Case Studies in Immunotherapy for the Treatment of Melanoma SITC CPG Webinar

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Disclosures

- Consulting as an advisory board member for Merck, Iovance, Sanofi, Xilio, Novartis, Instilbio, and Werewolf.
- Clinical trial support from Lilly, Novartis, Partners therapeutics, Genentech and BVD.

Case #1: stage IV

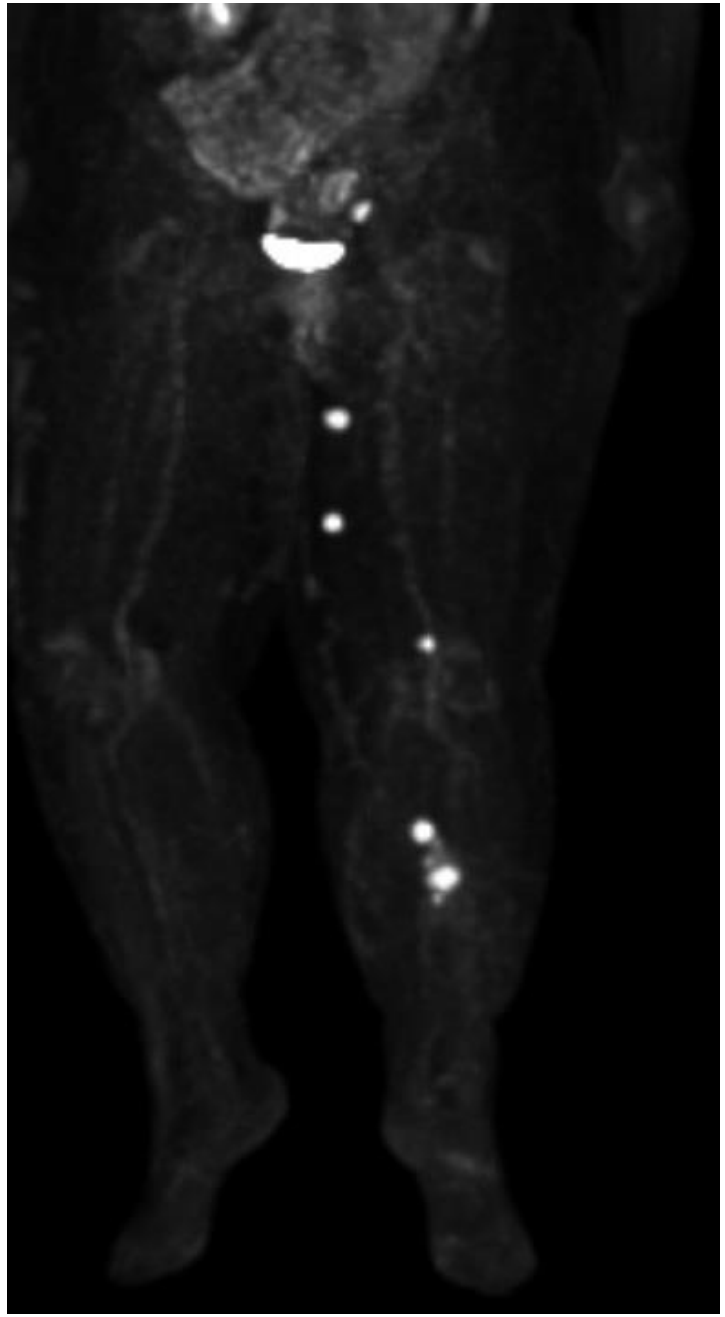
AS, female patient in 60s

- Patient with a history of melanoma 2 years prior, left leg lesion, 1.8mm, ulcerated
- Wide excision and sentinel lymph node performed, complicated by lymphedema
- Ultrasound to evaluate lymphedema noted new nodules and on biopsy found to be melanoma

Case #1 Stage IV

PET/CT with numerous subcutaneous nodules in her legs and pelvic lymph node uptake

No history of autoimmune disorders, generally in good health



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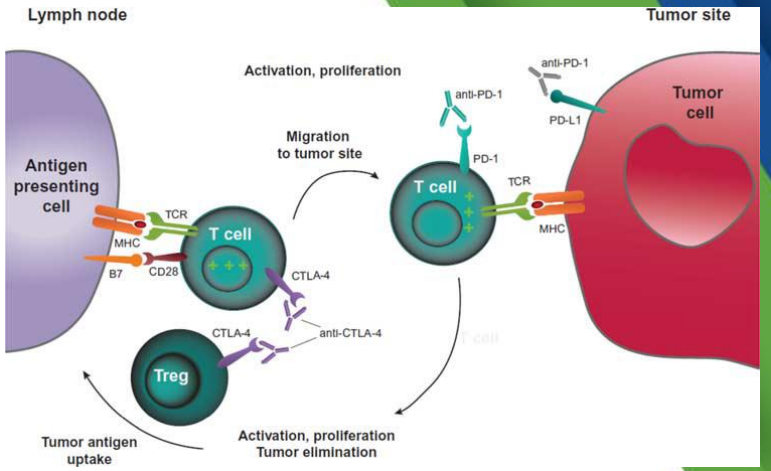
Case #1: stage IV BRAF wt

- Systemic therapy
  - Nivolumab/Pembrolizumab
  - Nivolumab 3mg/kg plus ipilimumab 1mg/kg
  - Nivolumab 1mg/kg plus Ipilimumab 3 mg/kg
  - Nivolumab with Relatlimab
  - Ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - Surgery/limb perfusion
  - Clinical trial

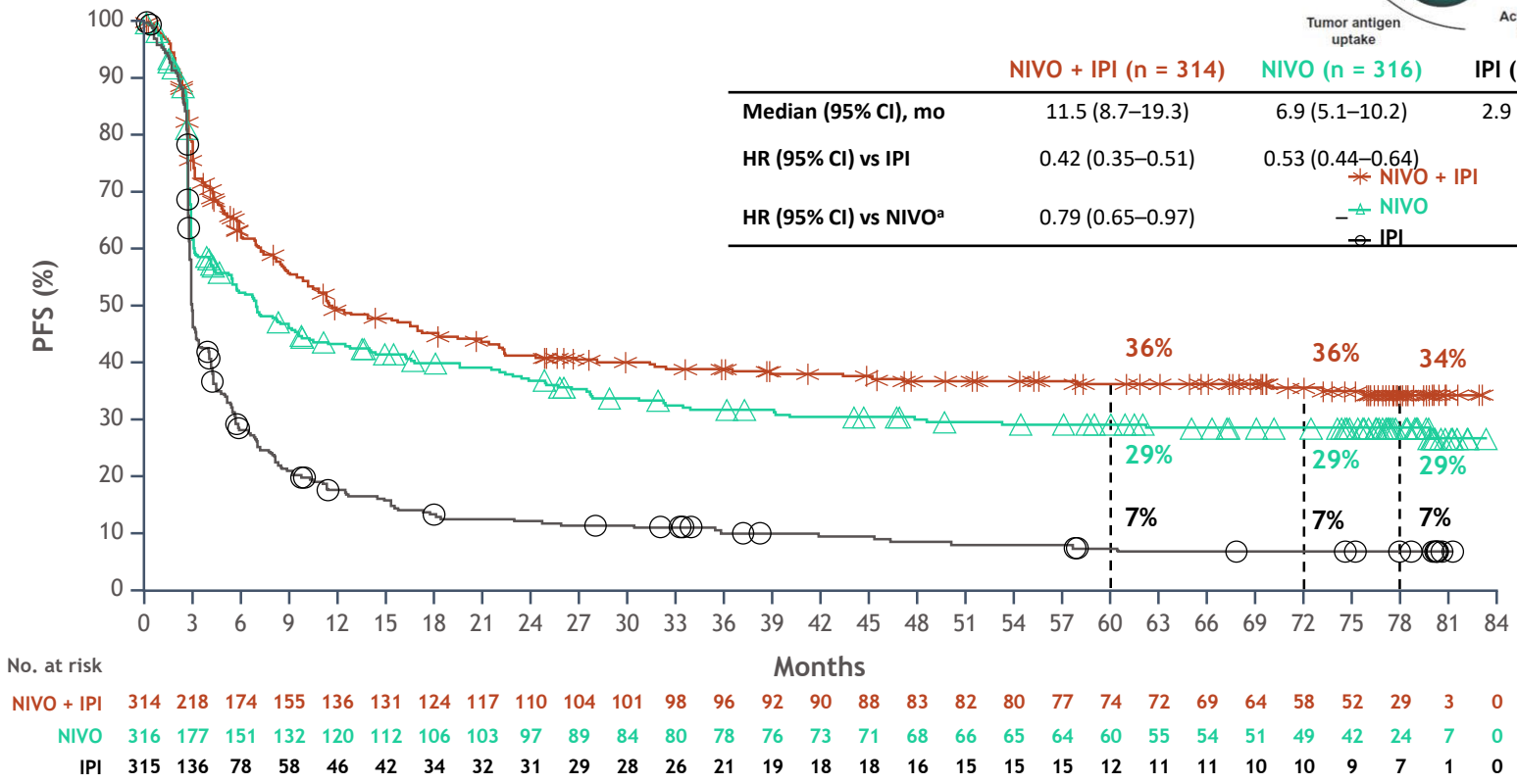
Panel recommendations

- Regardless of *BRAF*V600 mutation status, either single-agent anti-PD-1 therapy (LE:2) or front-line combination therapy with either ipilimumab plus nivolumab (LE:2) or nivolumab plus relatlimab (LE:2) is recommended, depending on the clinical scenario.

Checkmate 067: Ipilimumab and nivolumab in advanced melanoma - PFS



	NIVO + IPI (n = 314)	NIVO (n = 316)	IPI (n = 315)
Median (95% CI), mo	11.5 (8.7–19.3)	6.9 (5.1–10.2)	2.9 (2.8–3.2)
HR (95% CI) vs IPI	0.42 (0.35–0.51)	0.53 (0.44–0.64)	–
HR (95% CI) vs NIVO[a]	0.79 (0.65–0.97)	–	–



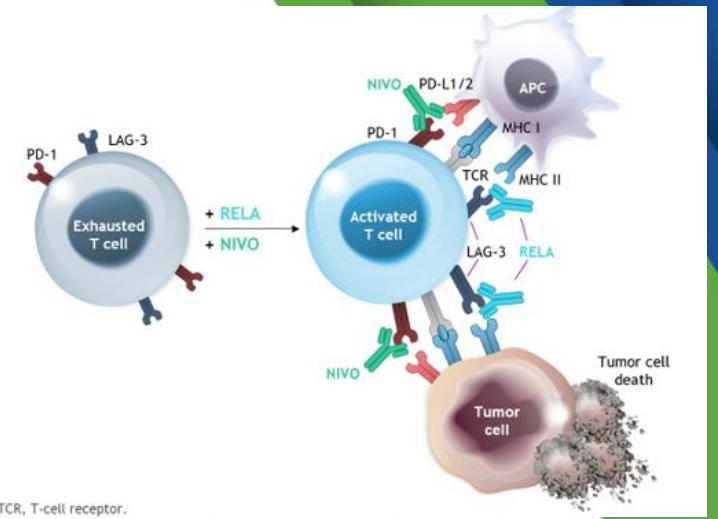
No. at risk

NIVO + IPI	314	218	174	155	136	131	124	117	110	104	101	98	96	92	90	88	83	82	80	77	74	72	69	64	58	52	29	3	0
NIVO	316	177	151	132	120	112	106	103	97	89	84	80	78	76	73	71	68	66	65	64	60	55	54	51	49	42	24	7	0
IPI	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	16	15	15	15	12	11	11	10	10	9	7	1	0

[a]Descriptive analysis.

Wolchok et al.
ASCO 2023

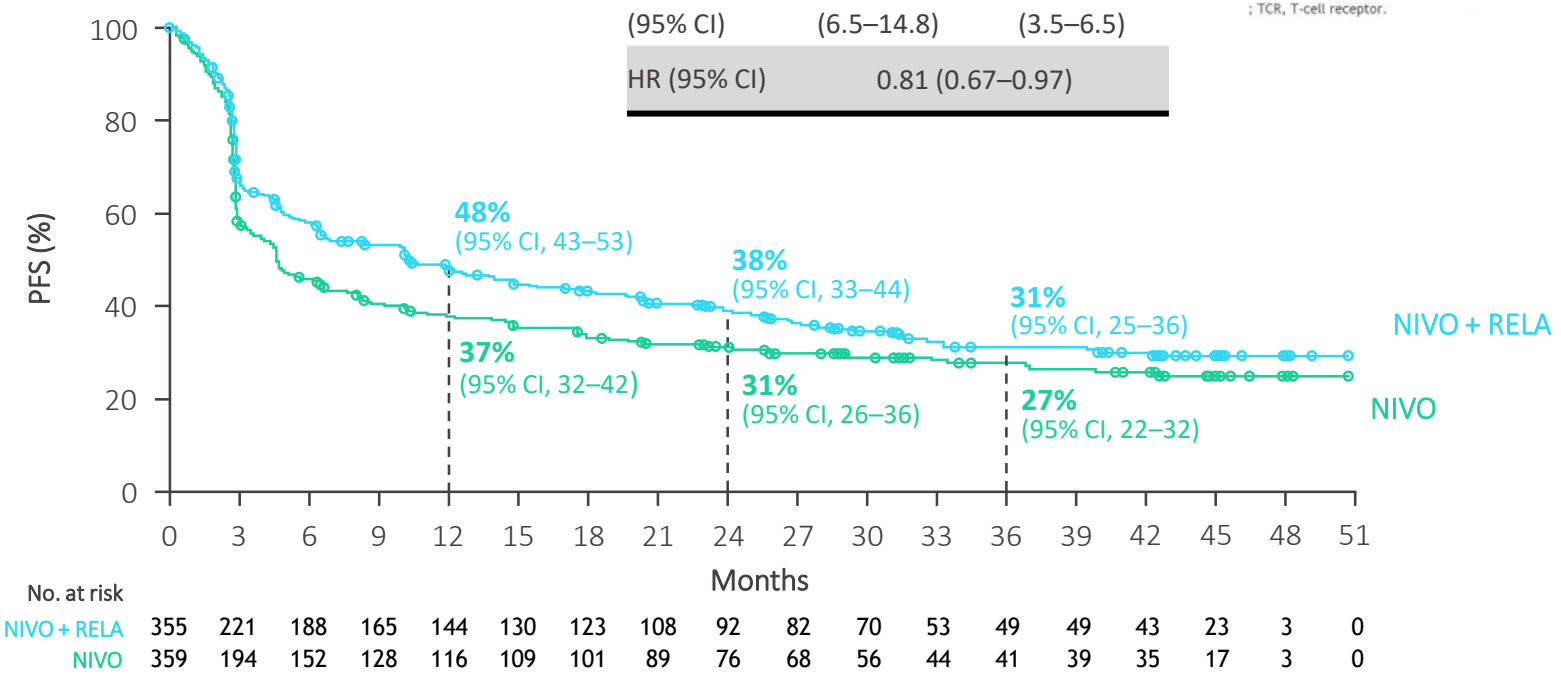
RELATIVITY-047: Relatlimab in combination with nivolumab in advanced melanoma



; TCR, T-cell receptor.

Updated primary endpoint

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo	10.2	4.6
(95% CI)	(6.5–14.8)	(3.5–6.5)
HR (95% CI)	0.81 (0.67–0.97)	



RELATIVITY-047 (NCT03470922). Median follow-up: 25.3 months.
Descriptive analysis. Statistical model for HR: stratified Cox proportional hazard model. Stratified by LAG-3, *BRAF* mutation status, and AJCC M stage. PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

Tawbi et al. ASCO 2023

Case #1: stage IV BRAF wt/unknown

- Systemic therapy
  - **Nivolumab/Pembrolizumab**
  - **Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg**
  - **Nivolumab and relatlimab**
  - **Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg ***
  - Ipilimumab
  - High-dose IL-2
  - Targeted Rx based on next-generation sequencing
  - **Surgery/Limb perfusion (center dependent)**
  - **Clinical trial**

***high toxicity**

Panel recommendations

- For patients with melanoma with poor prognostic features in whom combination therapy is desired but who may not tolerate TRAEs (ie, elderly patients or patients with poor Eastern Cooperative Oncology Group performance status [ECOG PS]), treatment with nivolumab plus relatlimab is a preferred combination regimen.
- For patients with low volume melanoma or histology that has demonstrated exceptional responses to anti-PD-1 monotherapy (desmoplastic melanoma), or for patients who are less likely to tolerate high-grade irAEs (eg, patients with a poor ECOG PS or concurrent autoimmune comorbidities), single agent anti-PD-1 therapy may be considered in the frontline.

Case #2: stage IV

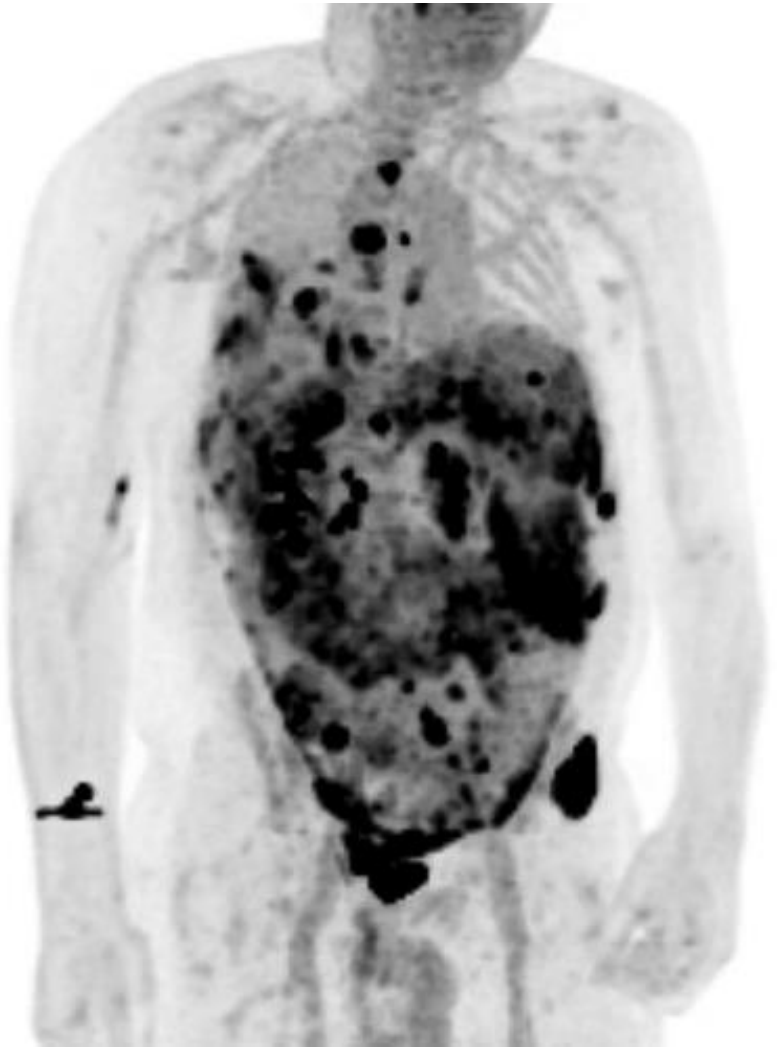
DL, male patient in 50s

- Patient with a history of melanoma 2 years prior, left thigh lesion, 2.4 mm, non-ulcerated
- Underwent wide excision and SLN
- Presented 2 years later for presumed diverticulitis and found to have extensive metastatic disease
- Biopsy performed and reveals malignant melanoma, **BRAF MUTATED**

Case #2 Stage IV

PET/CT with extensive metastatic disease including peritoneum, lung and liver

Symptomatic with abdominal distention/pain, fatigue and inability to eat well



Case #2: stage IV BRAF mutant symptomatic disease

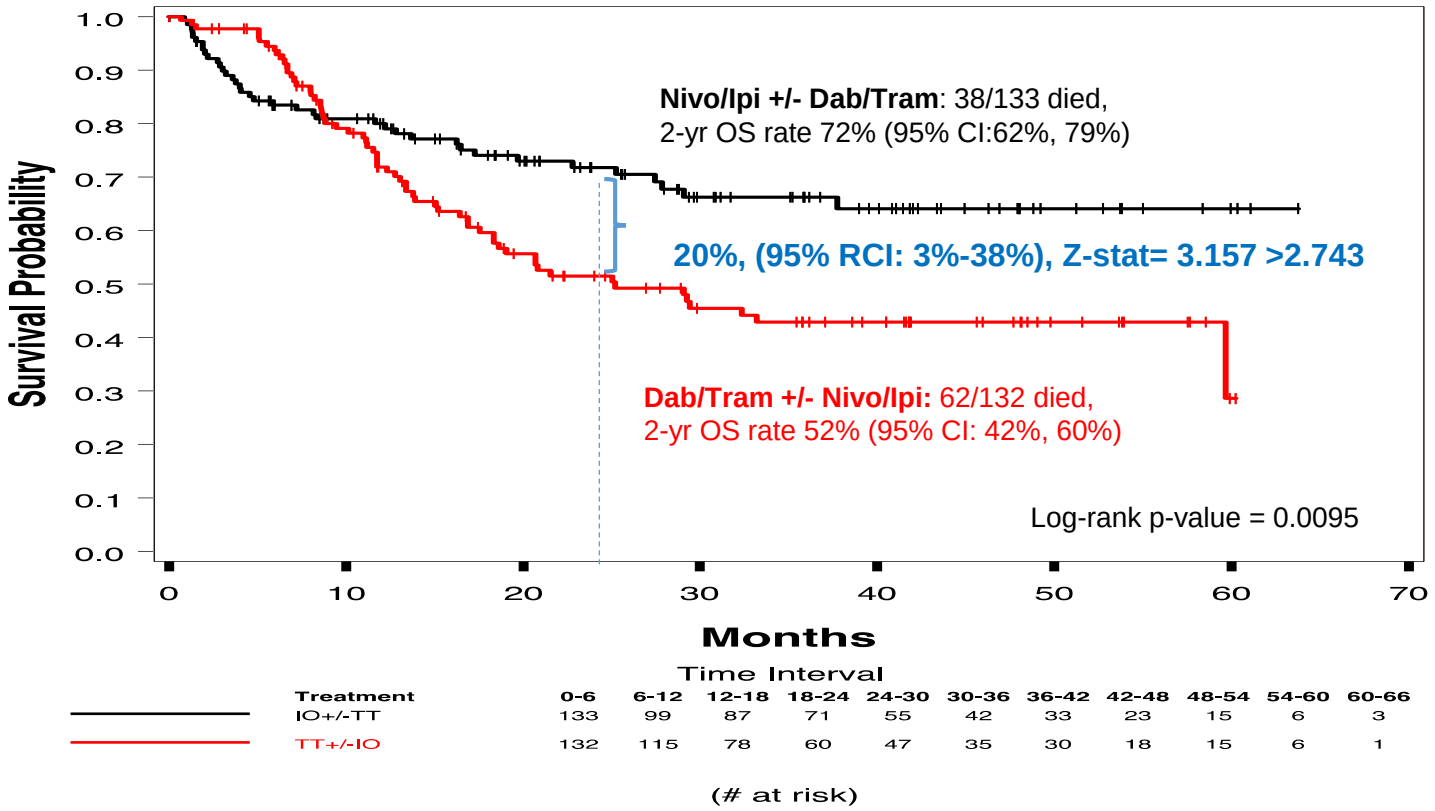
- Systemic therapy
  - Nivolumab/Pembrolizumab
  - Nivolumab 3mg/kg plus ipilimumab 1mg/kg
  - Nivolumab 1mg/kg plus Ipilimumab 3 mg/kg
  - Nivolumab and relatlimab
  - Ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy
  - Clinical trial

Panel recommendations

- For first-line therapy of stage IV melanoma, ipilimumab plus nivolumab is preferred over other anti-PD-1-based regimens in patients with poor prognostic features such as liver metastases, brain metastases, *BRAF* mutation, or high LDH.
- For patients with *BRAF*V600-mutated melanoma, despite the approval for vemurafenib, cobimetinib, and atezolizumab, the role of triplet therapy (as opposed to sequential combination ICI therapy followed by targeted therapy) is not clear but may be considered in selected patients (LE:2).

DREAMseq trial in metastatic melanoma: Immunotherapy vs. targeted therapy

Overall Survival (OS): Step 1 +/- Step 2



ASCO plenary series, 2022, Michael B. Atkins, MD

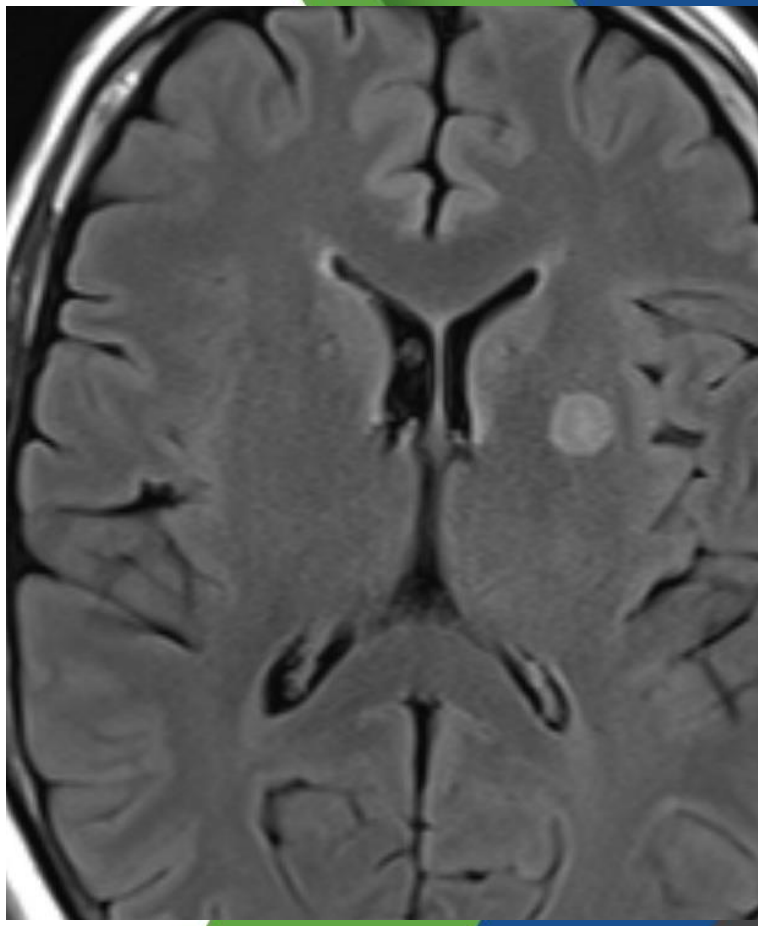
Case #2: stage IV BRAF mutant

- Systemic therapy
  - Nivolumab/Pembrolizumab
  - Nivolumab 3 mg/kg plus Ipilimumab 1 mg/kg
  - **Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg**
  - **Nivolumab and relatlimab (if less symptomatic)**
  - Ipilimumab
  - High-dose IL-2
  - BRAF/MEK targeted therapy
  - **Clinical trial**

Case #3

DH, male patient in 60s

- Patient with a history of melanoma 4 years prior, left back lesion, 2.2 mm, non-ulcerated
- Underwent wide excision and SLN
- Presented 2 years later for screening and found to have metastatic disease including brain metastasis.
- Biopsy of systemic disease performed and reveals malignant melanoma, **BRAF MUTATED**



Case #3: Stage IV with brain metastasis

- Systemic therapy
  - Nivolumab/Pembrolizumab
  - Ipilimumab
  - Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg
  - Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg
  - High-dose IL-2
  - BRAF/MEK targeted therapy
  - Clinical trial

Radiation to brain lesion?

Case #3: What if the patient is found to have a brain metastasis?

- Systemic therapy
  - Nivolumab/Pembrolizumab
  - Ipilimumab
  - Nivolumab 3 mg/kg plus ipilimumab 1 mg/kg
  - **Nivolumab 1mg/kg plus ipilimumab 3 mg/kg**
  - Nivolumab and relatlimab
  - High-dose IL-2
  - BRAF/MEK targeted therapy
  - Clinical trial

Radiation to brain lesion?

Panel recommendations

- For patients with asymptomatic MBMs for whom steroids have been tapered to the lowest tolerated dose and for whom potential toxicities are tolerable, ipilimumab plus nivolumab is recommended in the frontline (LE:1). There are no data supporting the use of nivolumab plus relatlimab in patients with MBMs. Multidisciplinary management is required for management of all patients with MBMs.

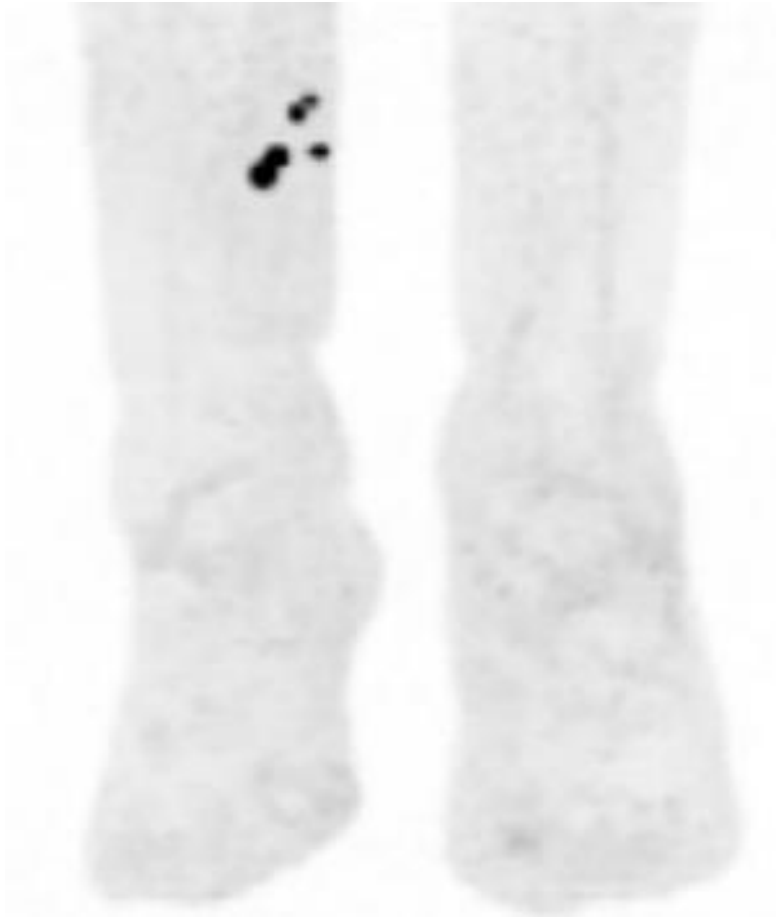
Front line therapy

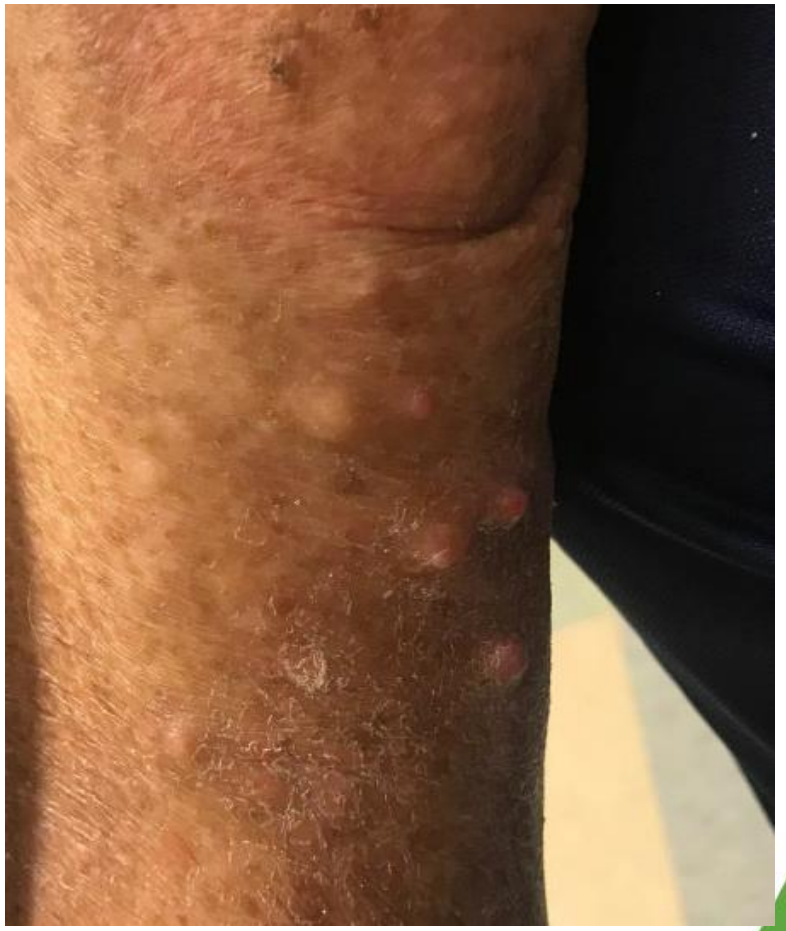
1	2	3	4
BRAF/MEK targeted therapy	PD-1 single agent	Nivolumab and relatlimab	Ipilimumab and nivolumab
•Really sick BRAF mutant patient who you think will not survive long enough for IO to work. •Consider planned switch to IO	•**Historically:** •Patients with lower M stage M1a and M1b •Patients with worse performance status	•Replacing PD-1 single agent for majority of patients in whom you aren't considering combination ipilimumab and nivolumab	•Brain mets •M1c disease •High LDH •BRAF mutant •Not so sick they will not survive for IO to work

Case #4: 80 yo male

- At the age of 40 had a melanoma removed from right calf and was told it was pretty “advanced”. No adjuvant therapy done at that time.
- 2016 noted growing mass proximal to his previous melanoma
- 2018 presented to dermatology with 5 X 4 cm mass on right medial calf, biopsy confirmed recurrent melanoma
- PET/CT with numerous nodules

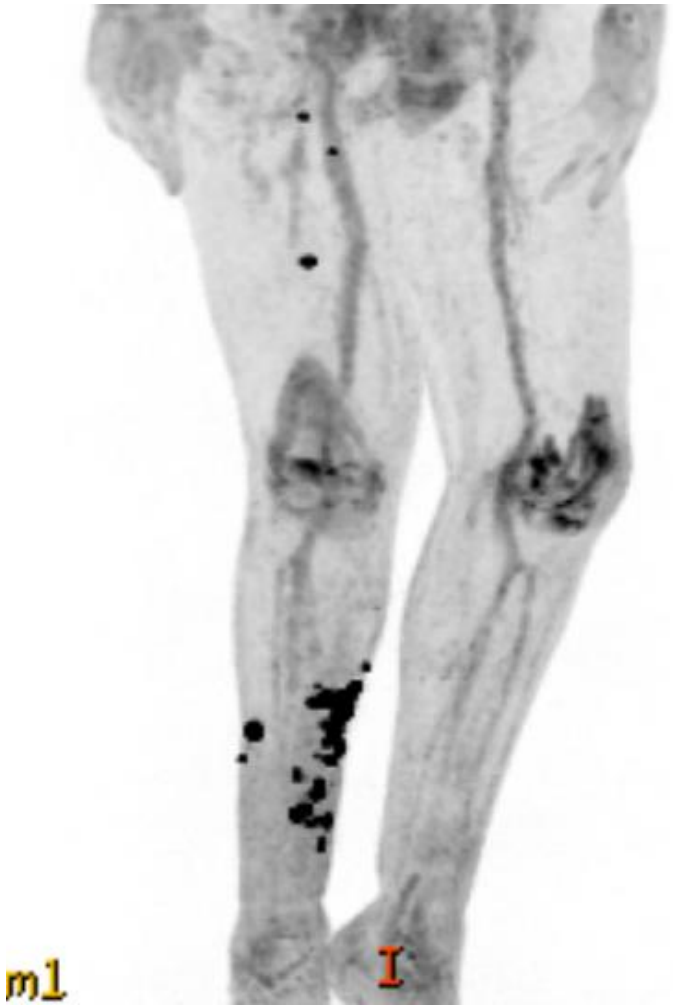
PET/CT and clinical images

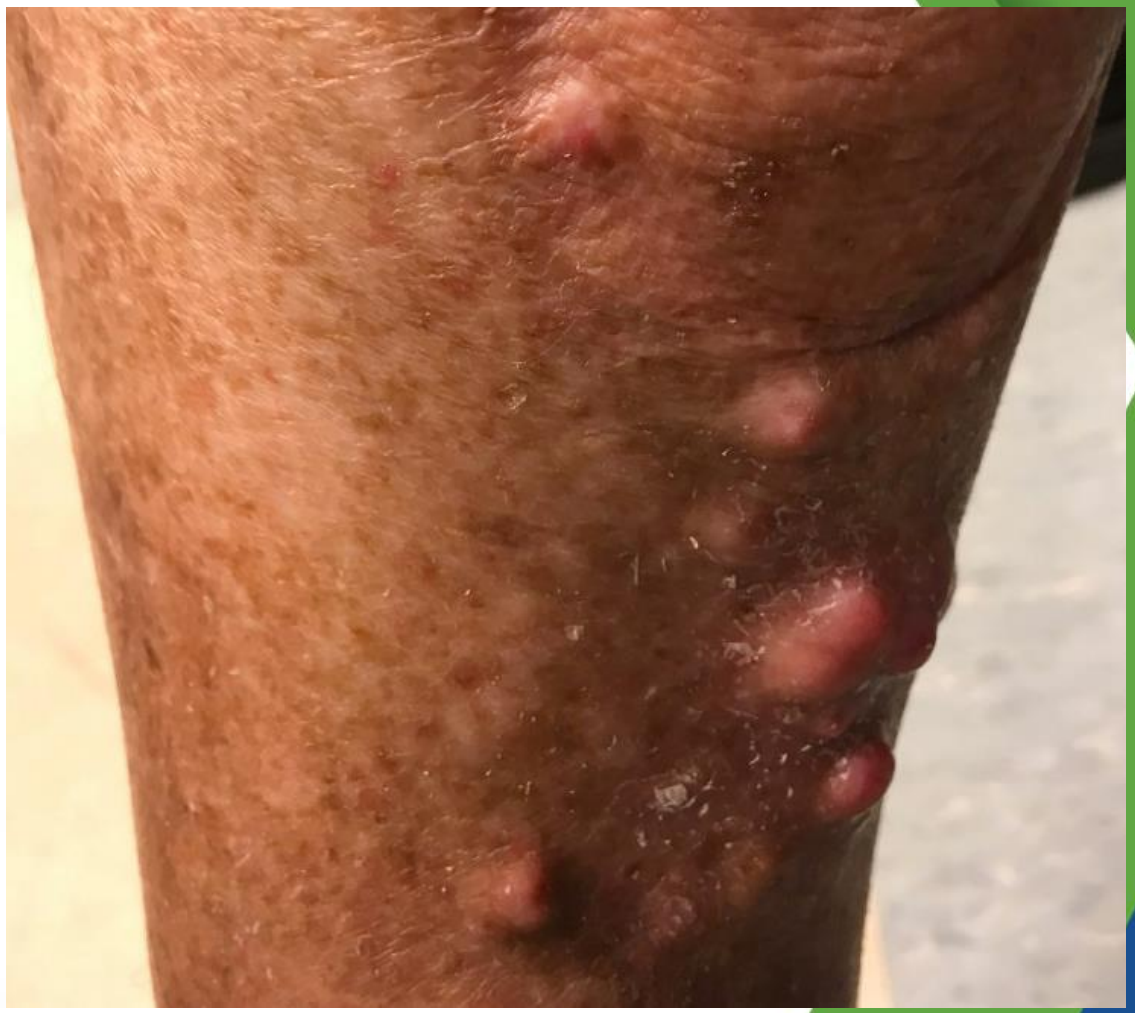




80 yo male treatment course

- 11/18 – Started on nivolumab without benefit

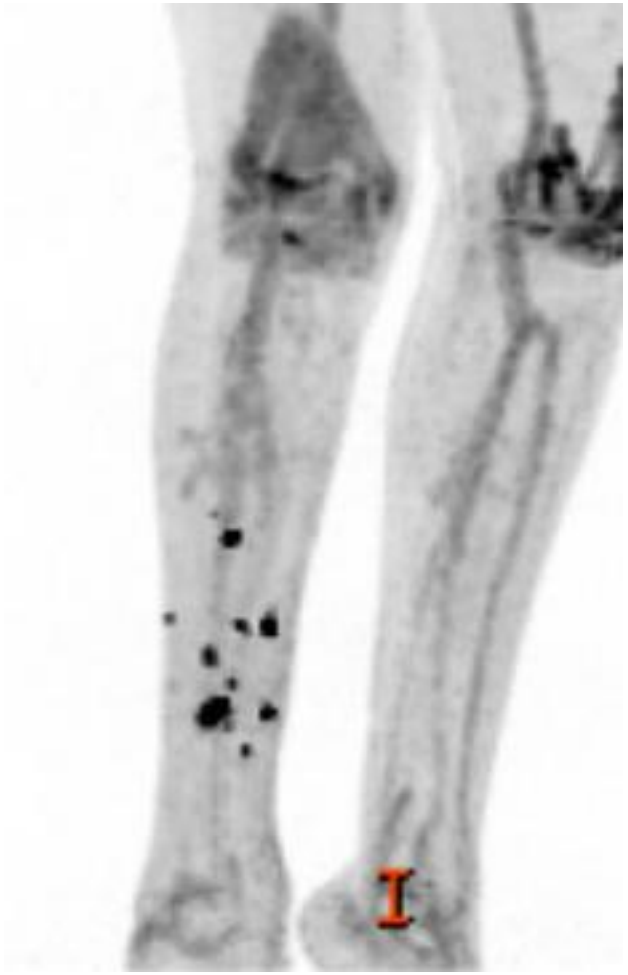


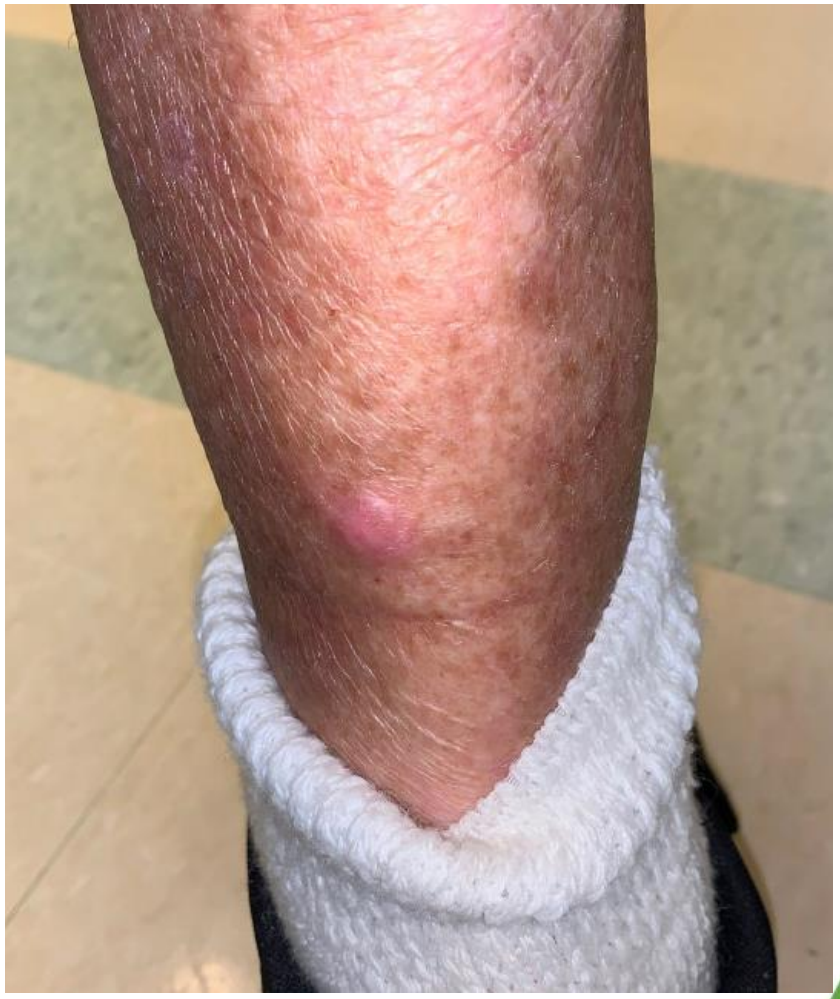


80 yo male treatment course

- 4/19 – Started on encorafenib and binimetinib with nice response to therapy
- 11/19 - stopped for malignant hypertension and concern for possible cardiac toxicity
- Subsequently started progressing again in his leg lesions

PET/CT and clinical imaging

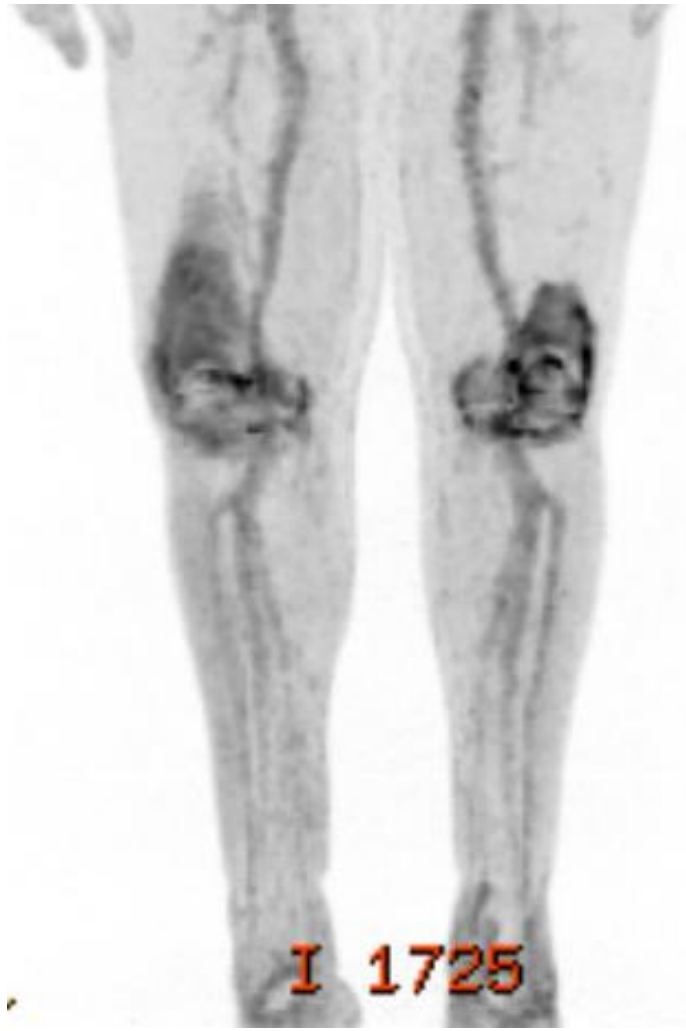


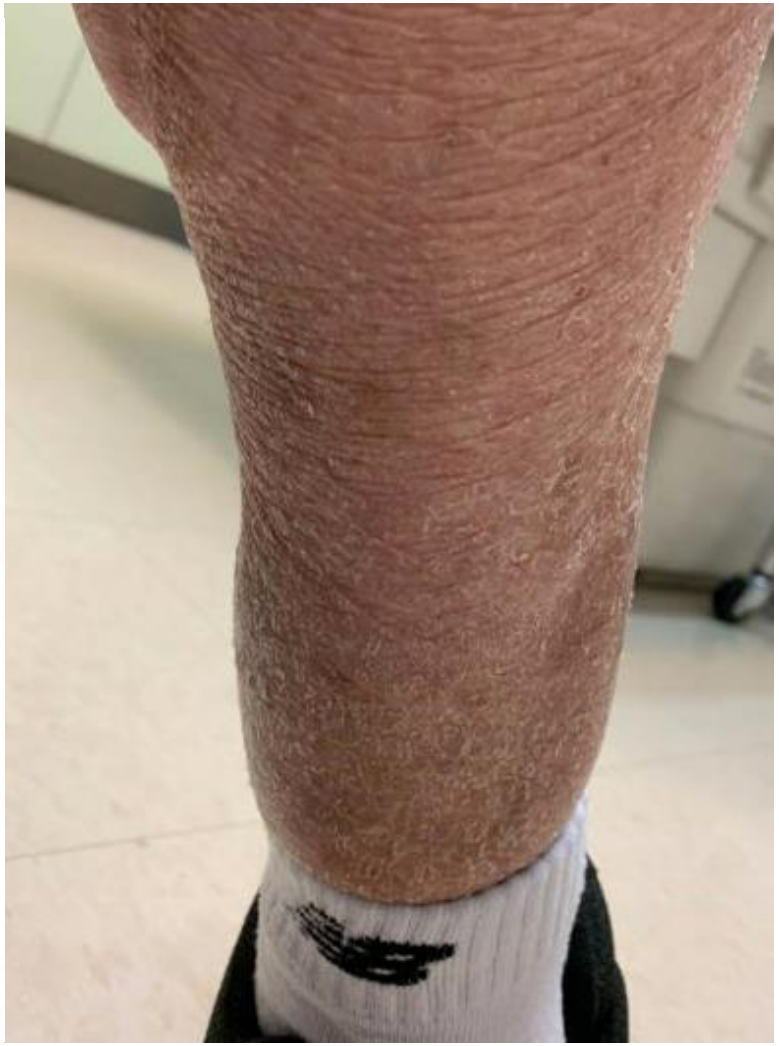


80 yo male treatment course

- 1/20 – Started on injection T-VEC therapy

PET/CT and clinical imaging





Panel recommendations

- T-VEC monotherapy is well tolerated, easily administered, and should be considered as part of the treatment plan for patients with predominantly injectable disease at any point in the treatment course for melanoma as part of a multidisciplinary approach.
- Intratumoral therapies may be considered throughout the treatment course, although with T-VEC, responses in non-injected visceral lesions are rare (LE:2).

Questions

Thank you.

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Cancer Immunotherapy GUIDELINES