Melanoma/Cutaneous Oncology

Panelists:

Sunil Reddy (Chair)
Susan Swetter
Scott Christensen
Amanda Kirane
Adil Daud
Katy Tsai
David Minor
Thach-Giao Truong
Kevin Kim
Evan Hall (Fellow)

Case #1

- **64 yo previously healthy F with a history of stage I melanoma diagnosed in 2011 on her R shoulder - pathology showed lentigo maligna, 0.38 mm depth, no ulceration**
- **2017 – Patient developed increasing mild-moderate abdominal pain and bloating**
  - **CT CAP w contrast showed a 9 cm necrotic appearing liver mass, mild-moderate ascites, and abdominal lymphadenopathy measuring up to 1.7 cm**

- **PET/CT showed: 1) the liver mass was FDG-avid, 2) abdominal lymphadenopathy had low-grade FDG-avid metabolism, and 3) development of moderate R pleural effusion also noted to have low-grade FDG avidity**
- **CT guided biopsy of the liver confirmed metastatic melanoma (+SOX-10+, -AE1/AE3, -Melan-A, -HMB-45)**
- **BRAF testing: wild-type**
- **MRI Brain: no evidence of intracranial metastases**
- **ECOG 1**

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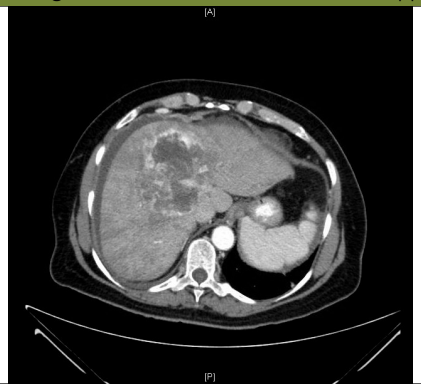

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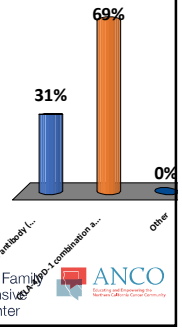
What would you recommend for initial treatment in this case?

A. Single-agent PD-1 antibody (e.g. pembrolizumab or nivolumab)
B. CTLA-4/PD-1 combination antibody therapy (ipilimumab/nivolumab)
C. Other



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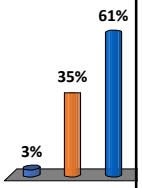
***If a BRAF V600E mutation had been identified*, what would be your first line systemic therapy of choice?**

A. Single-agent PD-1 antibody (e.g. pembrolizumab or nivolumab)
B. CTLA-4/PD-1 combination antibody therapy (ipilimumab/nivolumab)
C. BRAF/MEK inhibitor combination (e.g. dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib)
D. Other



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Case #1, continued:

- **The patient began therapy with ipilimumab and nivolumab**
- **Within two cycles, she began to feel improvement in her abdominal distention and bloating symptoms.**
- **Shortly after cycle #3, she developed progressive weakness and difficulty walking over a period of several days. She had one mechanical fall without LOC, but was now unable to climb stairs. She denied back pain, numbness, tingling, vertigo, diplopia, dysphagia or other symptoms.**

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Case #1, continued:

Clinical Exam:

Lower extremities with reduced strength, particularly in proximal muscles (3+-4/5 with hip flexion, leg extension/flexion and quadriceps, R>L)
Normal strength in upper extremities
Normal sensation
Normal Babinski
Diminished reflexes in lower extremities.
New intention tremor in upper extremities

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Case #1, continued:

- **MRI Complete Spine: no abnormal cord signal or enhancement to suggest myelopathy or metastasis.**
- **MRI Brain: no evidence of metastatic disease**
- **LP: WBC 15 (H) (87% lymphs), RBC 13; protein 167 (H), glucose 69 (nl); cytology negative for malignant cells**
- **Viral serologies: negative**

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Case #1, continued:

- **EMG/NCS: motor polyradiculopathy, with features of demyelination noted**
- **Diagnosis felt to be most consistent with Guillain-Barre like syndrome 2/2 immune checkpoint inhibitor therapy**

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Case #1, continued:

- **She was treated with corticosteroids (1 mg/kg prednisone) with a prolonged taper. She experienced rapid improvement in her symptoms, which ended up resolving within 3-4 weeks after initiation of steroids.**
- **PET/CT shortly after completion of steroids (after three cycles of ipilimumab/nivolumab) showed complete metabolic response and decreased size of liver lesion (now 5 cm – previously 9 cm).**
- **She continues in a CR by PET presently.**

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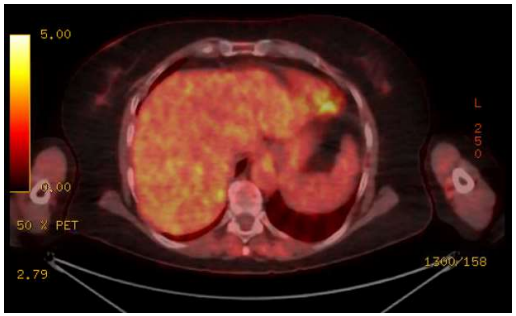

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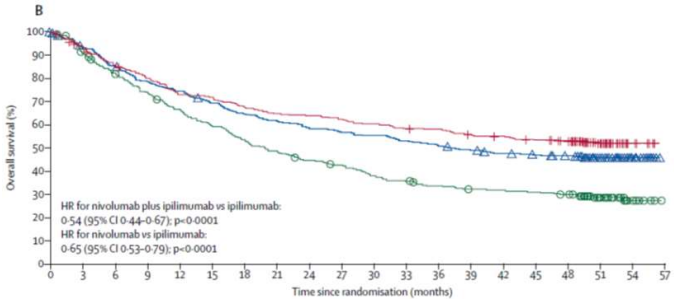
Updated results from CHECKMATE-067: Ipi/Nivo vs Nivo vs Ipi in Stage IV Melanoma



Hodi et al, *Lancet Oncology,* 2018, 19:1480-1492

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Updated safety data from CHECKMATE-067: Ipi/Nivo vs Nivo in Stage IV Melanoma

Any Grade 3 Treatment Related AE:
48% Ipi/Nivo vs 17% Nivo

Any Grade 4 Treatment Related AE:
11% Ipi/Nivo vs 5% Nivo

Grade 3 Colitis:
8% Ipi/Nivo vs 1% Nivo

Hodi et al, *Lancet Oncology,* 2018, 19:1480-1492

Neurologic Immune-Related Adverse Events:

Review of >3,700 pts treated on trials with nivolumab +/- ipilimumab:

35 patients (0.93%) had serious neurological IRAEs
- **22 Neuropathy**
- **6 Encephalitis**
- **5 Non-infective meningitis**
- **3 Neuromuscular disorders**

Larkin et al, *Oncologist,* 2017, 22:709-718

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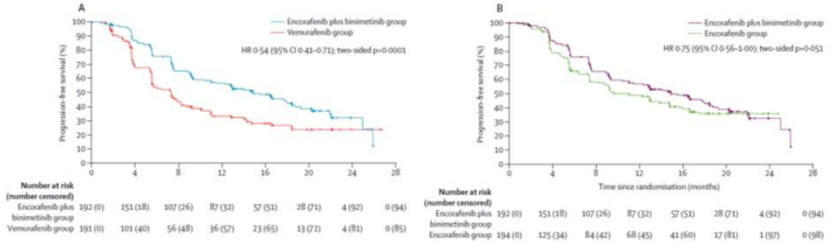
COLUMBUS TRIAL: Encorafenib/binimetinib vs vemurafenib vs encorafenib in *BRAF* Mutant Melanoma



Dummer et al, *Lancet Oncology,* 2018, 19:603-615

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Case #2

- **58 yo otherwise healthy male noted to have a hyperpigmented lesion of his back**
- **Biopsy showed invasive melanoma, nodular type, Breslow depth at least 3.7 mm, mitotic index 10/mm2, without ulceration. He had no clinically detectable lymph nodes.**

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Case #2

- **He underwent wide local excision with sentinel lymph node biopsy. Pathology showed uninvolved surgical margins with 1/8 total involved lymph nodes (four sampled in R axilla, four in L axilla), with melanoma in lymph node measuring 1.1 mm in greatest dimension. Final pathologic staging was pT3apN1a (stage IIIB by AJCC 8th edition)**
- **Post-operatively, PET/CT did not reveal evidence of metastatic disease.**
- **BRAF testing was *positive for V600E mutation.***

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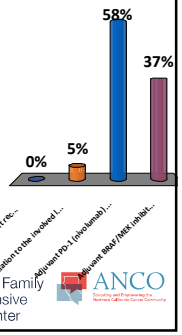
Which of the following would you recommend for further treatment at this time?

A. **No further treatment recommended**
B. **Radiation to the involved lymph node basin**
C. **Adjuvant PD-1 (nivolumab) for one year**
D. **Adjuvant BRAF/MEK inhibition (dabrafenib/trametinib) for one year**



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Case #2, continued

- **The patient began therapy with adjuvant nivolumab, and has been tolerating it well without evidence of recurrent disease thus far (approx. 7 months into his course).**

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AJCC Seventh Edition Melanoma

IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a	N2c	M0
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	M0
	Any T	N3	M0

Balch et al, *JCO,* 2009; 27:6199-6206

AJCC Eighth Edition Melanoma Stage III Subgroups

N Category	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[4]

Legend
A Stage IIIA
B Stage IIIB
C Stage IIIC
D Stage IIID

Gershenwald et al, *CA Cancer J Clin,* 2017; 67:472-492

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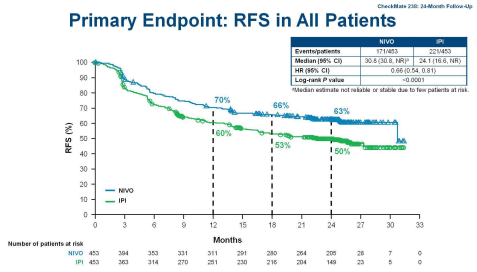
Updated Results from CHECKMATE-238 (Adjuvant Nivolumab vs Ipilimumab)



Weber et al, 2018 ASCO Annual Meeting

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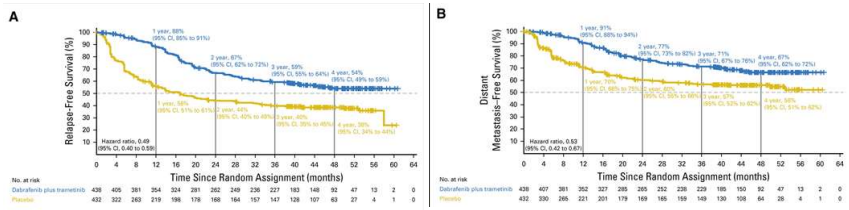
Updated Results from COMBI-AD (Adjuvant Dabrafenib/Trametinib vs Placebo)



Hauschild et al, *JCO,* 2018, 36:3411-3449

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Case #3

- **66 year old female with a history of Merkel cell carcinoma:**
- **2014 – Underwent surgical resection of R scalp Merkel cell carcinoma, followed by adjuvant radiation therapy**
- **2016 – Surveillance imaging detected an FDG-avid pulmonary nodule, which was removed by lobectomy with pathology showing metastatic Merkel cell carcinoma**
- **2017 – CT chest showed mildly enlarged subcarinal lymph adenopathy and a new R lung nodule measuring 1.5 cm. The lung nodule was biopsied and found to represent metastatic Merkel cell carcinoma.**

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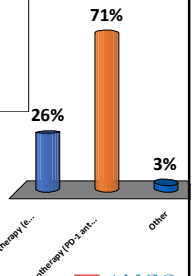
What strategy for systemic therapy would you recommend?

A. Cytotoxic chemotherapy (e.g. platinum/etoposide)
B. Immunotherapy (PD-1 antibody) (such as avelumab or pembrolizumab)
C. Other



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Case # 3 continued:

- **The patient began pembrolizumab with subsequent imaging showing stable disease for several months.**
- **Late 2018 – She began to feel increasing fatigue and was noted to have increase in number and FDG avidity of pulmonary nodules (largest 1.7 cm), new FDG avid lesion in her L gluteus muscle (biopsy proven metastatic MCC).**

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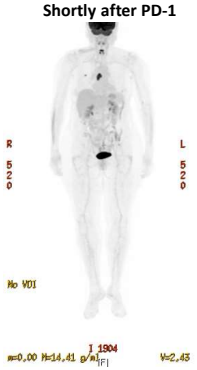
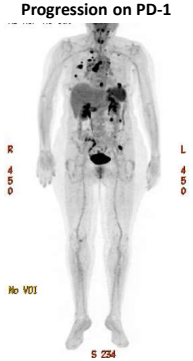
Shortly after PD-1



Progression on PD-1



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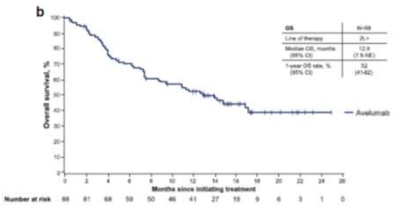
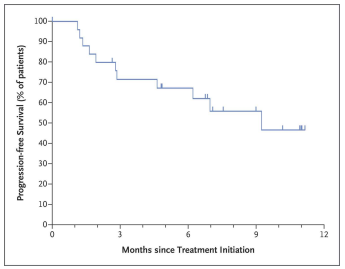
Avelumab in 2nd Line Advanced Merkel Cell Carcinoma: JAVELIN-200 Trial



Kaufman et al, *JITC*, 2018,6:7

Pembrolizumab in 1st line for Advanced Merkel Cell Carcinoma: KEYNOTE-017



Nghiem et al, *NEJM*, 2016, 374:2542-2552

Case #4

- **57 yo previously healthy M with progressive vision loss of the L eye**
- **August 2018 – He was found to have a large mass in the ciliary body concerning for uveal melanoma.**
- **CT CAP showed no evidence of metastatic disease**

Case #4, continued

- **Patient underwent enucleation with orbital implant. Pathology showed "choroidal melanoma" with basal diameter 14 mm, thickness 10 mm, size category 3. There were negative surgical margins. Staging was pT3a, G2, pNX, pMX.**
- **Gene expression profiling was obtained (Castle Biosciences) and showed GEP class 2 (high risk) and elevated expression of PRAME (+PRAME).**

Case #4, continued

- **The patient was recommended to undergo a plan of surveillance imaging (alternating CT CAP every 6 months with MRI Liver with Eovist every six months)**
- **MRI Liver showed >20 new liver lesions (largest 1.1 x 1.1 cm) concerning for metastatic disease**
- **Biopsy confirmed metastatic melanoma.**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uveal Melanoma

Version 1.2018 — March 15, 2018

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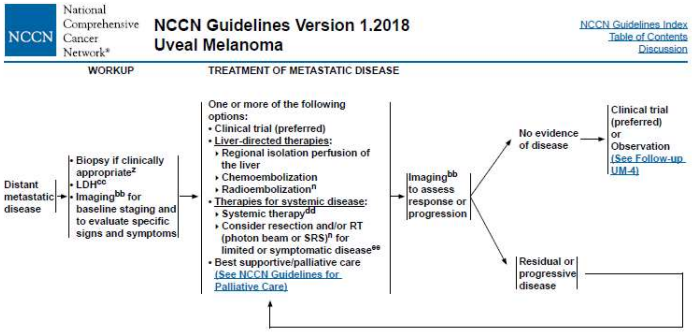

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Thank you to the panelists for their participation and expertise and to the audience for your attention!

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