What's New in Melanoma

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Disclosures

I have no relevant commercial or financial relationships to disclose.

I will be discussing investigational or unlabeled medications.

Objectives

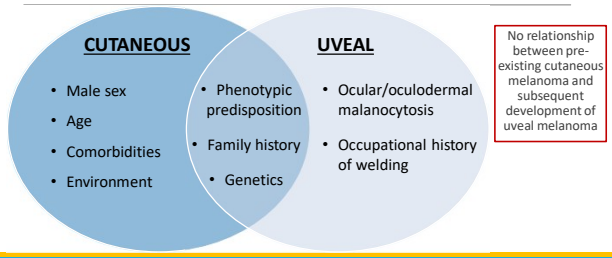
1. Discuss the changing landscape of melanoma treatment and impact on patient outcomes
2. Analyze the primary literature supporting emerging therapies in cutaneous melanoma
3. Evaluate the evidence supporting the recently FDA approved treatment in uveal melanoma
4. Outline patient and caregiver educational needs as they relate to medication adherence and toxicity management

Melanoma Histologic Subtypes

CUTANEOUS	NON-CUTANEOUS
○ Superficial spreading	○ Mucosal
○ Nodular	○ Uveal
○ Lentigo maligna	
○ Acral lentiginous	

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Risk Factors

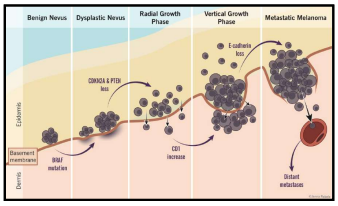


No relationship between pre-existing cutaneous melanoma and subsequent development of uveal melanoma

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

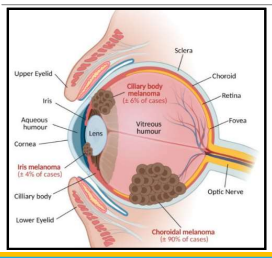
Melanoma Background

- Melanoma arises from melanocytes
- Cutaneous melanoma represents
  - < 5% of skin cancer diagnoses
  - > 70% of deaths
- Incidence is rapidly rising
  - 5th most common malignancy
  - In 2022:
    - Estimated new cases: 99,780
    - Estimated deaths: 7,650
- Estimated that 20.4 years of life is lost as a result of melanoma mortality



NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022. SEER epidemiology data. Available at: https://seer.cancer.gov/statfacts/html/melan.html. Accessed September 14, 2022. Image available at: Available at: http://www.pathophys.org/melanoma/melanoma-progression/. Accessed September 14, 2022.

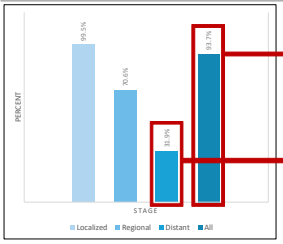
Melanoma Background, Continued



- Uveal melanoma is the most common primary intraocular malignancy in adults
  - Accounts for ~3% of all melanomas
  - In 2022:
    - Estimated new cases: 3,300
    - Estimated deaths: 400
- Most present as localized disease, < 3% present as metastatic disease
- Arises anywhere in the uveal tract
  - choroid plexus (most common)
  - iris
  - ciliary body

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.
Image available at https://www.mdpi.com/2072-6694/14/1/96. Accessed September 14, 2022.

5-Year Relative Survival - Cutaneous

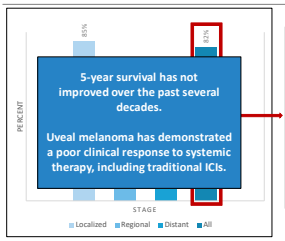


5-Year Relative Survival
93.7%
2012–2018

Prior to BRAF/MEK inhibitors and immune check point inhibitors, 5-year survival for distant/metastatic disease was < 10%.

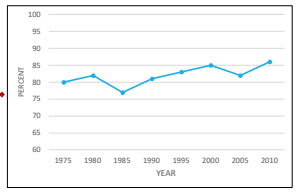
NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.
SEER epidemiology data. Available at: https://seer.cancer.gov/statfacts/html/melan.html. Accessed September 14, 2022

5-Year Relative Survival – Uveal



5-year survival has not improved over the past several decades.

Uveal melanoma has demonstrated a poor clinical response to systemic therapy, including traditional ICIs.



ICIs: immune checkpoint inhibitors; OS: overall survival

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022. Aronow ME, et al. *Ocul Oncol Pathol*. 2018; 4(3): 145-51. SEER epidemiology data. Available at: https://www.cancer.org/cancer/eye-cancer/detection-diagnosis-staging/survival-rates.html. Accessed September 14, 2022.

Audience response #1

Which of the following is true regarding the trends in outcomes among patients diagnosed with melanoma?

A. 5-year survival has improved by nearly 20% with the addition of BRAF/MEK inhibitors and immune checkpoint inhibitors to the treatment landscape of metastatic cutaneous melanoma.

B. Progression free survival and overall survival outcomes among patients with cutaneous melanoma have not changed over the last decade, despite the changing landscape of treatment.

C. Survival outcomes among patients with uveal melanoma have not drastically changed within the last four decades.

D. Both A and C

E. None of the above

Cutaneous Melanoma

Treatment: Stage I-III, Resectable

Stage	Treatment	Adjuvant Therapy
Stage I	Wide excision +/- SLNB	Observation
Stage II	Wide excision +/- SLNB	Observation Systemic therapy (IIB, IIC) Locoregional radiation*
Stage III, sentinel node positive	Nodal basin US surveillance Wide excision + CLND	Systemic therapy Observation
Stage III, clinical node positive	Wide excision + TLND Neoadjuvant therapy	Systemic therapy Locoregional radiation* Observation
Stage III, in-transit lesions limited resectable disease	Wide excision Intralesional T-VEC	Systemic therapy Observation

SLNB: sentinel lymph node biopsy; US ultrasound, CLND: complete lymph node dissection; TLND: total lymph node dissection; T-VEC: talimogene laherparepvec * Category 2B

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KEYNOTE-716

Design: randomized, double-blind, placebo-controlled, phase III trial

Inclusion: ≥ 12 years old, newly diagnosed, completely resected stage IIB or IIC melanoma

Exclusion: previously treated melanoma, ECOG > 1, autoimmune disease, uncontrolled infection, use of systemic glucocorticoids

Randomized 1:1 within 12 weeks of surgery

Stratified by T-category and age

Pembrolizumab 200 mg (2 mg/kg in pediatric patients) every 3 weeks x 17 cycles or disease progression/toxicity

N=487

Placebo every 3 weeks x 17 cycles or disease progression/toxicity

N=489

ECOG: Eastern Cooperative Oncology Group

Luke JJ, et al. *Lancet*. 2022; 399(10336): 1718-1729.

Efficacy Outcomes

Outcomes	Pembrolizumab (N=487)	Placebo (N=489)	HR (95% CI)
Median RFS, mo	NR	NR	-
Recurrence or death at 1st interim analysis, n (%)	54 (11)	82 (17)	0.65 (0.46-0.92)
Recurrence or death at 2nd interim analysis, n (%)	72 (15)	115 (24)	0.61 (0.45-0.82)
Estimated 12 mo RFS, %	90	83	-

RFS: recurrence free survival; mo: months; NR: not reached, HR: hazard ratio; 95% CI: 95% confidence interval

Luke JJ, et al. *Lancet*. 2022; 399(10336): 1718-1729.

Safety Outcomes

Adverse Events	Pembrolizumab (N=483)		Placebo (N=486)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE, n (%)	449 (93)	125 (26)	433 (89)	83 (17)
Treatment-related AE, n (%)	386 (80)	78 (16)	296 (61)	21 (4)
Discontinuation due to AE at 2nd interim analysis, n (%)	85 (18)	-	23 (5)	-

AE: adverse

IMPACT: Due to the reduction in risk of disease recurrence and manageable safety profile, pembrolizumab is now approved and incorporated into the NCCN guidelines as adjuvant therapy for stage IIB and IIC cutaneous melanoma

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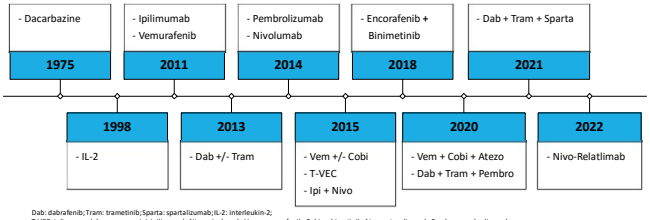
Treatment: Stage III-IV, Unresectable

Stage	Treatment
Stage III, in-transit lesions unresectable disease	Systemic therapy Intralesional injection: T-VEC, IL-2* Topical imiquimod* Radiation therapy* Palliative: limited excision, ablation* ILI/ILP
Stage IV	Systemic therapy Intralesional injection: T-VEC Palliative: resection and/or radiation

T-VEC: talimogene laherparepvec; IL-2: interleukin-2; ILI/ILP: isolated limb infusion/perfusion * Category 2B

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Treatment Evolution: Unresectable/Metastatic Disease



Dab: dabrafenib; Tram: trametinib; Sparta: spartalizumab; IL-2: interleukin-2; T-VEC: talimogene laherparepvec; Ipi: ipilimumab; Nivo: nivolumab; Vem: vemurafenib; Cobi: cobimetinib; Atezo: atezolizumab; Pembro: pembrolizumab

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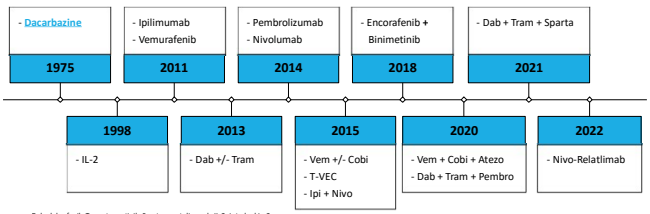

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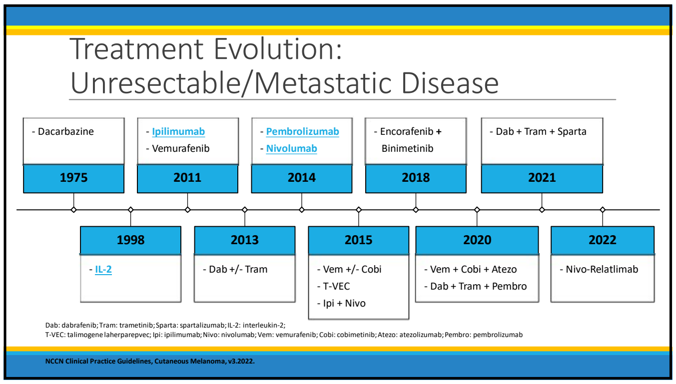
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Unresectable/Metastatic Disease
- Dacarbazine
1975
- Ipilimumab
- Vemurafenib
2011
- Pembrolizumab
- Nivolumab
2014
- Encorafenib + Binimetinib
2018
- Dab + Tram + Sparta
2021
1998
- IL-2
2013
- Dab +/- Tram
2015
- Vem +/- Cobi
- T-VEC
- Ipi + Nivo
2020
- Vem + Cobi + Atezo
- Dab + Tram + Pembro
2022
- Nivo-Relatlimab
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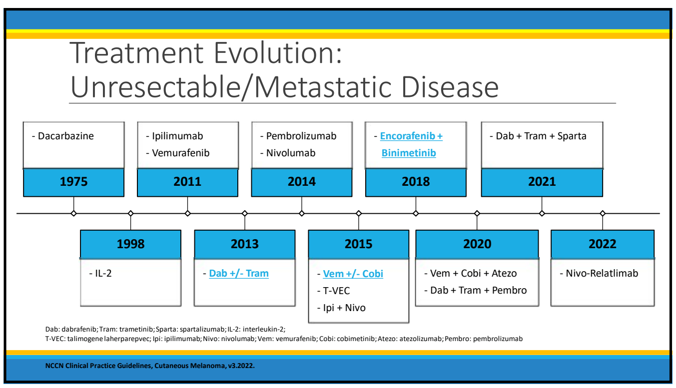
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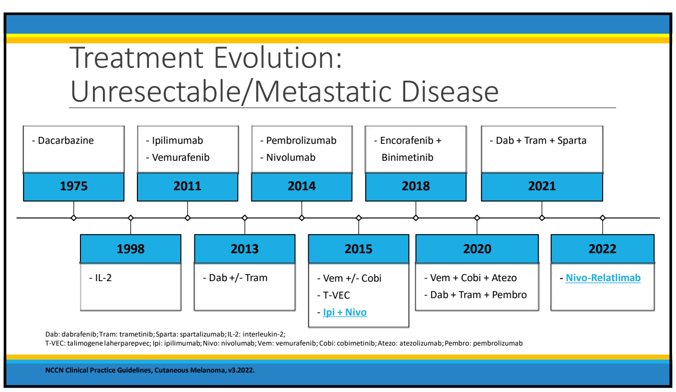
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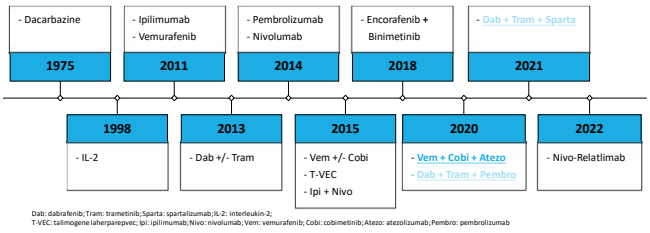

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Immunotherapy

Preferred, category 1:

- Single agent pembrolizumab: KEYNOTE 002, 006
- Single agent nivolumab: CheckMate 037, 066
- Combination ipilimumab/nivolumab: CheckMate 067, 511

Preferred:

- Combination nivolumab/relatlimab: RELATIVITY-047

Other recommended regimens:

- Combination pembrolizumab/low-dose ipilimumab: KEYNOTE 029*

* Category 2b

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Immunotherapy

Trial, year	Treatment Arms	RR (%)	mPFS (mo)	mOS (mo)	AE, G ≥3 (%)
KEYNOTE 002	Pembrolizumab 2 (n=180) Pembrolizumab 10 (n=181) Chemotherapy (n=179)	22 28 4	16 at 2 yrs 22 at 2 yrs <1 at 2 yrs	**36 at 2 yrs** 38 at 2 yrs 30 at 2 yrs	14 16 26
KEYNOTE 006	Pembro 10 Q2W(n=279) Pembro 10 Q3W (n=277) Ipilimumab 3 Q3W (n=278)	37 36 13	31 at 2 yrs 28 at 2 yrs 13 at 2 yrs	55 at 2 yrs 55 at 2 yrs 43 at 2 yrs	17 17 20
CheckMate 037	Nivolumab (n=272) chemotherapy (n=133)	27 10	3.1 3.7	15.7 14.4 P=0.716	15 18
CheckMate 066	Nivolumab (n=210) chemotherapy (n=208)	43 14 P<0.001	5.1 2.2 P <0.001	37.5 11.2 P <0.001	15 18

RR: response rate; mPFS: median progression free survival; mOS: median overall survival; mo: months; AE: adverse event; G ≥ 3: grade ≥ 3; pembro: pembrolizumab

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

	KEYNOTE-002 (n=540)	KEYNOTE-006 (n=834)
Design	Phase II, RCT Inclusion: ≥ 18 years old, progressive disease on ipilimumab; prior BRAF inhibitor if BRAF v600E mutant, ECOG 0-1 Exclusion: ongoing ipilimumab toxicity, active CNS metastases, autoimmune disease, hepatitis	Phase III, RCT Inclusion: ≥ 18 years old, unresectable Stage III or IV melanoma, ECOG 0-1 Exclusion: prior treatment with ICI, ocular melanoma, active CNS metastases or autoimmune disease
Intervention	pembrolizumab 2 mg/kg IV vs pembrolizumab 10 mg/kg IV vs investigator's choice	pembrolizumab 10 mg/kg IV Q2 weeks vs pembrolizumab 10 mg/kg IV Q3 weeks vs ipilimumab 3 mg/kg IV Q3 weeks x 4 then every 12 weeks
Efficacy	PFS improved with pembrolizumab 2 mg/kg and 10 mg/kg mOS: 13.4 (2 mg/kg) vs 14.7 (10 mg/kg) vs 11 mo (chemo) • 2 mg/kg vs chemo HR 0.86 (0.67-1.1), p=0.1173 • 10 mg/kg vs chemo HR 0.74 (0.57-0.96), p=0.0106	No significant difference between Q2 and Q3 week pembro mPFS: 11.6 vs 3.7 mo, HR 0.54 (0.44-0.67), p<0.0001 mOS: 32.7 vs 15.9 mo, HR 0.73 (0.61-0.88), p=0.00049
Safety	Any grade AE: 56.7% vs 59.2% vs 54.3% G3-4 AE: 13.5% vs 16.2% vs 26.3% irAE: 18% vs 21% vs 2%	Any grade AE: 79% vs 71% G3-4 AE: 18% vs 21%
Conclusion	No significant difference in OS between pembrolizumab doses; both improve PFS compared to chemotherapy Pembrolizumab 10 mg/kg improves OS compared to chemo	Pembrolizumab prolongs PFS and OS compared to ipilimumab for advanced melanoma Pembrolizumab has less high-grade toxicity

RCT: randomized controlled trial; CNS: central nervous system; PFS: progression free survival; mOS: median overall survival; AE: adverse event; G3-4: grade 3-4; irAE: immune-related adverse event; Q: week; mo: months

Ribas A, Puzanov I, Dummer R, et al. *Lancet Oncol*. 2015;16(8):908-918. Hamid O, Puzanov I, Dummer R, et al. *Eur J Cancer*. 2017;86:37-45. Robert C, Schachter J, Long GV, et al. *N Engl J Med*. 2015;372(26):2521-2532. Robert C, Ribas A, Schachter J, et al. *Lancet Oncol*. 2019;20(9):1239-1251.

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	CheckMate 037 (n=405)	CheckMate 066 (n=418)
Design	Phase III RCT Inclusion: ≥ 18 years old, unresectable stage IIIC or IV melanoma, progression on prior therapy Exclusion: active CNS metastases, prior treatment with anti-PD-1 or PD-L1 therapy	Phase III RCT Inclusion: ≥ 18 years old, unresectable, previously untreated stage III or IV melanoma, ECOG 0-1 Exclusion: active CNS metastases, uveal melanoma, autoimmune disease, BRAF mutation
Intervention	nivolumab 3 mg/kg IV Q2 weeks vs investigator's choice until progression or unacceptable toxicity	nivolumab 3 mg/kg IV Q2 weeks + dacarbazine 1000 mg/m^2 IV Q3 weeks vs nivolumab + placebo
Efficacy	ORR: 27% vs 10%, mDOR: 32 vs 13 months Median PFS: 3.1 vs 3.7 months, HR 1 (0.78-1.4) Median OS: 16 vs 14 months, HR 0.95 (0.73-1.24)	ORR 40% vs 13.9%, OR 4.06, p<0.001 Median OS 37.5 vs 11.2 months, HR 0.46 (0.36-0.59), p<0.001 OS benefit seen in all subgroups
Safety	G3-4 AE: 14% vs 34%	Treatment-related G3-4 AE: 15% vs 17.6% any grade AE: 74.3% vs 75.6%
Conclusion	Nivolumab improves ORR and has fewer side effects than standard chemotherapy	Nivolumab improves OS compared to dacarbazine in previously untreated BRAF wild type melanoma

RCT: randomized controlled trial; CNS: central nervous system; ORR: overall response rate; mDOR: median duration of response; PFS: progression free survival; OS: overall survival; AE: adverse event; G3-4: grade 3-4

Weber JS, D'Angelo SP, Minor D, et al. *Lancet Oncol.* 2015;16(4):375-384. Larkin J, Minor D, D'Angelo S, et al. *J Clin Oncol.* 2018;36(4):383-390. Robert C, Long GV, Brady B, et al. *N Engl J Med.* 2015;372(4):320-330. Ascierto PA, Long GV, Robert C, et al. *JAMA Oncol.* 2019;5(2):187-194.

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CheckMate 511	NIVO3/IPI1 NIVO1/IPI3	45.6 50.6	9.9 8.9	NR NR	34 48 P=0.006

RR: response rate; mPFS: median progression free survival; mOS: median overall survival; mo: months; AE: adverse event; G ≥ 3: grade ≥ 3; nivo: nivolumab, IPI: ipilumumab, pembro: pembrolizumab; NR: not reached

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

	CheckMate 067 (n=945)	CheckMate 511 (n=360)
Design	Phase III RCT Inclusion: ≥ 18 years old, unresectable stage III or IV melanoma, no prior systemic therapy, ECOG 0-1 Exclusion: active CNS metastases, ocular melanoma, autoimmune disease	Phase IIIb/IV RCT Inclusion: ≥ 18 years old, previously untreated, unresectable stage III or IV melanoma, ECOG 0-1 Exclusion: active CNS metastases, ocular melanoma, autoimmune disease
Intervention	NIVO1 IV + IPI3 IV Q3 weeks x 4 then nivolumab alone vs NIVO3 IV Q2 weeks + placebo vs IPI3 IV Q3 weeks + placebo	NIVO3 + IPI1 Q3 weeks x 4 then nivolumab maintenance vs NIVO1 + IPI3 Q3 weeks x 4 then nivolumab maintenance
Efficacy	Median OS: NR vs 36.9 vs 19.9 mo • IPI/NIVO vs NIVO HR 0.63 (0.52-0.76), p<0.001 • IPI/NIVO vs IPI HR 0.52 (0.42-0.64), p<0.001 Median PFS: 11.5 vs 6.9 vs 2.9 months	ORR 45.6% vs 50.6%; CR 15% vs 13.5% Median PFS 9.9 vs 8.9 months, Median OS immature
Safety	Any grade AE, %: 95.5 vs 82.1 vs 86.2 G3-4 AE, %: 68.7 vs 43.5 vs 55.6 Discontinuation due to AE, %: 36.4 vs 7.7 vs 14.8	G3-5 AE, %: 34 vs 48, p=0.006 Discontinuation due to AE, %: 17.2 vs 28.1
Conclusion	Combination immunotherapy leads to a significant improvement in OS compared to monotherapy but is associated with higher rates of toxicity	NIVO3 + IPI1 has a significantly lower incidence of G3-5 AE compared to NIVO1 + IPI3 without differences in efficacy

RCT: randomized controlled trial; CNS: central nervous system; NIVO: nivolumab; IPI: ipilimumab; Q: every; OS: overall survival; PFS: progression free survival; AE: adverse event; G3-4: grade 3-4

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. *N Engl J Med*. 2015;373(1):23-34. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. *N Engl J Med*. 2019;381(16):1535-1546. Lebbé C, Meyer N, Mortier L, et al. *J Clin Oncol*. 2019;37(11):867-875.

CheckMate 511: Three-Year Results

Outcomes	NIVO3+IPI1 (N=180)	NIVO1+IPI3 (N=178)	HR (95% CI)
Median PFS, mo	10.2	10	1.13 (0.85-1.5)
36-mo PFS rate, %	38	43	-
Median OS, mo	NR	NR	1.03 (0.75-1.41)
36-mo OS rate, %	59	61	-

NIVO3+IPI1: nivolumab 3 mg/kg + ipilimumab 1 mg/kg; NIVO1+IPI3: nivolumab 3 mg/kg + ipilimumab 1 mg/kg; PFS: progression free survival; OS: overall survival; mo: months; HR: hazard ratio

Lebbé C, et al. *Am J Clin Oncol*. 2021; 39(15): suppl

Safety Outcomes

Adverse Events	NIVO3+IPI1 (N=180)		NIVO1+IPI3 (N=178)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Treatment-related AE, n (%)	-	33.9	-	48.3
Discontinuation due to AE, %	26	-	39	-

IMPACT: NIVO3 + IPI1 continues to demonstrate improved safety profile compared to NIVO1 + IPI3. OS rates remain numerically similar. This remains a dosing option for patients who may be high-risk for developing irAEs.

AE: adverse event; NIVO3+IPI1: nivolumab 3 mg/kg + ipilimumab 1 mg/kg; NIVO1+IPI3: nivolumab 3 mg/kg + ipilimumab 1 mg/kg; OS: overall survival; irAEs: immune-related adverse events

Lebbé C, et al. *Am J Clin Oncol*. 2021; 39(15): suppl

Immunotherapy

Preferred, category 1:

- Single agent pembrolizumab: KEYNOTE 002, 006
- Single agent nivolumab: CheckMate 037, 066
- Combination ipilimumab/nivolumab: CheckMate 067, 511

Preferred:

- Combination nivolumab/relatlimab: RELATIVITY-047

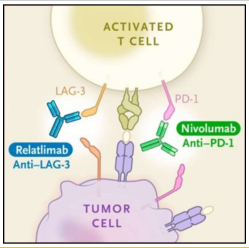
Other recommended regimens:

- Combination pembrolizumab/low-dose ipilimumab: KEYNOTE 029*

* Category 2b

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Opdualag (Nivolumab/Relatlimab)



Tawbi HA, et al. N Engl J Med. 2022 Jan 6;386(1):24-34

RELATIVITY-047

Design: randomized, double-blind, phase II/III trial

Inclusion: ≥ 12 years old, untreated and unresectable stage III/IV melanoma

Exclusion: uveal melanoma, active, untreated brain or leptomeningeal metastases, ECOG > 1, autoimmune disease, use of systemic glucocorticoids, previous systemic therapy for melanoma*

Randomized 1:1

Stratified by LAG-3 expression, PD-L1 expression, BRAF V600 mut status, and M stage

Nivolumab 480 mg / Relatlimab 160 mg every 4 weeks

N=355

Nivolumab 480 mg every 4 weeks

N=359

ECOG: Eastern Cooperative Oncology Group; mut: mutation

* Unless therapy was completed 6 months prior to disease recurrence.

Tawbi HA, et al. N Engl J Med. 2022 Jan 6;386(1):24-34

Efficacy Outcomes

Outcomes	Nivolumab/Relatlimab (N=355)	Nivolumab (N=359)	HR (95% CI); P-value
Median PFS, mo	10.1	4.6	0.75 (0.62-0.92); P=0.006
PFS at 12 mo, %	47.7	36.0	-
Median OS, mo	NR	34.1	0.80 (0.6-1.0); P=0.0593

PFS: progression free survival; mo: months; OS: overall survival; NR: not reached; HR: hazard ratio; 95% CI: 95% confidence interval

Tawbi HA, et al. N Engl J Med. 2022 Jan 6;386(1):24-34

Safety Outcomes

Adverse Events	Nivolumab/Relatlimab (N=355)		Nivolumab (N=359)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE, n (%)	345 (97)	143 (40)	339 (94)	120 (33)
Treatment-related AE, n (%)	288 (81)	67 (19)	251 (70)	35 (10)

IMPACT: Due to improved progression free survival over nivolumab monotherapy and the manageable safety profile with less grade 3/4 toxicity than IPI3 + NIVO1, nivolumab/relatlimab is now FDA approved and incorporated into the NCCN guidelines as a preferred first line agent for unresectable or metastatic cutaneous melanoma

AE: adverse event; IPI3+NIVO1: ipilimumab 3 mg/kg + nivolumab 1 mg/kg

Tawbi HA, et al. N Engl J Med. 2022 Jan 6;386(1):24-34. NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Immunotherapy

Preferred, category 1:

- Single agent pembrolizumab: KEYNOTE 002, 006
- Single agent nivolumab: CheckMate 037, 066
- Combination ipilimumab/nivolumab: CheckMate 067, 511

Preferred:

- Combination nivolumab/relatlimab: RELATIVITY-047

Other recommended regimens:

- Combination pembrolizumab/low-dose ipilimumab: KEYNOTE 029*

* Category 2b

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Combination Targeted Therapy

Preferred, category 1 if *BRAF V600*-activating mutation:

- Dabrafenib + trametinib: COMBI-v, COMBI-d
- Vemurafenib + cobimetinib: coBRIM
- Encorafenib + binimetinib: COLUMBUS

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Combination Targeted Therapy

	Trial	Treatment Arms	RR (%)	mPFS (mo)	mOS (mo)	AE, G ≥3 (%)
Treatment naive	COMBI-v	dab + tram (n=352) vem (n=352)	64 51 P<0.001	11.4 7.3 P<0.001	NR 17.2 P=0.005	52 63
	COMBI-d	dab + tram (n=211) dab + placebo (n=212)	69 53 P=0.0014	11 8.8 P=0.0004	25.1 18.7 P=0.0107	48 50
	coBRIM	vem + cobi (n=247) vem + placebo (n=248)	70 50 P<0.0001	12.3 7.2 P<0.0001	22.3 17.4 P=0.005	75 61
	COLUMBUS	encor + bini (n=192) ecor (n=194) vem (n=191)	64 52 41	14.9 9.6 7.3	33.6 23.5 16.9	64 67 66

RR: response rate; mPFS: median progression free survival; mOS: median overall survival; mo: months; AE: adverse event; G ≥ 3: grade ≥ 3; dab: dabrafenib; tram: trametinib; vem: vemurafenib; cobi: cobimetinib; encore: encorafenib; bini: binimetinib

Long GV, Stroyakovskiy D, Gogas H, et al. *N Engl J Med*. 2014;371(20):1877-1888. Robert C, Grob JJ, Stroyakovskiy D, et al. *N Engl J Med*. 2019;381(7):626-636. Dummer R, Ascierto PA, Gogas HJ, et al. *Lancet Oncol*. 2018;19(10):1315-1327. Larkin J, Ascierto PA, Dréno B, et al. *N Engl J Med*. 2014;371(20):1867-1876. Ascierto PA, McArthur GA, Dréno B, et al. *Lancet Oncol*. 2016;17(9):1248-1260.

Combination IO + Targeted Therapy

Other recommended regimens, if BRAF V600-activating mutation present:

- Vemurafenib/cobimetinib and atezolizumab: IMspire150

Not recommended by the NCCN guidelines:

- Dabrafenib/trametinib and pembrolizumab: KEYNOTE-022
- Dabrafenib/trametinib and spartalizumab: COMBI-i

IO: immunotherapy; NCCN: National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Combination IO + Targeted Therapy

Trial	Treatment Arms	RR (%)	mDOR (mo)	mPFS (mo)	mOS (mo)	AE, G ≥3 (%)
IMspire150	atezo + vem + cobi (n=256) vem + cobi (n=258)	66 65	21 12.6	15.1 10.6 P=0.0249	- -	79 73
KEYNOTE-022	pembro + dab + tram (n=60) dab + tram (n=60)	63 72	25.1 12.1	16.9 10.7 HR 0.53 (0.34-0.83)	NR 26.3 HR 0.64 (0.38-1.06)	58 25
COMBI-i	sparta + dab + tram (n=267) dab + tram (n=265)	69 64	NR 20.7	16.2 12 HR 0.82 (0.66-1.03)	NR NR	55 33

RR: response rate; mDOR: median duration of response; mPFS: median progression free survival; mOS: median overall survival; mo: months; AE: adverse events; G≥3: grade ≥3; mo: months; atezo: atezolizumab; vem: vemurafenib; cobi: cobimetinib; pembro: pembrolizumab; dab: dabrafenib; tram: trametinib; sparta: spartalizumab; nivo: nivolumab; NR: not reached; N/A: not reported;

Gutzmer R, et al.. Lancet. 2020;395:1835-1844.; Ferrucci PF, et al. J Immunother Cancer 2020;8(2):e001806; Dummer R, et al. J Clin Oncol. 2022 May 1;40(13):1428-1438.

Combination IO + Targeted Therapy

Trial, year	Treatment Arms	RR (%)	mDOR (mo)	mPFS (mo)	mOS (mo)	AE, G ≥3 (%)
IMspire150	atezo + vem + cobi (n=256) vem + cobi (n=258)	66 65	21 12.6	15.1 10.6 P=0.0249	- -	79 73
KEYNOTE-022	pembro + dab + tram (n=60) dab + tram (n=60)	63 72	25.1 12.1	16.9 10.7 HR 0.53 (0.34-0.83)	NR 26.3 HR 0.64 (0.38-1.06)	58 25
COMBI-i	sparta + dab + tram (n=267) dab + tram (n=265)	69 64	NR 20.7	16.2 12 HR 0.82 (0.66-1.03)	NR NR	55 33

NCCN other recommended regimen if a BRAF V600-activating mutation is present

RR: response rate; mDOR: median duration of response; mPFS: median progression free survival; mOS: median overall survival; mo: months; AE: adverse events; G≥3: grade ≥3; mo: months; atezo: atezolizumab; vem: vemurafenib; cobi: cobimetinib; pembro: pembrolizumab; dab: dabrafenib; tram: trametinib; sparta: spartalizumab; nivo: nivolumab; NR: not reached; N/A: not reported;

Gutzmer R, et al.. Lancet. 2020;395:1835-1844.; Ferrucci PF, et al. J Immunother Cancer 2020;8(2):e001806; Dummer R, et al. J Clin Oncol. 2022 May 1;40(13):1428-1438.

Remaining Questions / Emerging Therapy

- What is the role of **neoadjuvant therapy** for the treatment of cutaneous melanoma?
  - Currently recommended in the setting of a clinical trial for stage III, clinical node positive disease
- Is there value to **tumor infiltrating lymphocytes (TIL)** in the treatment of cutaneous melanoma?
- What is the optimal **treatment sequence** for BRAF-mutant melanoma?
  - Immunotherapy or BRAF/MEK inhibitor therapy first?
  - **DREAMseq, SECOMBIT**
- What is the **optimal duration** of therapy for cutaneous melanoma?

NCCN Clinical Practice Guidelines, Cutaneous Melanoma, v3.2022.

Audience response #2

Opdualag (nivolumab/relatlimab) gained FDA approval and incorporation into NCCN guidelines due to which of the following outcomes:

A. A statistically significant overall survival benefit observed in RELATIVITY-047
B. An 8-month progression free survival benefit over IPI3 + NIVO1
C. A 6-month progression free survival benefit over nivolumab monotherapy
D. Fewer treatment-related adverse events than nivolumab in RELATIVITY-047

Uveal Melanoma

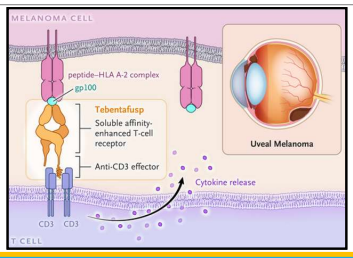
Treatment Summary

Tumor Size	Primary Treatment
Largest diameter 5-19 mm, Thickness < 2.5 mm	Brachytherapy plaque, particle beam radiation, observation
Largest diameter ≤ 19 mm Thickness 2.5-10 mm	Brachytherapy plaque, particle beam radiation, enucleation
Largest diameter > 19 mm Any thickness	Particle beam radiation, stereotactic radiation, enucleation
Any diameter Thickness > 10 mm*	Particle beam radiation, stereotactic radiation, enucleation
Metastatic	Clinical trial (preferred), liver-directed therapies, systemic therapy, resection or radiation therapy for symptomatic extrahepatic disease

* > 8 mm if optic nerve involvement

NCCN Clinical Practice Guidelines, Uveal Melanoma, v2.2022.

Tebentafusp (Kimmtrak)



Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

IMCgp 100-202

Design: open-label, phase III trial

Inclusion: ≥ 18 years old, ECOG 0-1, previously untreated HLA-A*02:01 positive patients with metastatic uveal melanoma

Exclusion: symptomatic CNS metastases, active autoimmune disease receiving systemic glucocorticoids or other immunosuppressive therapy

Primary Endpoint: OS at 12 months

Randomized 2:1

Stratified by LDH level

Tebentafusp 20 mcg IV Day 1, 30 mcg Day 8, then 68 mcg weekly

N=252

Investigator's choice

N=126

ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system; OS: overall survival; LDH: lactate dehydrogenase

Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

Efficacy Outcomes

Outcomes	Tebentafusp (N=252)	Investigator's Choice (N=126)	HR (95% CI); P-value
PFS at 6 mo, %	31	19	-
Estimated median PFS, mo	3.3	2.9	0.73 (0.58-0.94); P=0.01
OS at 12 mo, %	73	59	-
Estimated median OS, mo	21.7	16	0.51 (0.37-0.71); P<0.001

PFS: progression free survival; mo: months; 95% CI: 95% confidence interval

Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

Safety Outcomes

Adverse Events	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Treatment-related AE, n (%)	243 (99)	109 (44)	91 (82)	19 (17)
Discontinuation due to AE, %	2	-	5	-

AE: adverse event

Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

Safety Outcomes, Continued

Adverse Events	Any Grade	Grade ≥ 3
CRS, %	89	1
Rash, %	83	18
Pyrexia, %	76	4
Pruritus, %	69	4
Chills, %	47	<1
N/V, %	43 / 26	1 / <1
Fatigue, %	41	3
Erythema, Dry skin, %	23, 29	0
AST/ALT increased, %	19 / 18	4 / 3

CRS: cytokine release syndrome; N/V: nausea/vomiting; AST/ALT: aspartate aminotransferase/alanine aminotransferase

Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

Safety Outcomes, Continued

Adverse Events	Any Grade	Grade ≥ 3
CRS, %	89	1
Rash, %	83	18
Pyrexia, %	76	4
Pruritus, %	69	4
Chills, %	47	<1
N/V, %	43 / 26	1 / <1

IMPACT: Due to the overall survival benefit with tebentafusp compared to investigator's choice, tebentafusp is now FDA approved and incorporated into the NCCN guidelines as a category 1, preferred first line agent for metastatic uveal melanoma in patients who are HLA A*02:01 positive.

CRS: cytokine release syndrome; N/V: nausea/vomiting; AST/ALT: aspartate aminotransferase/alanine aminotransferase

Nathan P, Hassel JC, Rutkowski P et al. *N Engl J Med*. 2021;385(13):1196-206.

Audience response #3

Tebentafusp is a first-in-class T cell engager directed against uveal melanoma tumor cells in patients with metastatic disease who are HLA-A*02:01 positive. Which of the following statements is true regarding the IMCgp100-202 trial?

A. The estimated median overall survival seen with tebentasfusp was 21.7 months, extending survival benefit by almost 6 months compared to investigator's choice.

B. The most common adverse events of any grade in the tebentafusp group were CRS, rash, pyrexia, pruritus, and chills.

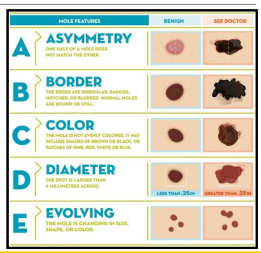
C. Both A and B

D. None of the above

Patient & Prescriber Education:
Prevention, Adherence, Toxicity Management

Prevention

- Educate patients to minimize sun and artificial UV radiation exposure
  - Avoid tanning beds and sun lamps
  - Avoid the sun between 10:00 and 16:00
  - Wear sun-protective clothing outdoors
  - Apply broad spectrum sunscreen with a Sun Protection Factor of ≥ 30 every two hours
- Educate patients to perform regular skin exams



American Academy of Dermatology. Prevent Skin Cancer. https://www.aad.org/public/diseases/skin-cancer/prevent/how. Image available at: https://familycaregiversonline.net/wp-content/uploads/ABCDE.jpg. Accessed September 18, 2022.

Systemic Therapies in Melanoma

TARGETED THERAPIES	IMMUNOTHERAPIES
Dabrafenib	Ipilimumab
Encorafenib	Nivolumab
Vemurafenib	Pembrolizumab
Binimetinib	Atezolizumab
Cobimetinib	Nivolumab/relatlimab
Trametinib	Tebentafusp

Targeted Therapy Counseling

- Educate patients on the nuances of BRAF/MEK inhibitors:
  - Administration:
    - Empty stomach vs with food
    - Twice daily vs once daily; consider total pill burden
  - Drug-drug interactions / drug-food interactions
  - Storage & handling:
    - Refrigerate vs store at room temperature
  - Side effects, and side effect management:
    - BRAF inhibitors: cutaneous squamous cell carcinoma, diarrhea, arthralgias, QTc prolongation
    - MEK inhibitors: cardiomyopathy, ocular toxicity
- Provide tips and tricks for adherence: pill box, alarm clock, calendar, family

Tafinlar [dabrafenib] [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019. Zelboraf [vemurafenib] [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2017. Braftovi [encorafenib] [prescribing information]. Boulder, CO: Array BioPharma Inc; 2019. Mekinist [trametinib] [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2019. Cotellic [cobimetinib] [prescribing information]. South San Francisco, CA: Genentech USA, Inc; 2018. Mektovi [binimetinib] [prescribing information]. Boulder, CO: Array BioPharma Inc; 2019.

Targeted Therapy Counseling, Continued

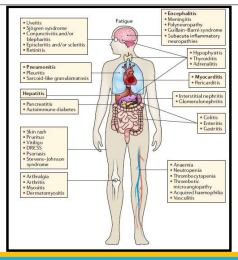
	Dabrafenib (Tafinlar®)	Vemurafenib (Zelboraf®)	Encorafenib (Braftovi®)	Trametinib (Mekinist®)	Cobimetinib (Cotellic®)	Binimetinib (Mektovi®)
PK/PD	Renal: No Hepatic: No **DDI: CYP3A4, CYP2C8**	Renal: No Hepatic: No **DDI: CYP3A4, CYP1A2**	Renal: No Hepatic: No **DDI: CYP3A4**	Renal: No Hepatic: No DDI: None	Renal: No Hepatic: No **DDI: CYP3A4**	Renal: No **Hepatic: Yes** DDI: No
Administration	150 mg BID **EMPTY STOMACH**	960 mg BID	450 mg daily	2 mg daily **EMPTY STOMACH**	60 mg daily for 21/28 days	45 mg PO BID
Preparation	50 mg, 75 mg cap	240 mg tabs	50 mg, 75 mg cap	0.5 mg, 2 mg tabs **REFRIGERATE**	20 mg tabs	15 mg tabs
Toxicities	HA, pyrexia, hyperkeratosis, hyperglycemia	Rash, CuSCC, arthralgia, diarrhea, nausea, photosensitivity	Fatigue, abdominal pain, nausea, vomiting, uveitis	Rash, diarrhea, fatigue, peripheral edema	Diarrhea, photosensitivity, nausea, vomiting	Fatigue, nausea, vomiting, abdominal pain

PK/PD: pharmacokinetics/pharmacodynamics; DDI: drug-drug interaction; BID: twice daily; cap: capsules; tabs: tablets; HA: headache; CuSCC: cutaneous squamous cell carcinoma

Tafinlar [dabrafenib] [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2019. Zelboraf [vemurafenib] [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2017. Braftovi [encorafenib] [prescribing information]. Boulder, CO: Array BioPharma Inc; 2019. Mekinist [trametinib] [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2019. Cotellic [cobimetinib] [prescribing information]. South San Francisco, CA: Genentech USA, Inc; 2018. Mektovi [binimetinib] [prescribing information]. Boulder, CO: Array BioPharma Inc; 2019.

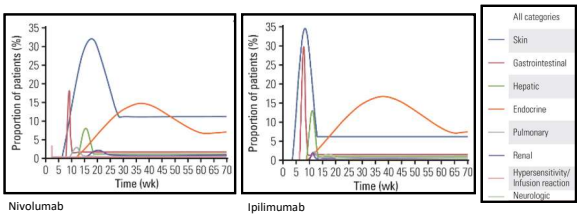
Immunotherapy Counseling

- Educate patients on the nuances of immunotherapy:
  - Administration:
    - Duration of infusion
    - Frequency of infusion
    - Novel mechanisms of action
  - Drug-drug interactions
  - Side effects:
    - Immune-related adverse events



Esfahani K, et al. Nature.2020;17:504-515. National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. v1.2022.

Immunotherapy Counseling, Continued

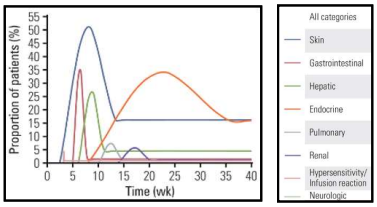


Nivolumab

Ipilimumab

Tang S, et al. Cancer Res Treat.2021;53(2):339-354. National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. v1.2022.

Immunotherapy Counseling, Continued



Ipilimumab + nivolumab

Tang S, et al. Cancer Res Treat.2021;53(2):339-354. National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. v1.2022.

Toxicity Management

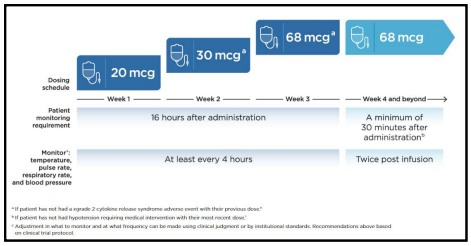
Depending on toxicity grade, initiate high-dose steroids: 0.8-2 mg/kg IV methylprednisolone or PO prednisone

If steroid refractory, initiation additional immunosuppression: infliximab or vedolizumab or mycophenolate, etc.

Taper steroids over 4-6 weeks once symptoms improve

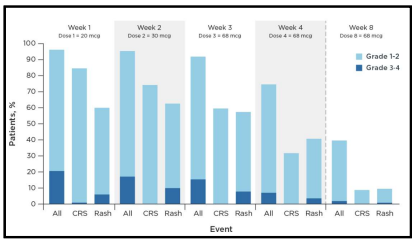
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. v1.2022.

Tebentafusp Counseling



Kimmtrak (tebentafusp) [prescribing information]. Conshohocken, PA: Immunocore Commercial LLC; February 2022.

Tebentafusp Counseling, Continued



Kimmtrak (tebentafusp) [prescribing information]. Conshohocken, PA: Immunocore Commercial LLC; February 2022.

Audience response #4

JW is a 67 YO female recently diagnosed with metastatic uveal melanoma, found to be HLA-A*02:01 positive. Her oncologist plans to start her on tebentafusp. Which of the following key points should be incorporated into patient education?

A. Tebentafusp is a new immunotherapy designed to activate the immune system to target cancer cells in patients with metastatic uveal melanoma, regardless of HLA-A*02:01 expression.

B. Tebentafusp is given once a week, intravenously, over 15 minutes. You will be observed for at least 16 hours after the first three doses to monitor for a potential side effect known of cytokine release syndrome.

C. One of the most common side effects observed with tebentafusp is a rash that can manifest as: itching, swelling, peeling, and/or dry skin. This will become milder over time.

D. Both B and C

What's New in Melanoma

CAMBREE FILLIS, PHARMD, BCOP