Improving Survival in Metastatic Uveal Melanoma

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Question

- A 53-year-old woman was diagnosed with a class 2 uveal melanoma two years ago. She underwent plaque brachytherapy. On routine surveillance she was found to have 5 liver lesions and two lung lesions. A biopsy was positive for melanoma. She is HLA A*02:01 positive. She walks two miles per day and works full time. Which is the best option for her first treatment at this time?

A. Ipilimumab and nivolumab

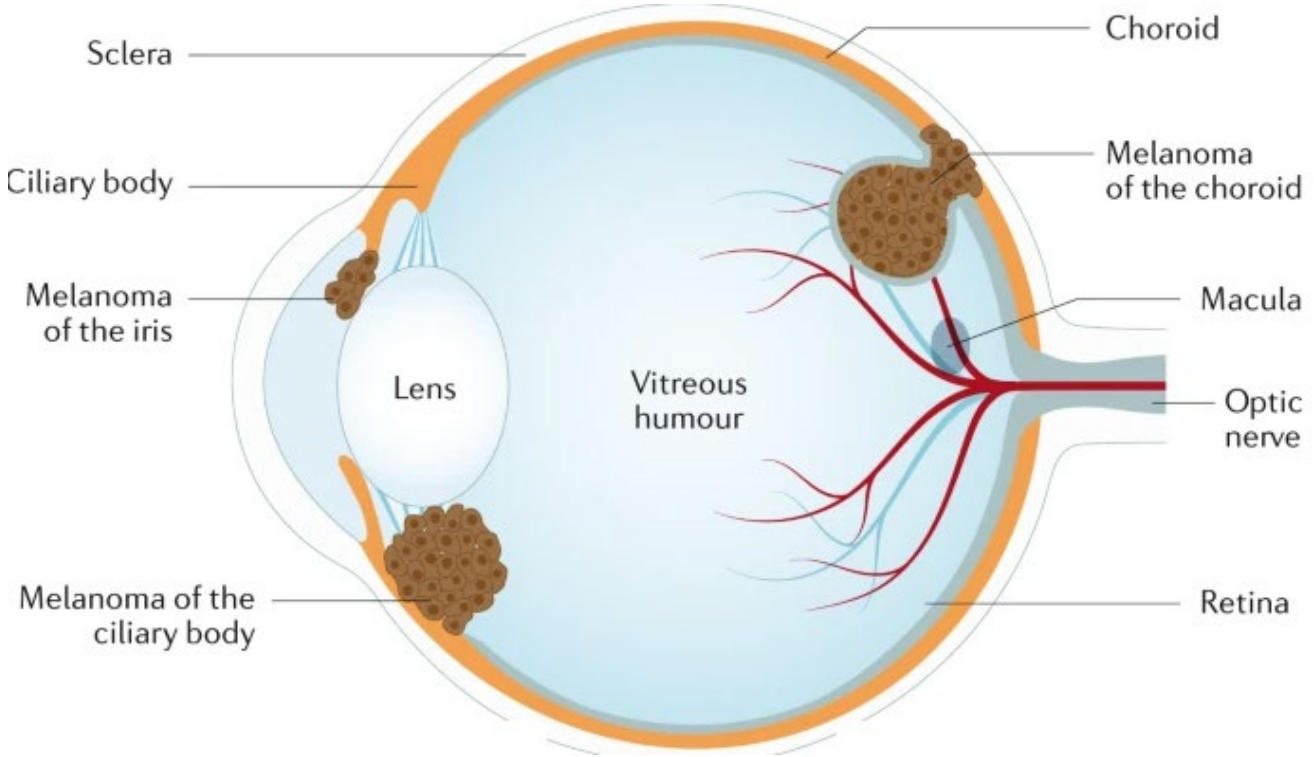
B. Tebentafusp

C. Pembrolizumab

D. Liver directed therapy

Uveal Melanoma

- Most common intra-ocular malignancy
- Risk factors include fair skin, light eye color, BAP-1 mutation
- Rare
  - 5.1 cases per million per year in U.S.



Jager, M.J., Shields, C.L., Cebulla, C.M. *et al.* Uveal melanoma

Development of Metastatic Disease

- Common sites of disease
  - Liver
  - Lung
  - Bone
- Genetic Mutations
  - Rare BRAF
  - GNAQ/GNA11
- Historically overall survival around one year

Treatment for Patients

- Liver directed therapies
- Treatment approved for cutaneous melanoma
  - Response rate significantly lower in uveal melanoma
- Tebentafusp

Liver Directed Therapies

- Surgery
  - Carefully selected patient population, most not eligible
  - Retrospective review showed of 798 patients with liver mets, only 29% were able to have R0 resections. Median OS was 14 months.
- Embolization
  - Y-90 case series with h-PFS of 5.9 months and OS of 12.3 months
  - TACE showing improvement in h-PFS, but no change in OS
- Hepatic Perfusion
  - Carefully selected patient population, expanded access only
  - PFS 8.4 months and OS 12.9 months

Eur J Surg Oncol. 2009 Nov;35(11):1192-7
Melanoma Res. 2014 Jun;24(3):244-51
Am J Clin Oncol. 2014 Jan 16
Melanoma Research. 2022 Apr; 32(2) :103-111

Systemic Options

- Ipilimumab and Nivolumab
  - Single arm phase II study with 35 patients
  - Response rate of 18% (1 CR, 5 PR)
  - PFS 6 months, OS 19 months
- Nivolumab
  - Retrospective review, 14 patients
  - ORR 7.1%, PFS, 2.3 months, OS 13.8 months
- Pembrolizumab
  - Observational study of 17 patients
  - PFS 3.8 months

J Clin Oncol. 2021;39(6):599.

Melanoma Res. 2020 Feb;30(1):76-84

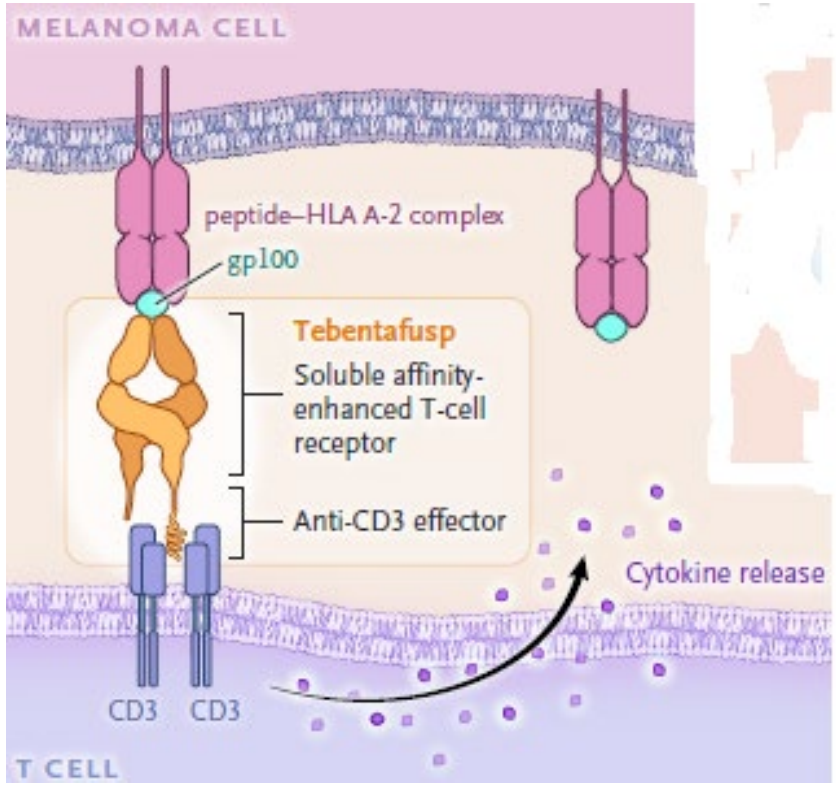
Cancer Immunol Immunother. 2019Jul;68(7):1179-1185.

Tebentafusp

- Bi-specific TCR that binds to gp100 peptide presented on HLA A*02:01 on the cancer cell with a non-specific T cell through anti-CD-3 single chain variable fragment

- First systemic therapy shown to improve overall survival in uveal melanoma

- Recent FDA approval



Overall Survival Benefit in Uveal Melanoma. N Engl J Med 2021; 385:1196-1206

Tebentafusp Phase III trial

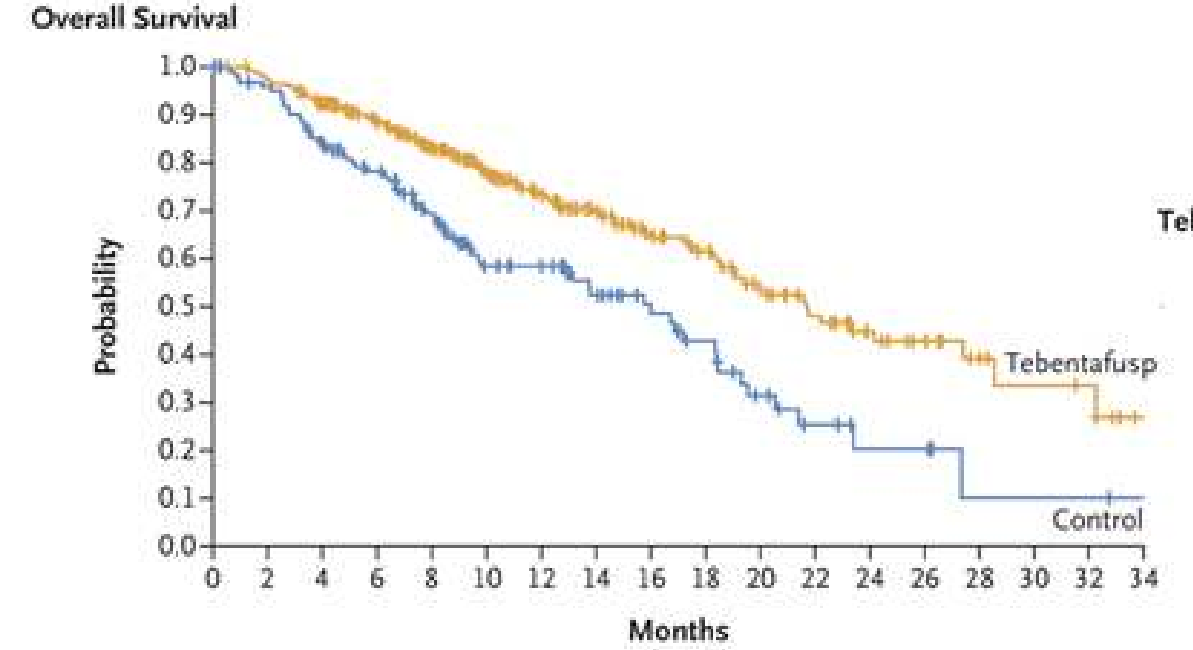
- HLA A*02:01
- No prior treatment
- Randomized 2:1 to tebentafusp vs. investigator's choice

Overall Survival Benefit in Uveal Melanoma. N Engl J Med 2021; 385:1196-1206

Administration

- Weekly doses via IV
- Dose escalation for first three doses
- First three doses given in the hospital

Results



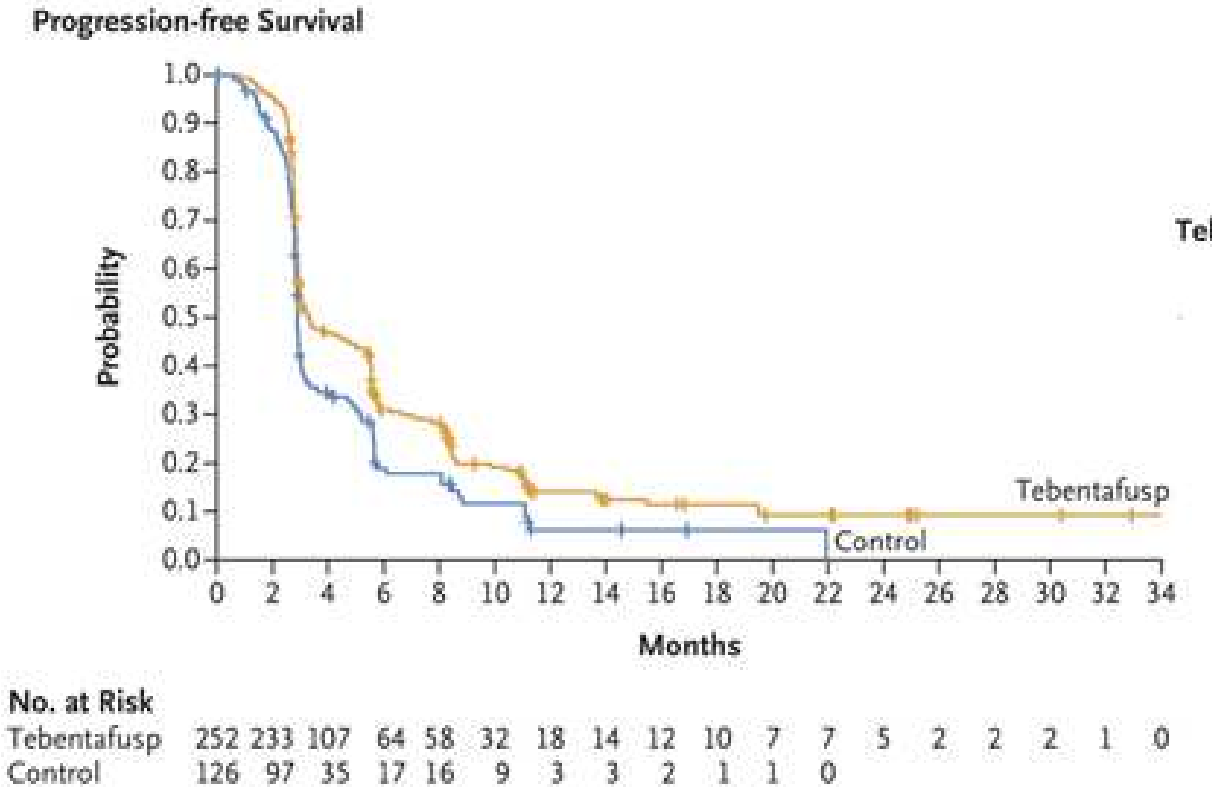
	Median Overall Survival (95% CI)
	mo
Tebentafusp	21.7 (18.6–28.6)
Control	16.0 (9.7–18.4)

Stratified hazard ratio for death, 0.51 (95% CI, 0.37–0.71)

Nathan et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N Engl J Med 2021; 385:1196-1206

Overall Survival Benefit in Uveal Melanoma. N Engl J Med 2021; 385:1196-1206

Results



	Median Progression-free Survival (95% CI)
	mo
Tebentafusp	3.3 (3.0–5.0)
Control	2.9 (2.8–3.0)

Stratified hazard ratio for disease progression or death, 0.73 (95% CI, 0.58–0.94)

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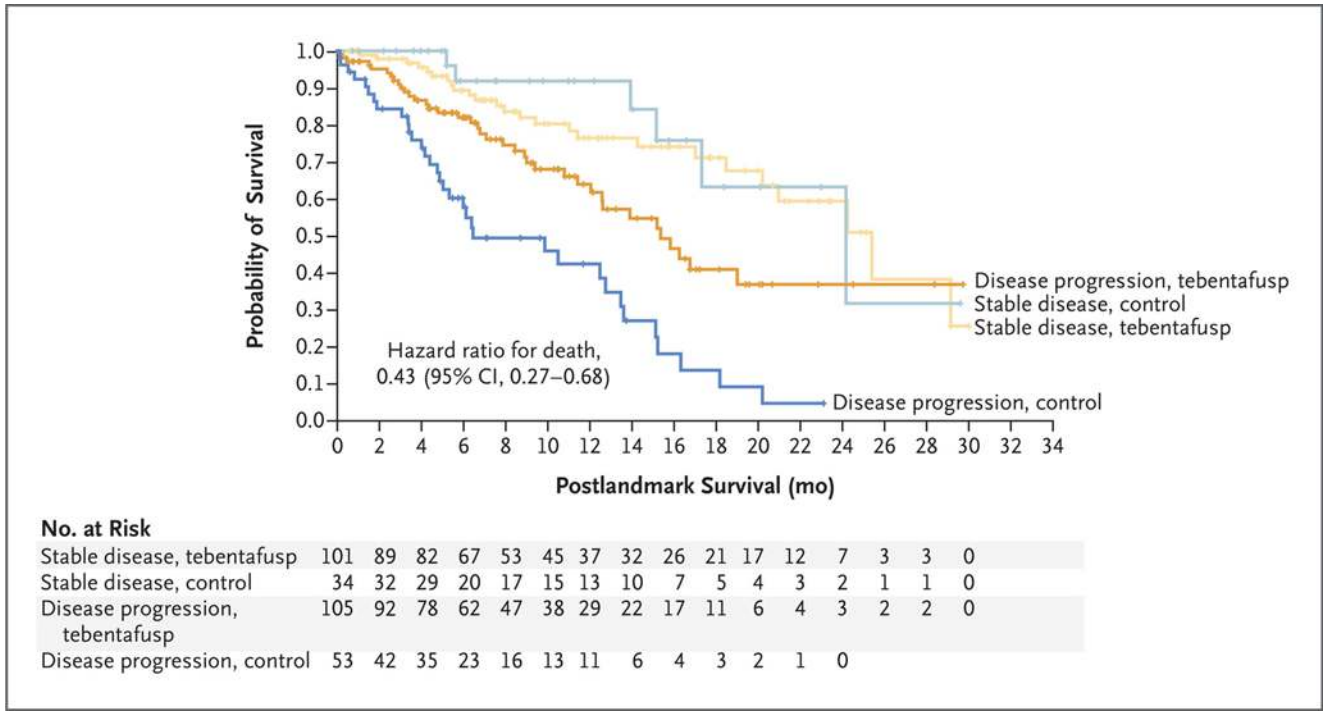
Tebentafusp

- Survival improved even if patients progressed on treatment



No. at Risk

Stable disease, tebentafusp	101	89	82	67	53	45	37	32	26	21	17	12	7	3	3	0
Stable disease, control	34	32	29	20	17	15	13	10	7	5	4	3	2	1	1	0
Disease progression, tebentafusp	105	92	78	62	47	38	29	22	17	11	6	4	3	2	2	0
Disease progression, control	53	42	35	23	16	13	11	6	4	3	2	1	0			

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Toxicity

Table 2. Treatment-Related Adverse Events (Safety Population).*

Event	Tebentafusp Group (N=245)		Control Group (N=111)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	243 (99)	109 (44)	91 (82)	19 (17)
Cytokine release syndrome†	217 (89)	2 (1)	3 (3)	0
Rash‡	203 (83)	45 (18)	27 (24)	0
Pyrexia	185 (76)	9 (4)	3 (3)	0
Pruritus	169 (69)	11 (4)	23 (21)	0
Chills	114 (47)	1 (<1)	3 (3)	0
Nausea	105 (43)	2 (1)	21 (19)	0
Fatigue	101 (41)	7 (3)	29 (26)	1 (1)
Hypotension	93 (38)	8 (3)	0	0
Dry skin	72 (29)	0	4 (4)	0
Vomiting	64 (26)	1 (<1)	7 (6)	0
Erythema	56 (23)	0	1 (1)	0
Headache	53 (22)	1 (<1)	3 (3)	1 (1)
Aspartate aminotransferase increased	47 (19)	11 (4)	9 (8)	0
Alanine aminotransferase increased	43 (18)	7 (3)	8 (7)	2 (2)
Lipase increased	32 (13)	9 (4)	7 (6)	6 (5)
Diarrhea	31 (13)	2 (1)	16 (14)	3 (3)
Lymphopenia	22 (9)	6 (2)	2 (2)	0
Hyperbilirubinemia	21 (9)	5 (2)	2 (2)	0
Hypophosphatemia	19 (8)	7 (3)	1 (1)	0
Hypertension	15 (6)	9 (4)	2 (2)	1 (1)

* Shown are treatment-related adverse event that were reported in at least 20% of patients (any grade) or in at least 2% of patients (grade ≥3) in either group.
† Cytokine release syndrome was graded according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy for consensus grading for cytokine release syndrome.[21]
‡ Rash is a composite term for a list of skin-related adverse events of any grade (see Table S2).

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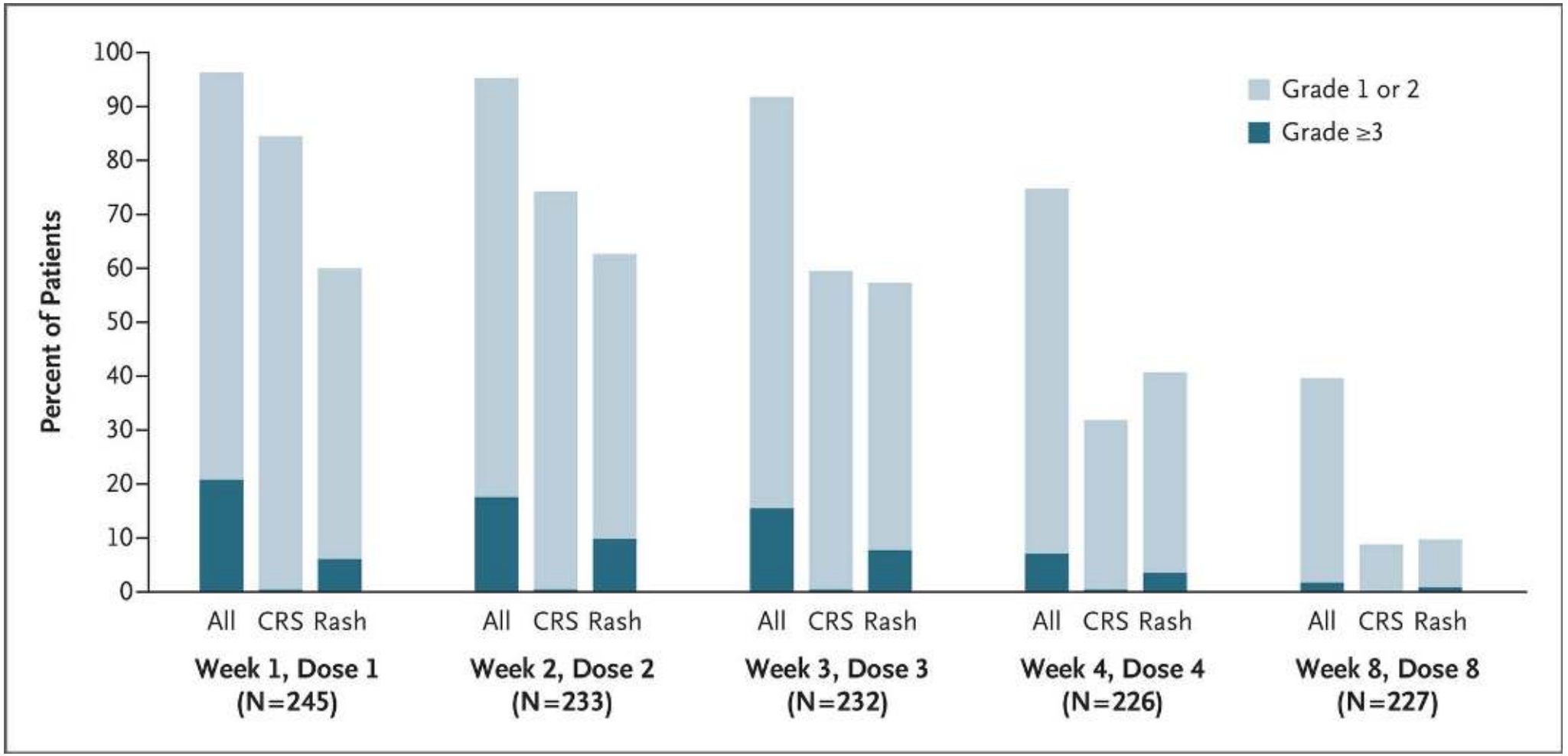
Timeline of Toxicity



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Management of Toxicity

- CRS
  - Fluids, steroids, tocilizumab
- Periorbital edema
  - Montelukast
- Rash
  - Loose fitting clothing, anti-histamines, topical steroids
- Fever
  - Anti-pyretics
- LFT abnormalities
  - Generally transient, monitor

Question

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Current Treatment Paradigm

- HLA A*02:01 positive patients
  - Tebentafusp
  - Clinical trials
- HLA A*02:01 negative patients
  - Ipilimumab and nivolumab
  - Clinical trials

Challenges in Clinical Practice with Tebentafusp

- How best to deliver care
  - Potential for significant toxicity
  - Weekly treatments
- Cost
- How to sequence therapies

Uveal Melanoma

- Tebentafusp is the first drug to improve overall survival in patient with metastatic uveal melanoma and is the new standard of care for patients who are HLA A*02:01 positive

- HLA A*02:01 negative patients need additional options

Questions and Discussion