities. Secondary skin cancers are not seen with the hedgehog inhibitors, weight loss (rather than weight gain) is seen in about 45% of patients and hypothyroidism is also not a common side effect with the drug.

G. Therapy for disseminated MCC[73]

1. Clinical trial (preferred)

2. Immunotherapy: non-randomized trials indicate rates of durable response are improved with PD-1/PD-L1 inhibitors compared with chemotherapy (All NCCN category 2A level recommendations)

    a. Avelumab

        3) JAVELIN Merkel 200 trial[80, 81]

            a) 88 patients with metastatic MCC who had not received prior therapy were treated with avelumab 10 mg/kg over 1 hour every 2 weeks

b) The ORR was 33% including 10 patients (11.4%) with a complete response. The median duration of response was 40.5 months with a 42-month OS of 31%.

iii. Avelumab was granted FDA accelerated approval for adults and pediatric patients 12 years of age or older with metastatic MCC. Approval was granted based on tumor response and duration of response.

b. Pembrolizumab

1) Multicenter, phase 2, single arm trial[82, 83]

a) 50 patients with advanced MCC who had not received prior therapy were enrolled to receive pembrolizumab 2 mg/kg IV every 3 weeks for a maximum of 2 years

b) The ORR was 56% in patients with Merkel cell polyomavirus (MCPyV)-positive tumors (n=32) and 53% in MCPyV-negative tumors (n=18).

c) The median PFS in the whole population was 16.8 months and the 24-month OS was 68.7%.

2) Pembrolizumab has been granted FDA accelerated approval for adults and pediatric patients with recurrent locally advanced or metastatic MCC. Approval was granted based on tumor response rate and duration of response.

c. Nivolumab

1) CheckMate 358 phase I/II trial[84]

a) 25 patients with MCPyV-positive MCC who had received $\leq$ 2 prior therapies were enrolled to receive nivolumab 240 mg IV every 2 weeks

b) The overall response rate was 68% with 3 patients have complete responses and 12 having partial responses.

c) A separate cohort of 29 patients with resectable stage IIA to IV were also enrolled at the same dose and demonstrated a 40% radiographic regression of more than 30% and the pathologic complete response rate was 47%.

2) Has not received FDA-approval for this indication yet

3. Chemotherapy

a. Considered in patients who are not candidates for immune checkpoint inhibitors

b. Options include cisplatin or carboplatin alone or with etoposide, topotecan, or the combination of cyclophosphamide, doxorubicin/epirubicin, and vincristine (CAV)

H. Therapy for metastatic or locally advanced SCC[72]

1. Cemiplimab-rwlc[85]

a. Approved for patients with metastatic or locally advanced cutaneous SCC who are not candidates for curative surgery or curative radiation and recommended by the NCCN guidelines as a preferred regimen

b. Approval based on R-2810-ONC-1423 and R2810-ONC-1540 which included 75 patients with metastatic and 33 patients with locally advanced disease

1) The ORR was 47% with 4% complete responses and 44% partial responses in the overall population

2) For the 75 patients with metastatic disease, the ORR was 47%

3) For the 33 patients with locally advanced disease, the ORR was 49%

4) The median duration of response was not reached and 61% of responses were durable for 6 months or longer

2. Pembrolizumab

a. Approved for patients with metastatic, recurrent or locally advanced SCC who are not candidates for curative surgery or curative radiation and recommended by the NCCN guidelines as a preferred regimen

b. Approval based on KEYNOTE-629 which included 105 patients with relapsed/metastatic disease[86]

1) The ORR was 34.3% with 4 complete responses and 32 partial responses

2) Disease control rate: 52.4%

3) Median PFS was 6.9 months and median OS was not reached

c. Additional data published separately included 54 patients with locally advanced SCC[87]

1) The ORR was 50%, including 16.7% CR and 33.3% PR

3. Additional options in the NCCN guidelines for patients who are ineligible or who have progressed on immune checkpoint inhibition and clinical trials

a. Carboplatin and paclitaxel is another recommended regimen

b. Cetuximab, capecitabine, cisplatin +/- fluorouracil and carboplatin may be useful in certain circumstances

c.

V. Survivorship and Long-Term Follow-up[71-73]

A. Nonmelanoma skin cancers generally have a favorable prognosis. There are only ~ 2000 deaths out of 1-2 million new diagnoses each year.

B. Local recurrence is the most common problem; however, the rare patient who has metastatic disease has < 50% chance of being alive at 5 years.

C. Close follow-up is extremely important with prevention counseling

1. BCC – every 6-12 months for the first 5 years then at least annually for life

2. SCC – every 2-3 months for 1 year, then every 2-4 months for 1 year, then every 4-6 months for 3 years, then every 6-12 months for life

3. MCC – every 3-6 months for 3 years and then every 6-12 months thereafter

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Recommended Reading

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