Creating Clarity in Metastatic Melanoma

Optimizing Treatment and Improving Outcomes

Amanda Viereck, PA-C
Fox Chase Cancer Center, Temple Health

Anthony Olszanski, RPh, MD
Fox Chase Cancer Center, Temple Health

Welcome and Introductions

Disclosures

Amanda Viereck, PA-C, has nothing to disclose.

Anthony Olszanski, RPh, MD

- Research Support/Consultant: Alkermes, Array, Merck, Merck_EMD Serono, Novartis
- Consultant: Pfizer

This activity is supported by educational grants from
Array BioPharma Inc., Bristol-Myers Squibb Company, and Merck Sharp & Dohme Corp.

This activity may include discussion of agents that have not yet been approved by the US FDA and investigational uses of approved products. Please consult prescribing information and practice guidelines for detail regarding safe and effective use of therapeutic agents.

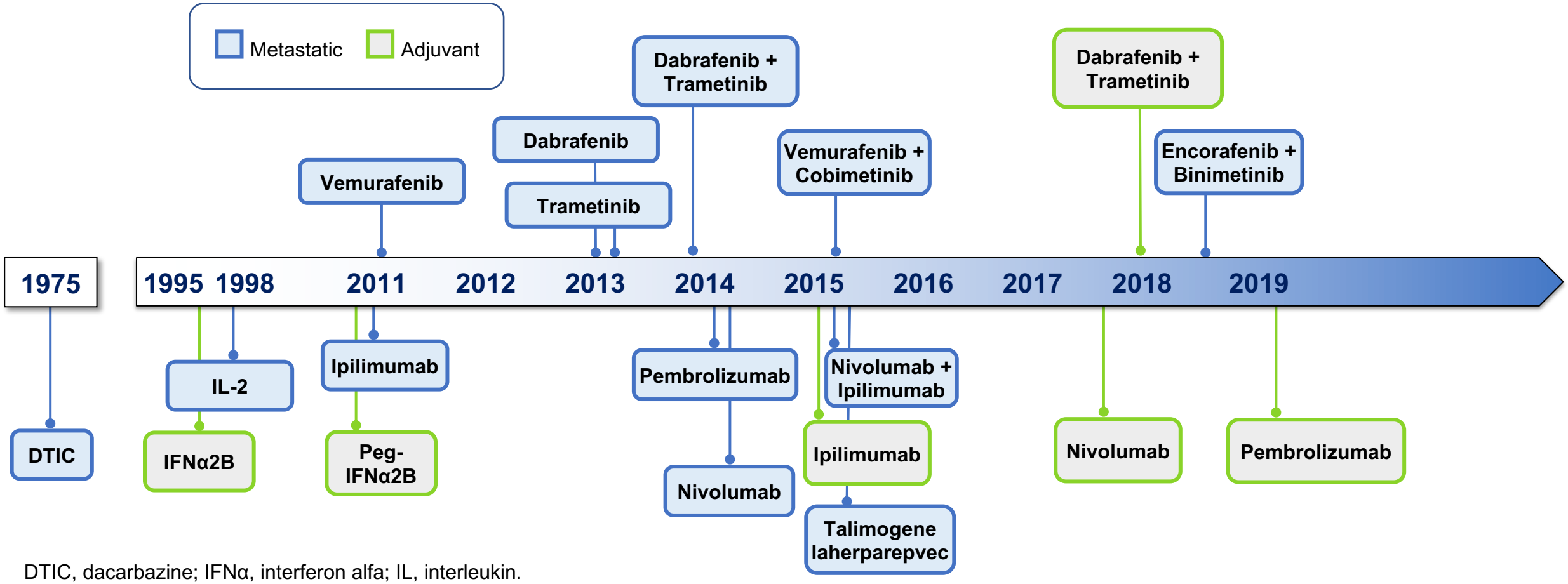
Learning Objectives

At the conclusion of this continuing education activity, advanced practitioners in oncology will be better able to:

1. Interpret the implications for treatment of the clinicopathologic features of metastatic melanoma.
2. Interpret clinical data regarding mechanistic activity, efficacy, and safety of approved and emerging therapeutic options for metastatic melanoma.
3. Devise strategies for integrating contemporary standard-of-care management practices for metastatic melanoma.
4. Formulate plans for enhancing collaboration and communication within a multidisciplinary, interprofessional team that fosters shared decision-making.

The Evolution of Melanoma Treatment

Current Melanoma Landscape

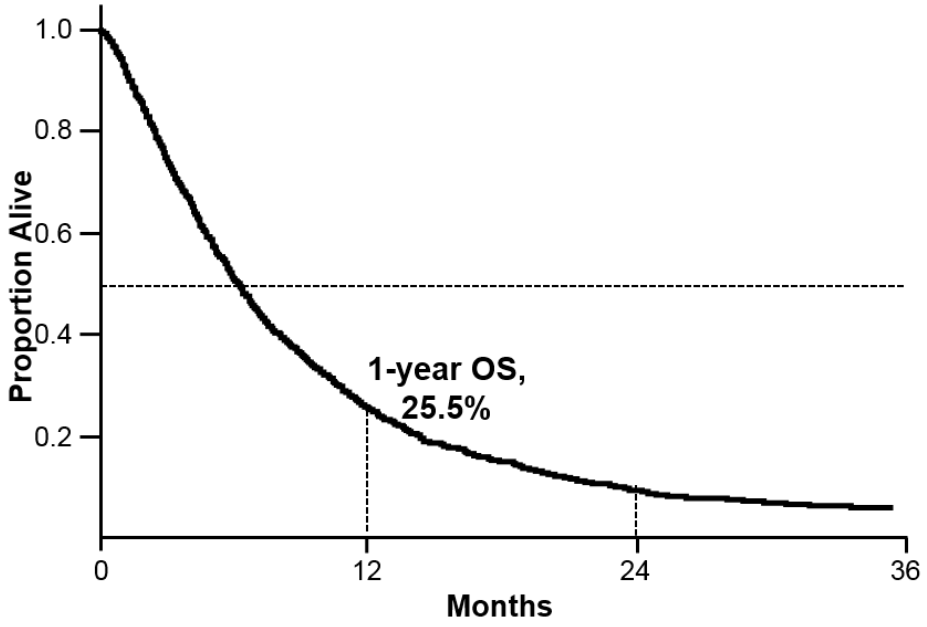


DTIC, dacarbazine; IFNα, interferon alfa; IL, interleukin.

Approved in the United States.

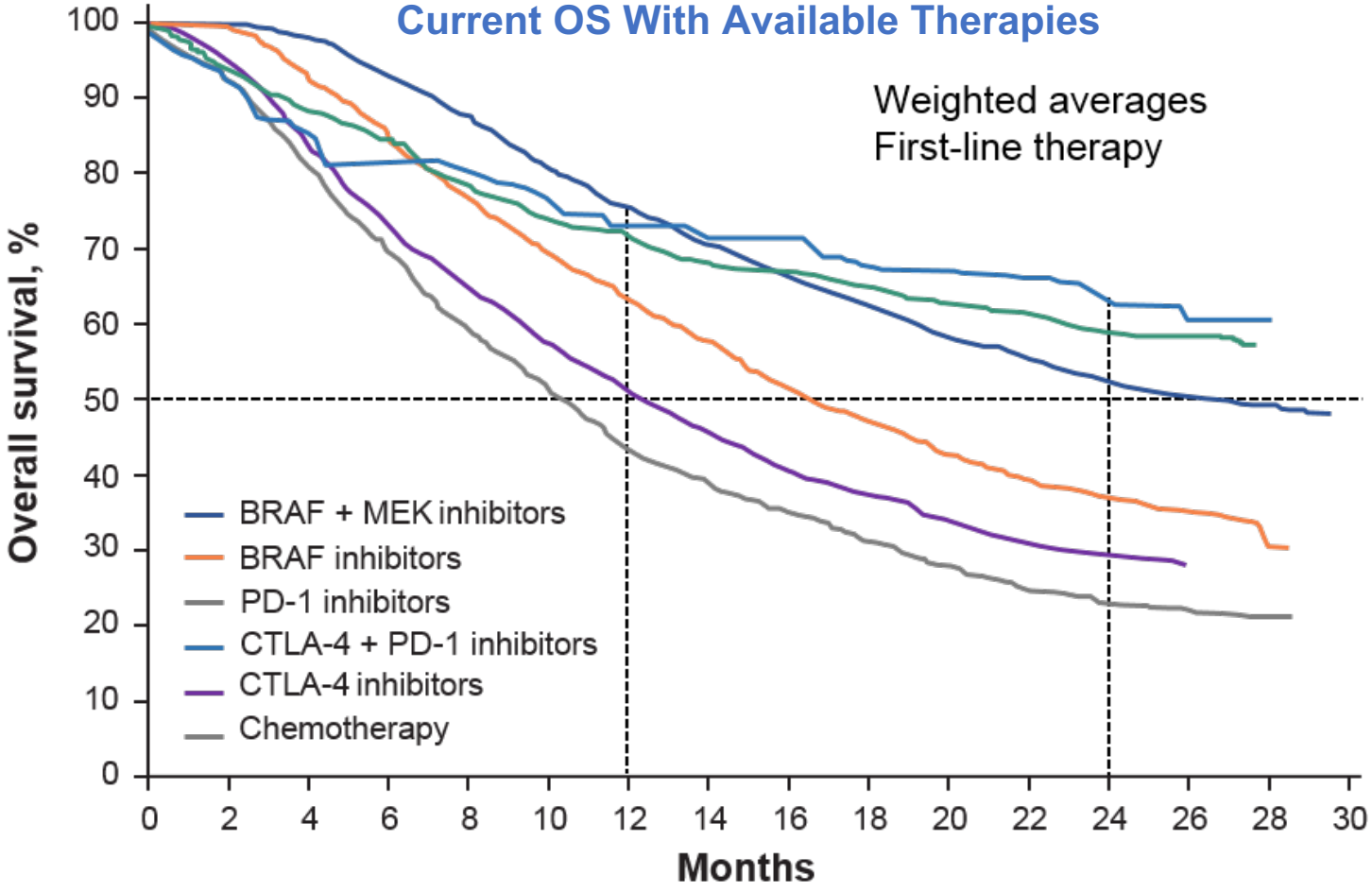
Impact of Current Therapies

Historical OS



Korn EL, et al. *J Clin Oncol*. 2008;26(4):527-534.

Current OS With Available Therapies



Ugurel S, et al. *Eur J Cancer*. 2017;83:247-257

Clinical Case #1

Pathologic features

Immunotherapy potential

CASE 1

50-year-old male, melanoma of right neck

- ≥ 6.5 mm, ulceration (T4b), mitoses ~ 12/mm^2, no LVI.
- MRI brain: No evidence of metastatic disease
- PET/CT: Right neck lymph node and right axillary tail node/mass FDG avid, cN2b disease (palpable)
- Final workup stage: IIIC (pT4b, cN2b, cM0)

Pathology Synoptic Report: The Good and the Bad

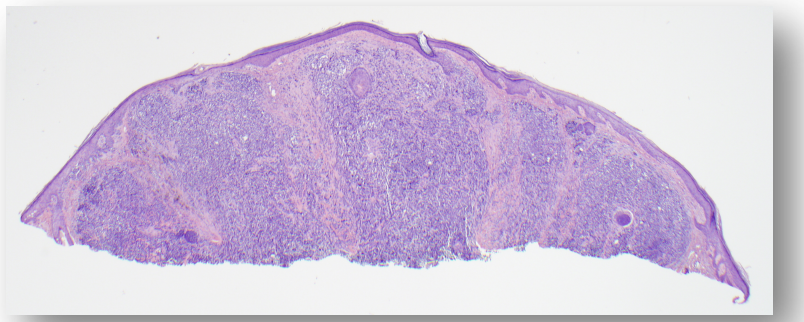
Higher Risk

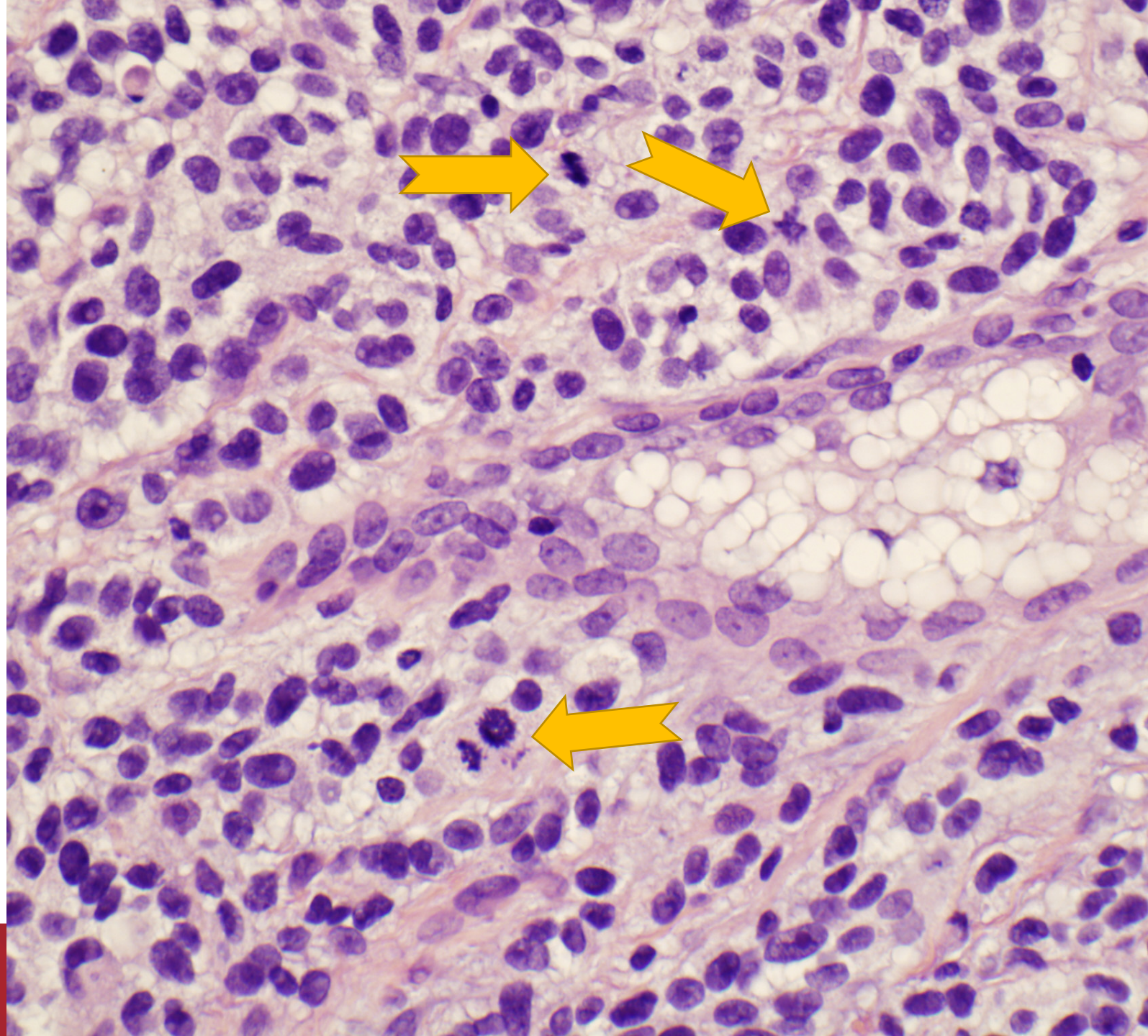
- Positive nodes
  - Most important finding
- Ulceration
- Depth
- Mitotic figures
- Lymphovascular invasion

Better Risk

- Regression
- Tumor infiltrating lymphocytes

Mitotic Figures





Question

50-year-old male with newly diagnosed stage III melanoma, BRAF unknown.

What is the next best plan of treatment?

1. Complete lymphadenectomy
2. BRAF targeted therapy
3. Observation
4. Immunotherapy
5. Talimogene laherparepvec

Answer

4. Immunotherapy

(today!)

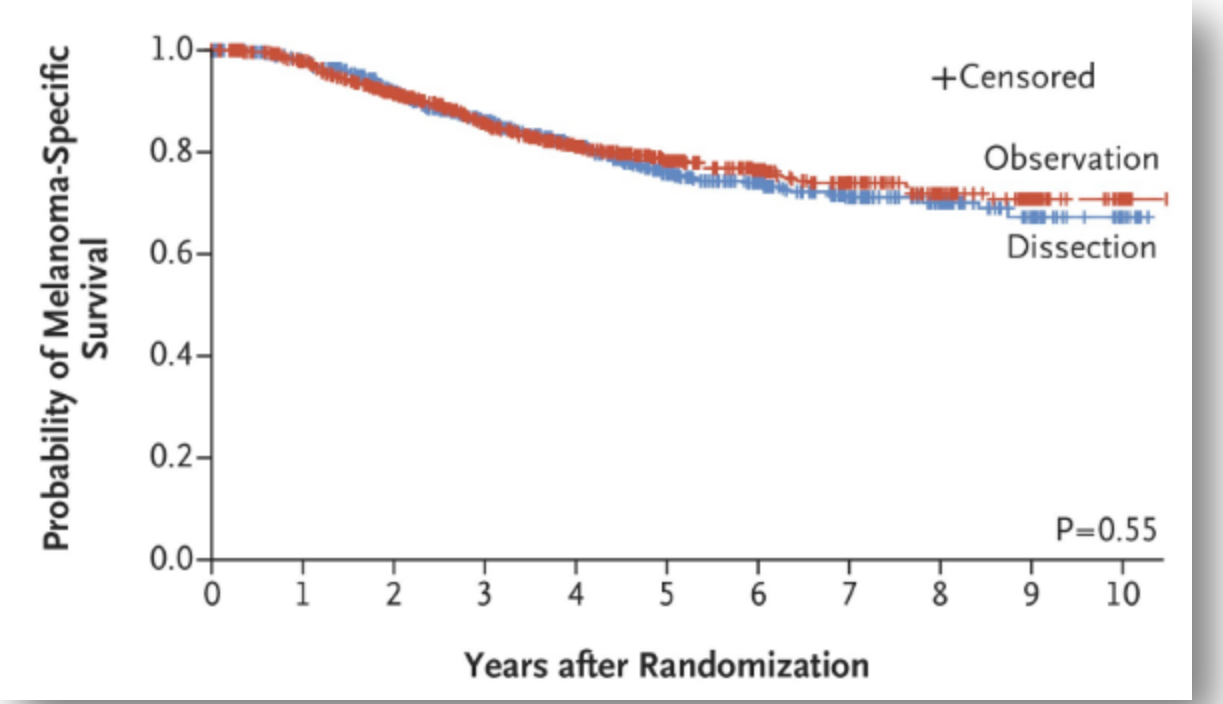
Patient course

- 10/8/14: s/p CLND
- RT to right neck
- 12/30/2014: pegylated-interferon initiated
  - Discontinued s/p 3 doses secondary to severe toxicities

Role of Complete Lymph Node Dissection in SLN+

MSLT2 trial: CLND vs observation (with ultrasound)

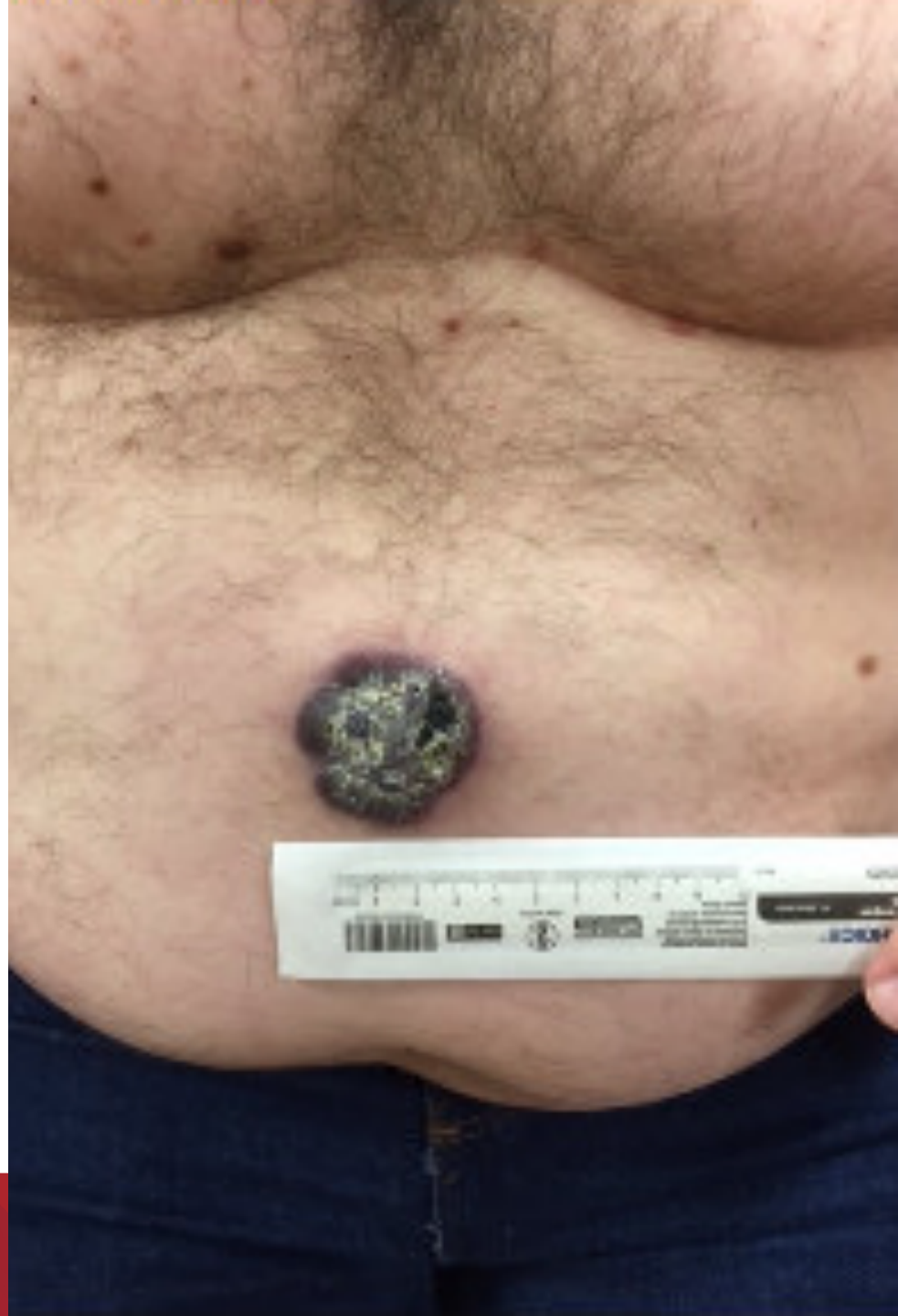
- ~70% of patients had 1 positive node
  - Node metastasis
    - 0.1-1 mm ~ 55%
    - > 1 mm ~33%
- Lymphedema
  - Surgical arm: 24.1%
  - Observation: 6.3%



Faries MB, et al. *New Engl J Med*. 2017;376:2211-22.

Recurrence in 2016

- PET/CT: widespread metastatic disease
  - Neck
  - Chest
  - Abdomen
  - Pelvis
  - Upper and lower extremities



Question

What are the current best options for this patient?

50-year-old male with recurrent/metastatic melanoma:
BRAF V600E+

1. High-dose IL-2
2. Darcarbazine
3. PD-1 and CTLA4 combination
4. Ipilimumab
5. BRAF/MEK – targeted therapy

Answer

3. Combination immunotherapy

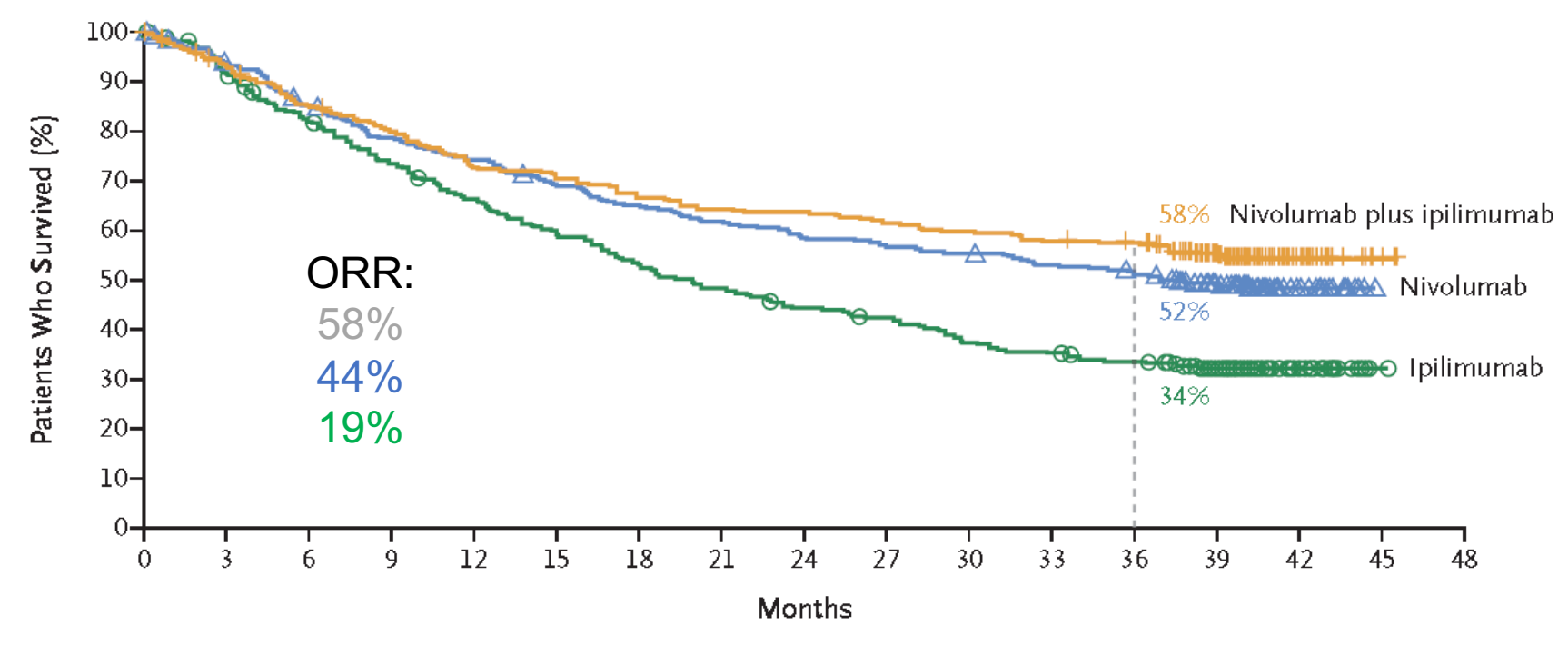
- Nivolumab and ipilimumab

OR

5. BRAF targeted therapy

- Dabrafenib and trametinib

CTLA4 + PD-1 vs Single Agent



- Combination is better than any single agent in unselected population
- PD-1 single agent may retain efficacy and decrease AEs in PD-L1 positive patients
- Nivolumab appears better than ipilimumab even in PD-L1 negative patients

Wolchok J, et al. *New Engl J Med*. 377:1345-1356; 2017

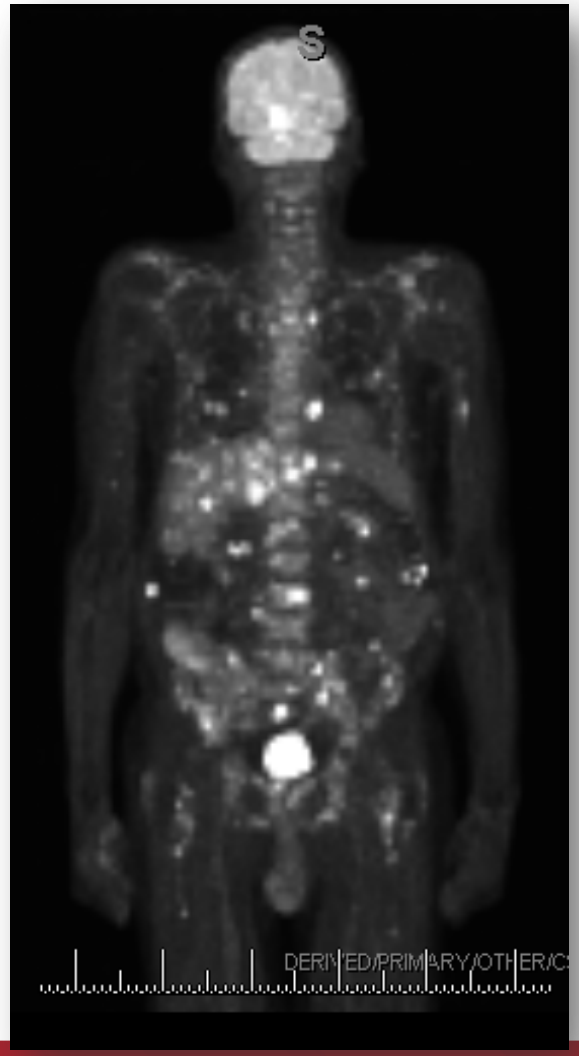
Efficacy: PD-1 + CTLA4

	Nivolumab (n=316)	Nivo + IPI (n=314)	Ipilimumab (n=315)
mOS, months	NR	NR	20
18m OS, %	59	64	45
mPFS, months	6.9	11.5	2.9
18m PFS, %	39	46	14
ORR, %	43.7	57.6	19
DoR, months	22.3	NR	14.4
Ongoing response, %	72.4	72.5	51.7

Wolchok JD, et al. *J Clin Oncol*. 2016;34 (suppl); Abstract 9505.

Checkpoint Efficacy

Before treatment



After treatment

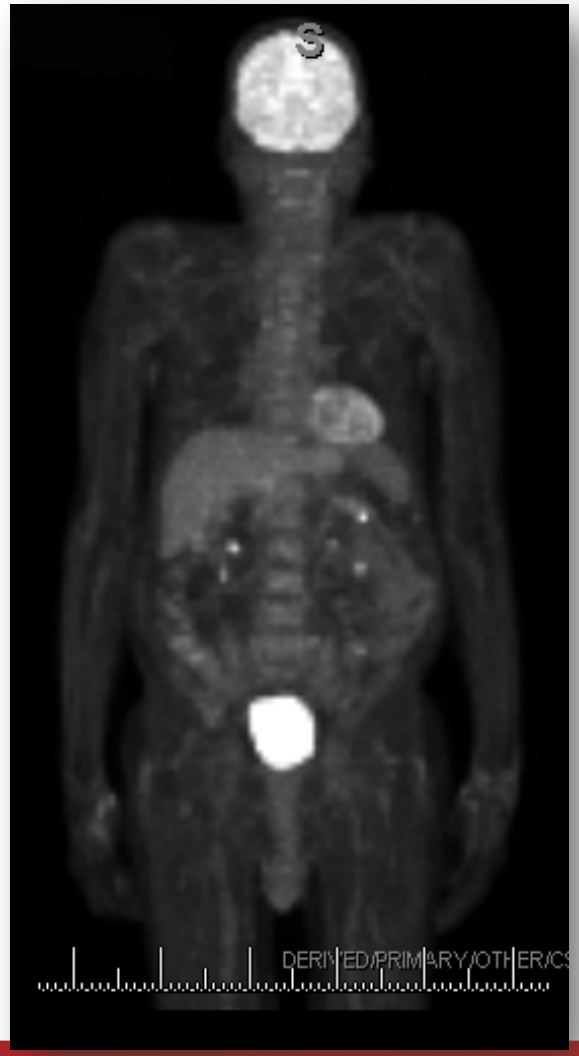


Image © AJ Olszanski

Is cure possible in this case?

Received ~ 3 years of therapy

- Typical duration 2 full years
- Extended course due to continued radiographic response

Four subcutaneous nodules remained

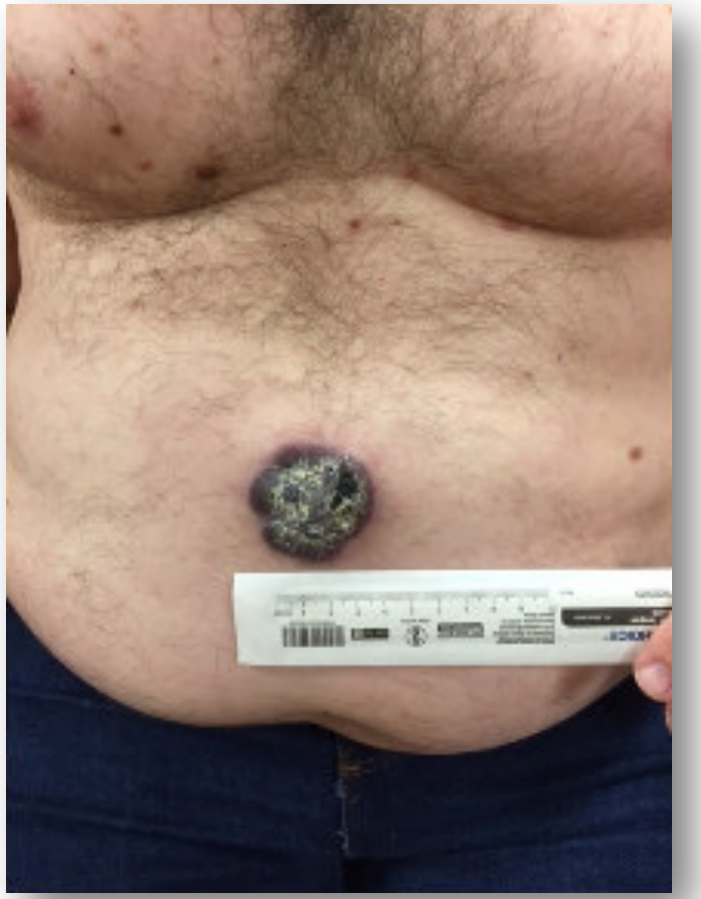
- Stable, on therapy, 1 year
- Sites of active disease?
- Remaining tumor tissue?

Is cure possible in this case?

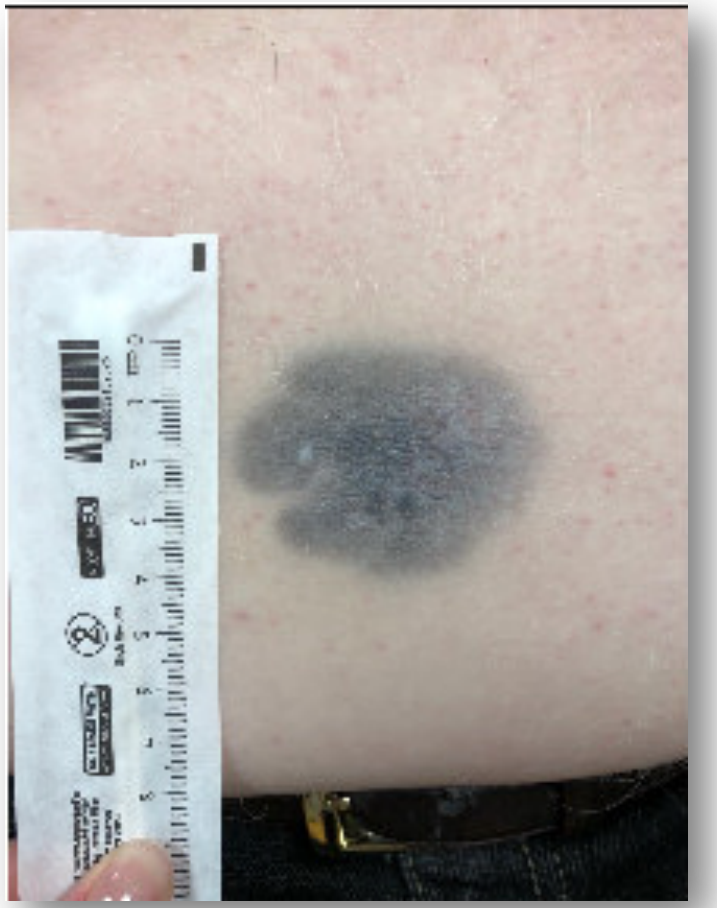
- Underwent surgical resection of subcutaneous nodules
- Wide local excision of the abdominal lesion failed to show any viable tumor
  - (+) heavily pigmented cells
- Apparent complete pathologic response to therapy

PICTURES (are worth a thousand words…)

Before



After



Is cure possible in this case?

- Continues on observation
- July 2019 scan: no apparent disease
- Continue to scan every 3 to 4 months

Clinical Case #2

Real-world challenges

Work-up

Vigilance

CASE 2

30-year-old female, initially stage IIIC melanoma RUE

- WLE and SLNB: 2.5 mm nodular melanoma with 15 mitoses/mm^2
- Ulcerated
- No LVI
- 2 of 6 sentinel nodes positive
- pT3b, pN2a

Work-up

- MRI brain: normal
- PET/CT: worrisome lesion in right iliac bone
- Biopsy
- NGS sent

→ metastatic melanoma

Pathologic stage IV disease

- Final TNM stage pT3b, pN2a, pM1c

Question

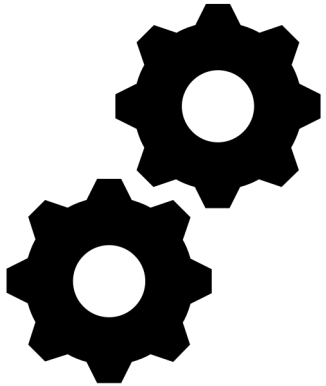
30-year-old female, stage IV melanoma, BRAF WT

What is the best first-line treatment?

1. BRAF/MEK therapy
2. Chemotherapy
3. IL-2 with XRT
4. PD-1 + CTLA-4 combination
5. Resection of metastatic site

Answer

4: Nivolumab and ipilimumab combination immunotherapy

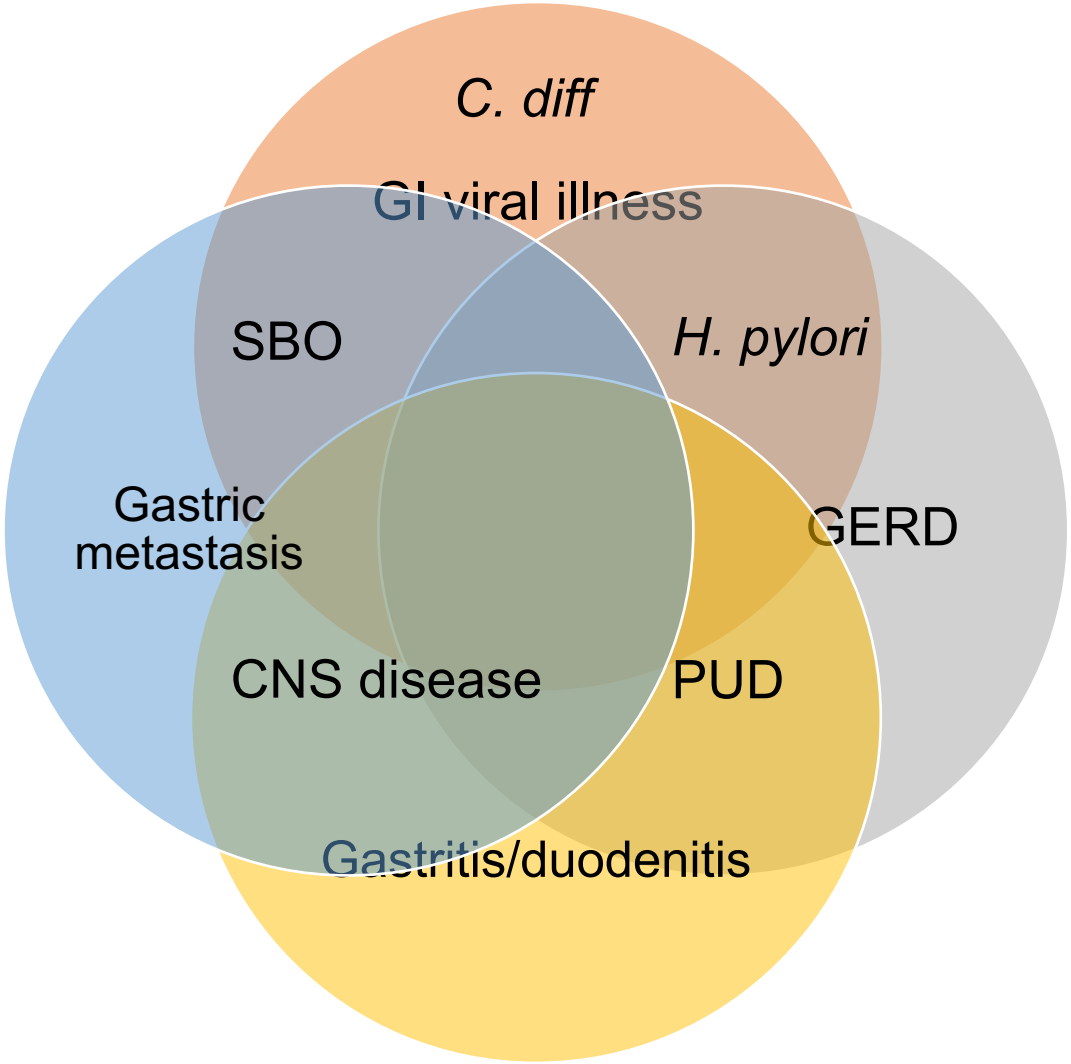


Toxicity Management

After receiving 3 doses of dual agent immunotherapy, she started to develop side effects:

- Nausea, vomiting
- GERD symptoms
- Weight loss
- Early satiety
- Anorexia

Differential Diagnosis? Treatment and Work-up?



Ondasetron, prochlorpherazine, omeprazole:

No improvement

Consult with GI team:

- Recommend EGD

Results of EGD

Stomach	• Severe active gastritis • consistent with immune checkpoint inhibitor therapy effect
Duodenum	• Erosive duodenitis • consistent with immune checkpoint inhibitor therapy effect

Question

What treatment(s) for immune-mediated gastritis would be appropriate?

1. Proton pump inhibitor
2. *H. pylori* prophylaxis
3. Oral steroids 0.5 mg/kg
4. High-dose IV steroids 1-2 mg/kg
5. Dose reduction of immunotherapy

Answer

4: Hospital admission and IV steroids 1-2 mg/kg

Symptoms resolved completely

Resumed treatment after 1 month taper

Treatment Course

Completed 4 doses of ipi/nivo combo, initiated single-agent nivolumab

Developed severe arthralgias and myalgias after 1 dose

Second hospital admission for IV steroids

- Symptoms again resolved with a 1-month taper of steroids

Treatment Course

Reinitiated single-agent nivolumab

- Received 2 additional doses

New Symptoms

- significant fatigue
- new headaches
- mild nausea
- general malaise

Question

What is the most likely diagnosis?

1. Recurrent gastritis/duodenitis
2. Hypophysitis
3. CNS metastasis
4. Viral illness
5. Hyperthyroidism

Answer

2. Hypophysitis

- inflammation of the pituitary gland
- adrenal insufficiency

Question

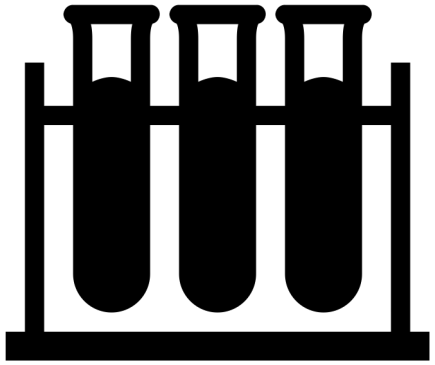
Which diagnostic test should be ordered?

1. Prolactin
2. Cortisol and ACTH
3. TSH
4. FSH/LH levels
5. Human gonadotropin

Answer

2. Cortisol and ACTH

- Random cortisol (12:10 PM) = 0.5 (3-16)
- 9 AM cortisol < 0.4 (5-23)
- ACTH < 5 (6-50)



Immune-Mediated Side Effects

Immune-related AEs	• Occurs across a wide range of organ systems • HCPs must remain vigilant and have heightened sensitivity
Hypophysitis	• Required 3rd hospital admission for IV steroids • Now requires lifelong steroid repletion for hypophysitis/adrenal insufficiency

The Art of Re-Challenge in the Setting of Immune-Related Adverse Events

- Permanent discontinuation of a given class of immunotherapy is typically warranted for severe irAEs induced by that class of agent.
- However, guideline recommendations for re-challenge allow for clinical judgment depending on toxicity grade level and type of immunotherapy.
  - For grade 3 GI toxicities, consider permanently discontinuing CTLA-4 agents.[1-2]
  - Consider restarting PD-1, PD-L1 agents if patient can recover to G1 or less.
  - A small proportion of patients with immune checkpoint inhibitor-related colitis are reported to experience recurrences after resuming treatment with anti-PD-1 monotherapy.[3-4]
- Caution, clinical judgment, and discussion of risks/benefits with the patient are key when considering re-challenge with immunotherapy following significant toxicity.

Re-challenge with anti-PD-1 monotherapy was an option for patient #2 because she was young, has children, had an otherwise good response to treatment, and had limited therapeutic options.

1. NCCN Guidelines V2.2091. Management of Immune Checkpoint Inhibitor-Related Toxicities; 2. Brahmer J, et al. *J Clin Oncol*. 2018;13(17):1714-68; 3. Pollack MH, et al. *Ann Oncol*. 2017;29:250-5; 4. Abu-Sbeih H, et al. *J Clin Oncol*. 2019;37(30):2738.

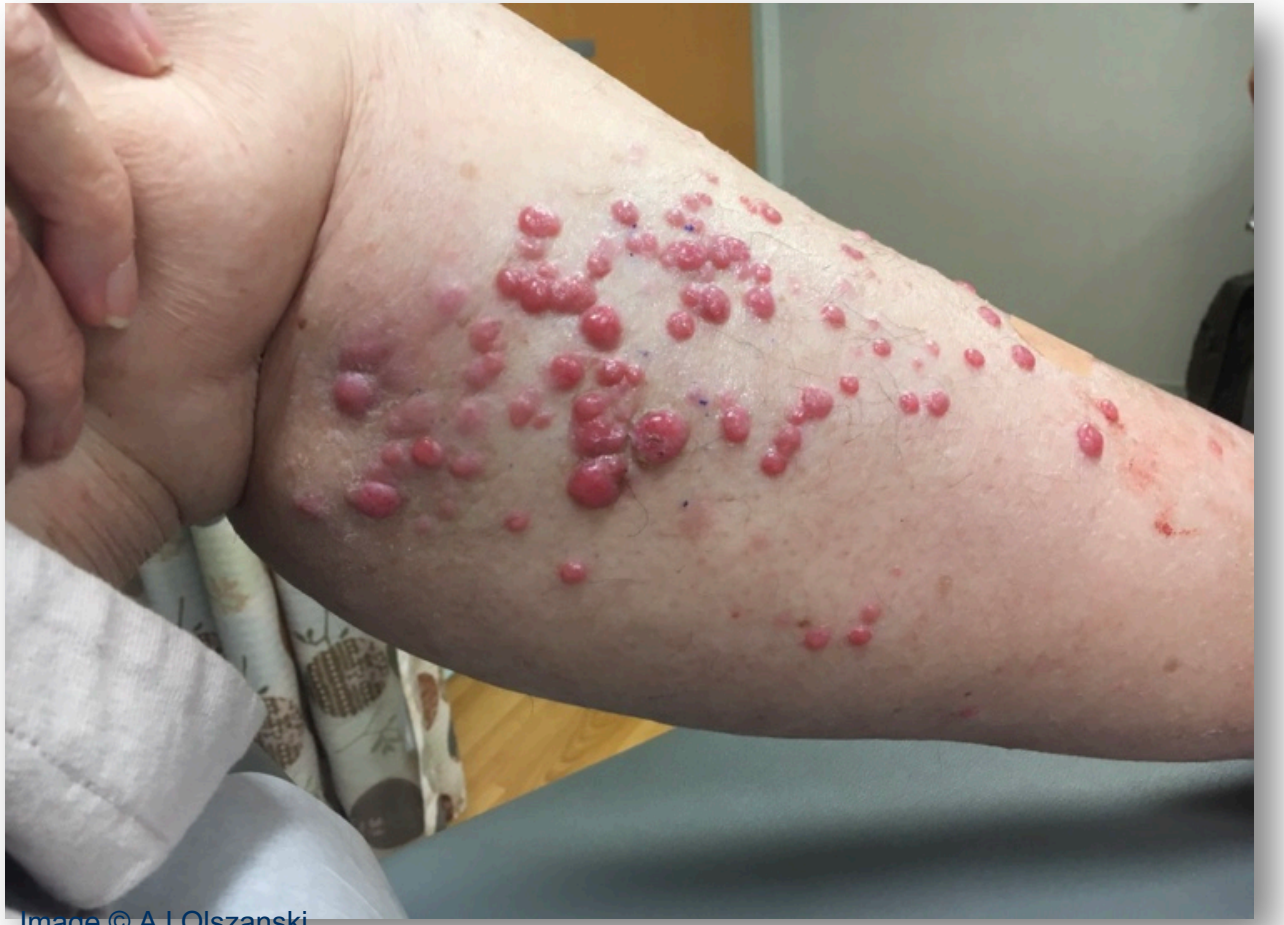
Clinical Case #3

Comorbidities

New skills

Case 3: In-transit Metastasis

- 76-year-old female
  - Develops “rash” fall 2016
  - Unresolved with antibiotics
  - Worsens
- 1/2018: biopsy → melanoma
- PET scan
  - No clear primary
    - Left inguinal adenopathy
- History of ulcerative colitis (active)
- BRAF negative



Question

Significant comorbidity of ulcerative colitis

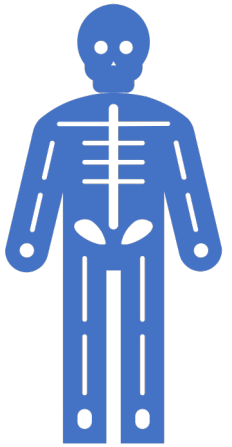
- required immunosuppression
- Intermittent diarrhea/abdominal pain

What is the most appropriate recommendation?

1. Topical imiquimod
2. PD-1 therapy
3. CTLA-4 therapy
4. Oncolytic vaccine
5. Palliative care

Answer

- 4. Oncolytic therapy
- No randomized studies suggesting benefit of imiquimod
- PD-1 and CTLA-4 may exacerbate autoimmune disease
  - Use of immunosuppressive therapy is a relative contraindication for immunotherapy use



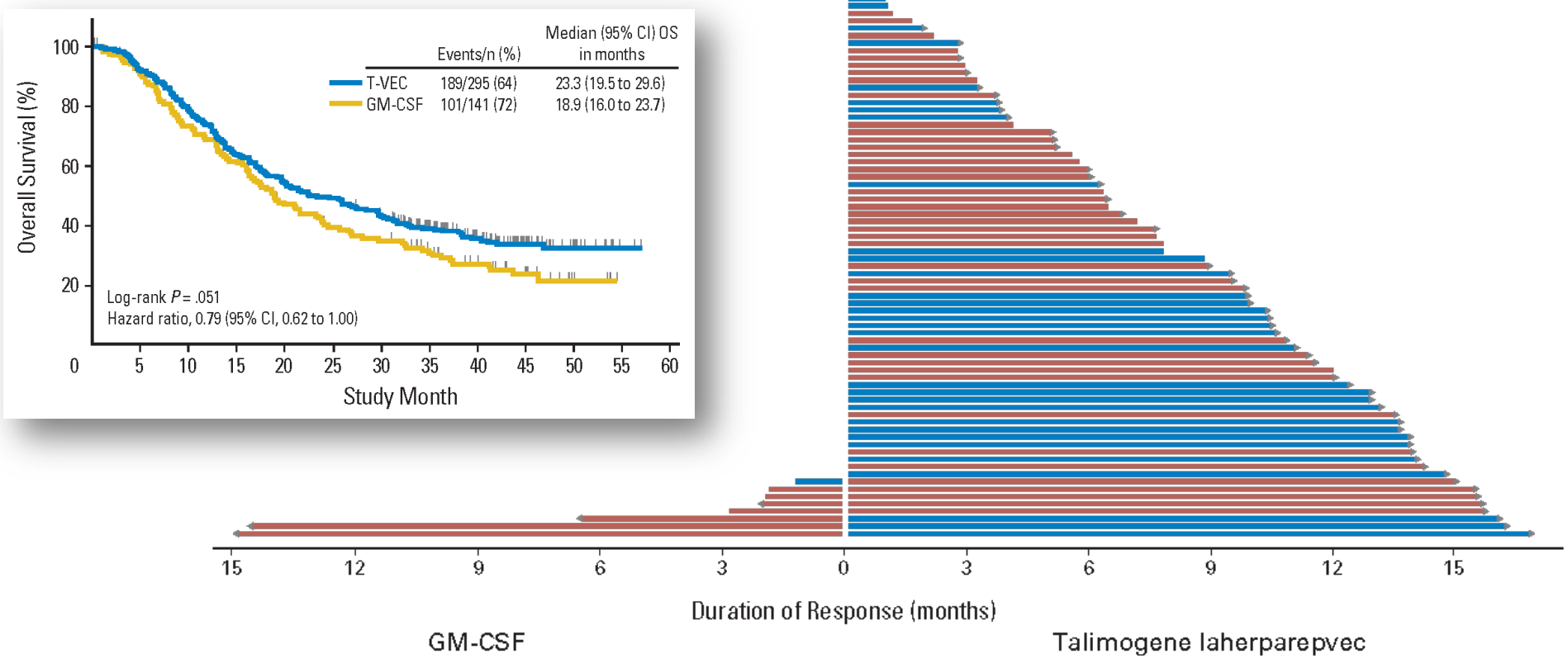
Oncolytic Therapy

- 419-patient phase III trial (2:1 randomization) of TVEC vs GM-CSF
  - Met primary endpoint of durable response rate (DRR)
    - DRR = % of patients with a response (>50% reduction in sum of the products of perpendicular diameters)
    - DRR 16.3% vs 2.1%
  - AE profile: Fatigue, chills, fever, flu-like symptoms, injection site pain

Andtbacka RHI, et al. *J Clin Oncol* 2015;33:2780-8

TVEC – talimogene laherparepvec

TVEC Response Duration/OS



Andtbacka RHI, et al. *J Clin Oncol* 2015;33:2780-8

TVEC (Talimogene Laherparepvec)

Attenuated herpes simplex virus (HSV) type 1

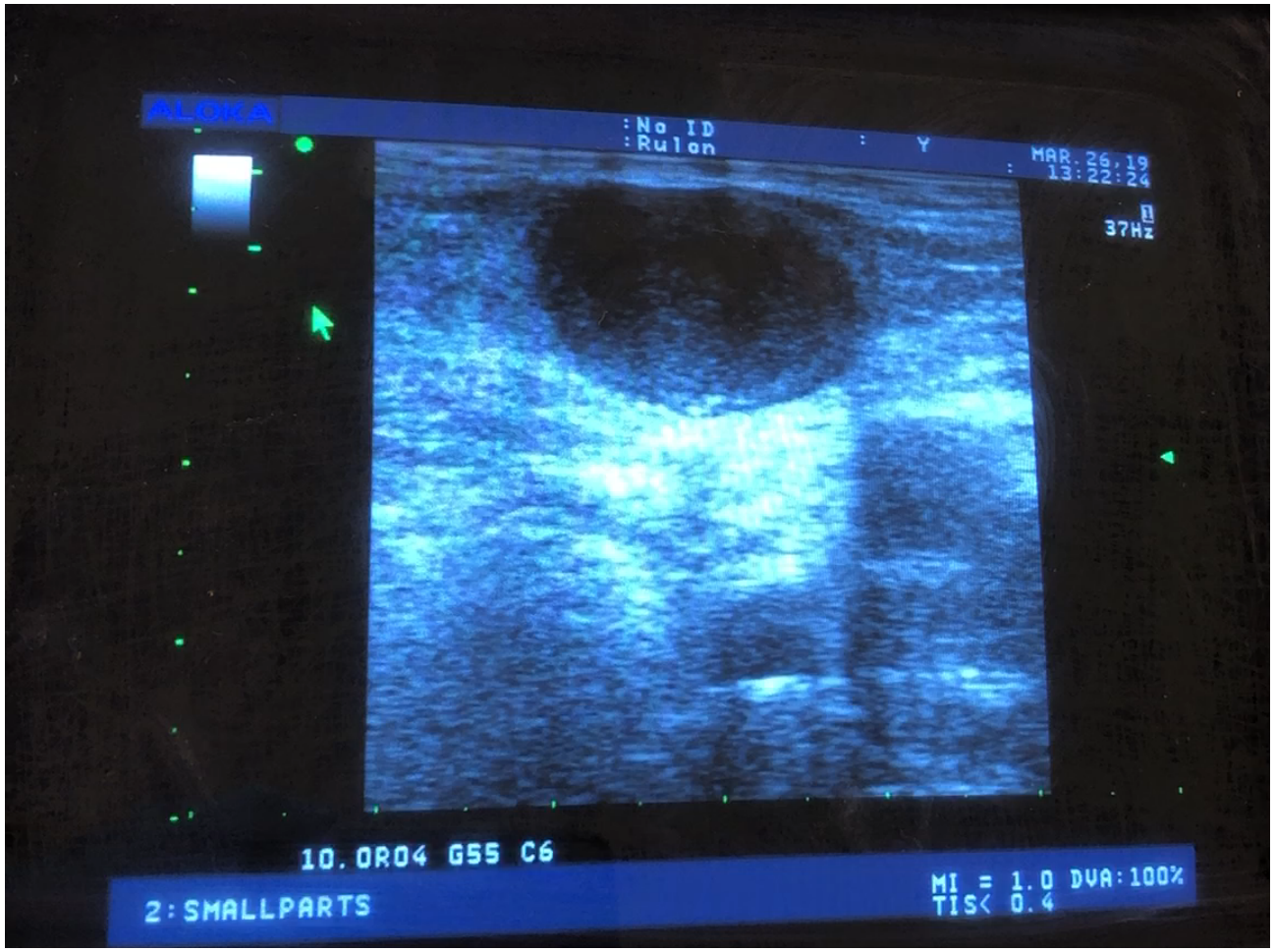
Intra-tumoral/nodal injections once every 3 weeks

Injections

AP performed:

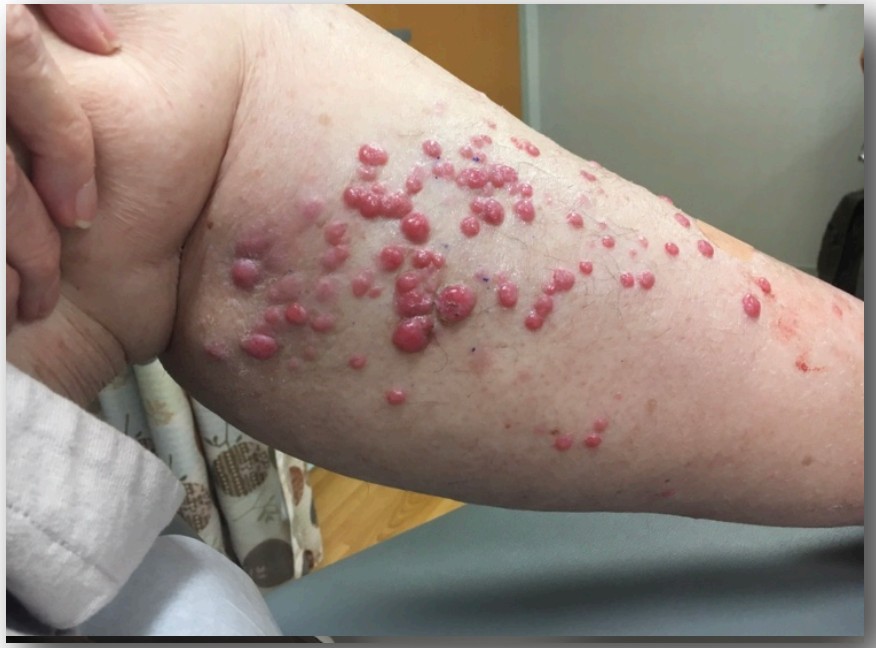
- In office
- Local anesthetic
- Minimally invasive
- US guidance with appropriate training
  - Intra-nodal injections

Video Demonstration



Post TVEC

- Initiated TVEC 3/8/2017
- Completed 1/2/2018 (no injectable disease)
- 15 injection sessions
- Groin node (not injected) smaller
- Now 78 years old and ambulating again



Clinical Case #4

Multidisciplinary review

Critical deliberation

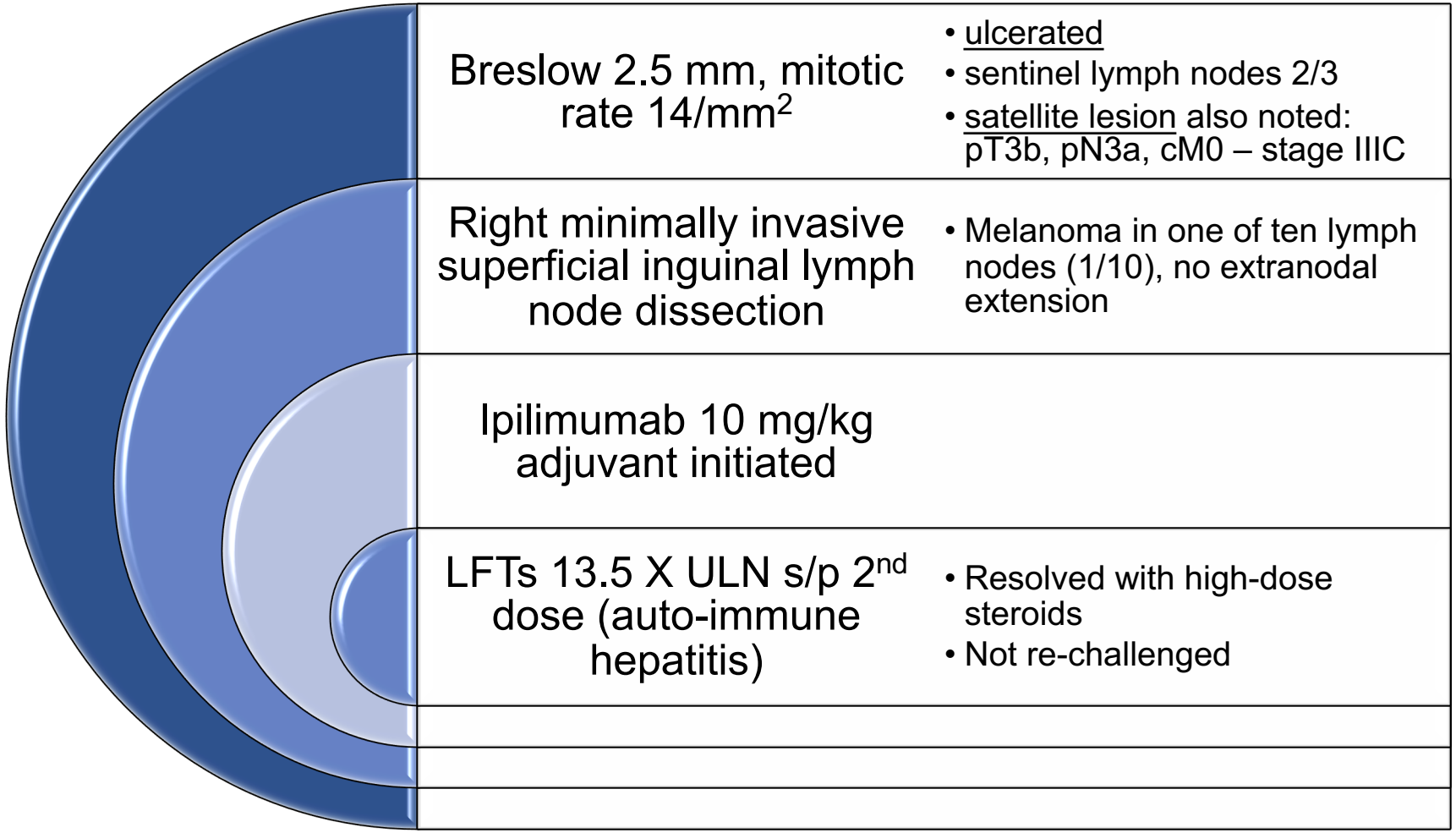
Treatment evolution

CASE 4

47-year-old female

Stage IIIC melanoma of right heel

BRAF unknown



Breslow 2.5 mm, mitotic rate 14/mm^2	• ulcerated • sentinel lymph nodes 2/3 • satellite lesion also noted: pT3b, pN3a, cM0 – stage IIIC
Right minimally invasive superficial inguinal lymph node dissection	• Melanoma in one of ten lymph nodes (1/10), no extranodal extension
Ipilimumab 10 mg/kg adjuvant initiated	
LFTs 13.5 X ULN s/p 2nd dose (auto-immune hepatitis)	• Resolved with high-dose steroids • Not re-challenged

Work-up

Presents ~1.5 years later

- Multiple new nodules of right leg
- Biopsy (+) in-transit melanoma

PET/CT – right leg lesions only

Brain MRI negative for disease

Discussion at tumor board

- Limb perfusion/infusion procedure
- PD-1 inhibitor +/- investigational drugs
- TVEC

Clinical Course

- Patient undergoes isolated limb infusion with dramatic response
- 8 months later, new cutaneous lesions of right leg
  - 3 very small erythematous nodules of the right thigh, all positive for melanoma
- Tissue sent for genomic testing

Question

What treatment option(s) is next?

1. Repeat limb infusion
2. CTLA-4 therapy
3. Injection clinical trial
4. PD-1 therapy
5. BRAF/MEK

ANSWER

Possible answers: 1 and 4

1. Repeat limb infusion but patient has poor healing heel wound and pain
2. CTLA-4 is contraindicated due to prior irAE
3. No measurable disease for clinical trials
   - TVEC considered, but better option exists
4. PD-1 therapy is rational, despite prior hepatitis on CTLA-4
5. Genomic results not available

Patient Course

- Nivolumab 480 mg single agent, IV once every 4 weeks
- Pathology: BRAF V600E positive
- 5 courses of nivolumab
  - Stable disease as best response per RECIST
  - Increased pigmentation and slightly more prominent lesions noted
    - Considered clinical progression

Question

What is the next treatment option(s)?

1. Continue with nivolumab
2. Pursue clinical trial using PD-1 plus an investigational agent
3. Switch to BRAF + MEK inhibitors
4. Begin TVEC injections
5. Amputate

ANSWER

- 2: Pursued clinical trial using PD-1 plus an investigational agent
  - Stable disease with PD-1 noted. Felt there may be some benefit in continuing.
  - Pursed trial of PD-1 + ONCOS-102 (oncolytic adenovirus)

- 3 (BRAF + MEK) or D (TVEC) is also rational

Clinical Progression

6 injections over 2 months on trial

no new lesions

no significant response

Clinical progression without radiographic progression

Decision made to pursue other treatment option

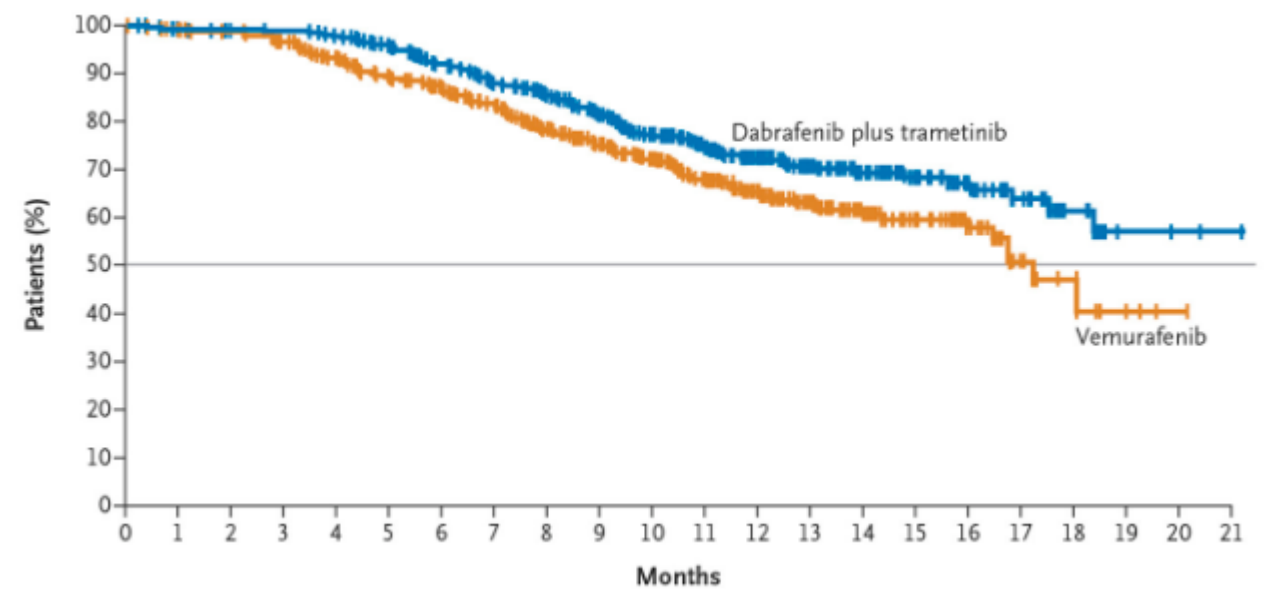
Targeted Therapy

Initiated targeted therapy with BRAF/MEK inhibitors

Dabrafenib 150 mg twice daily and trametinib 2 mg a day

Total daily pill load is 5 tablets, compared to 11 tablets for the other regimens

BRAF/MEK Inhibitors: Targeted Therapy



- ORR 64 vs 51%
- DOR 13.8 vs 7.5 m
- Grade 3 AE 48 vs 57%

Updated survival (ASCO 2019)

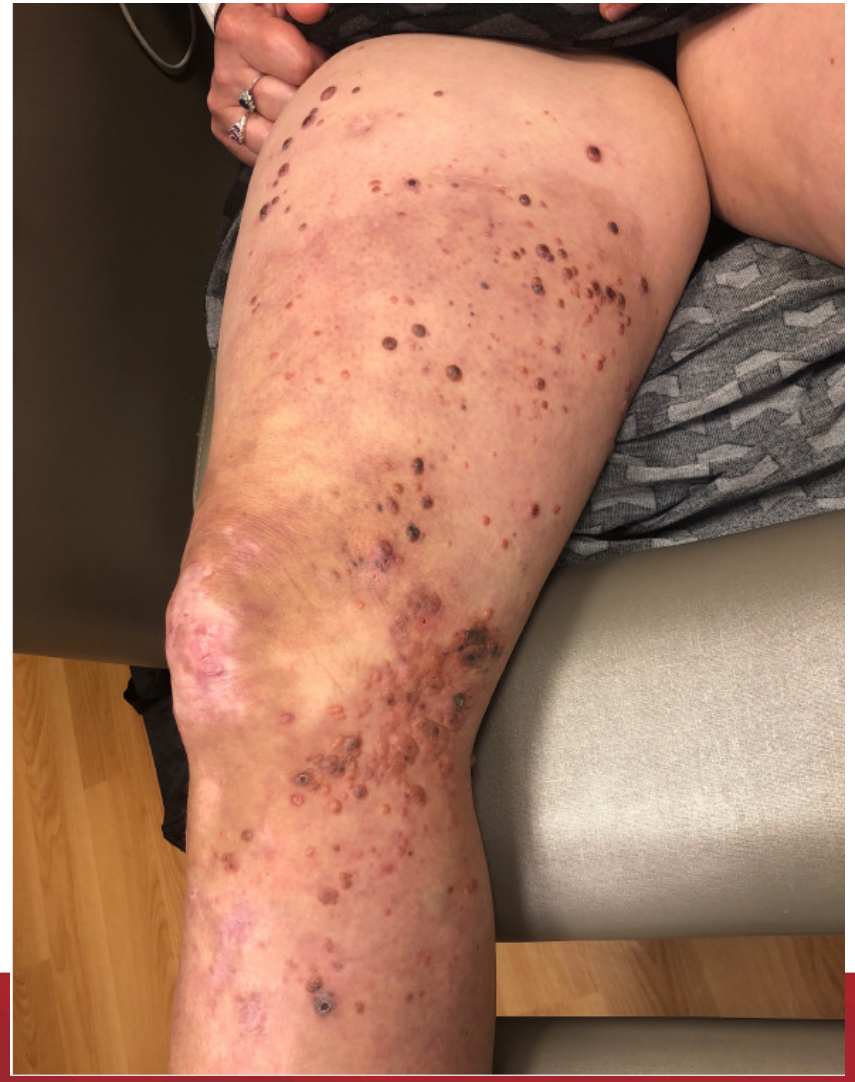
- OS at 5 years was 34%
  - First-line setting

Robert C, et al. *New Engl J Med*. 372:30-39 2015

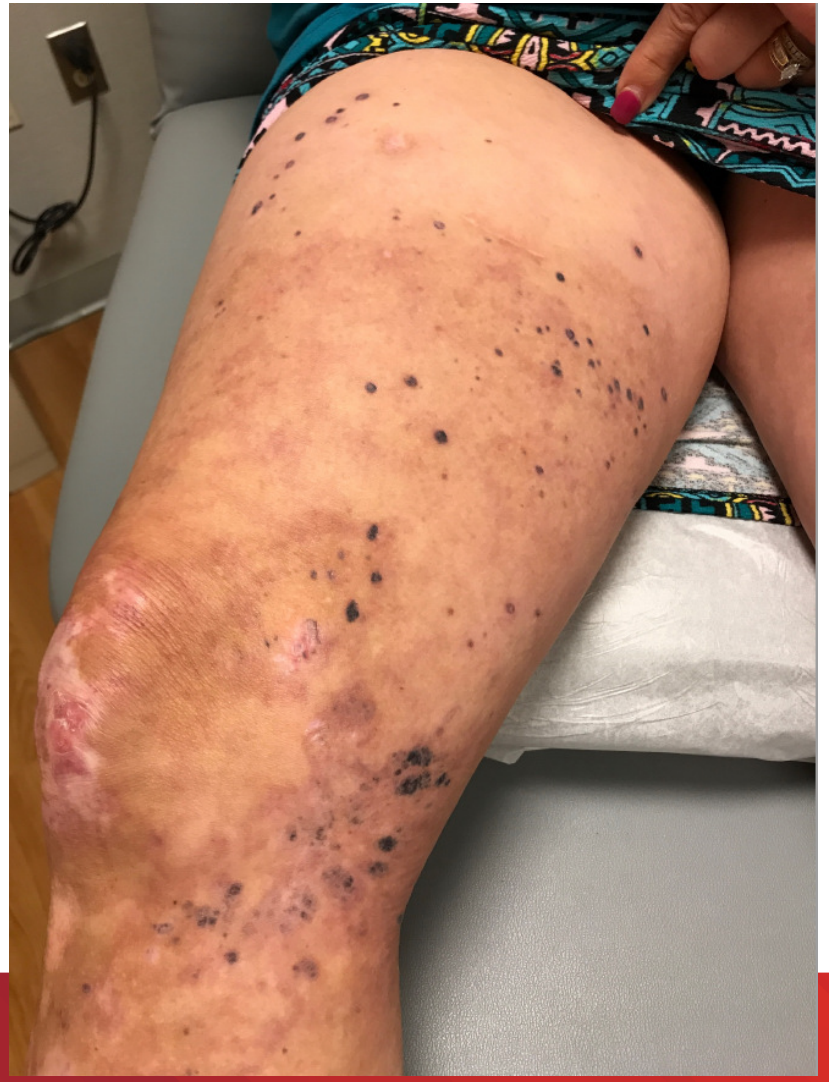
Nathan PD, et al. *J Clin Oncol* 37, 2019 (suppl; abstr 9507)

Response

s/p immunotherapy



On BRAF/MEK



Clinical Pearls

- Significant advances in melanoma over last 5 years
- Multidisciplinary review is imperative
- Long-term survival (? cure) is possible
- Adverse event recognition, diagnosis, and management is critical
- Immune management expertise often called on by peers
- Multiple treatment options provide ongoing hope
- New invasive skills are growth opportunities for the HCP
  - ultrasound guided injections, punch biopsies, FNA, core biopsies, viral vector safety
- New management skills are growth opportunities for the HCP
  - e.g., thyroid replacement initiation, etc.
  - robust patient education
  - consultant collaboration

Our Purpose

Love

Q&A

Creating Clarity in Metastatic Melanoma

Optimizing Treatment and Improving Outcomes

Thank you for joining us!
Please complete your evaluation.