4.33: Melanoma: Tebentafusp, Stage Migration, Adjuvant Therapy, Training with Dr. Adil Daud

Season	4
Type	Plenary Session

We Discuss:

- Introduction [0:32]
- Melanoma [11:38]
- Triple Therapy [16:00]
- Tebentafusp [22:00]
- Localized melanoma [28:41]
- Will Rogers Effect [31:41]
- IO [37:00]
- Academic Medicine [44:00]

Plenary Session 4.33 Show Notes

Overview

Conversation with Dr. Adil Daud

- **Introduction [0:32]**

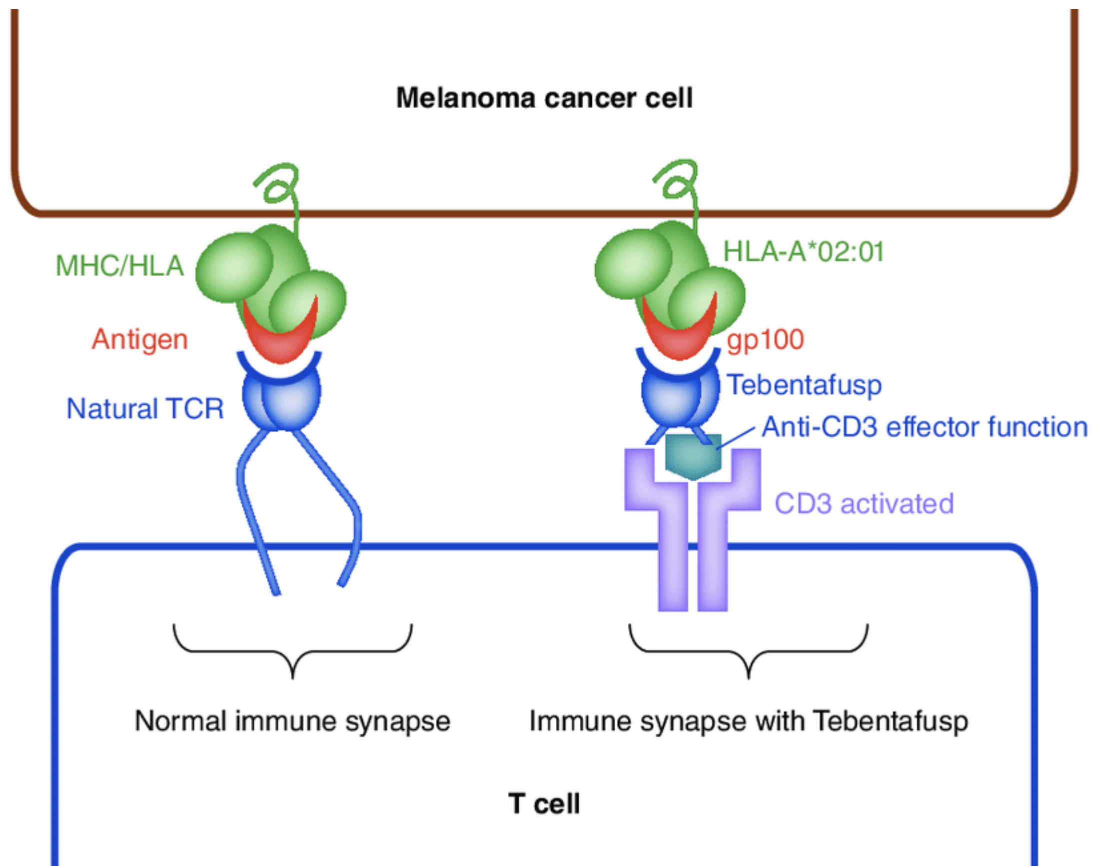
- Dr. Adil Daud is a Clinical Professor in the Department of Hematology/Oncology at UCSF
  - He is the Director of Melanoma Clinical Research at the UCSF Cancer Center
- Training
  - Dr. Daud earned his MBBS in Nagpur
    - He completed his internal medicine residency at Indiana University
      - He completed his hematology/oncology fellowship at Memorial Sloan-Kettering Cancer center

- **Melanoma [11:38]**
  - Patient populations
    - Scenario:
      - For the patient who arrives in Dr. Daud's practice with relapsed or metastatic melanoma (BRAF V600D) → what are the next steps in clinical care?
        - Option 1
          - In academia, BRAF inhibitors are seldom used for BRAF mutant patients; instead, immunotherapy is almost always used.
        - Are there are there any unusual situations where you reach for the BRAF inhibitor? What if the patient has brain metastases?
          - In the academy, unless you have symptoms of progression, seizures, or anything along those lines → steroids would not be started immediately
            - However, for many care providers, they will automatically put patients on steroids, in which case BRAF inhibitors will be administered

              > "The problem with the high volume rapidly progressive disease is that you can get a

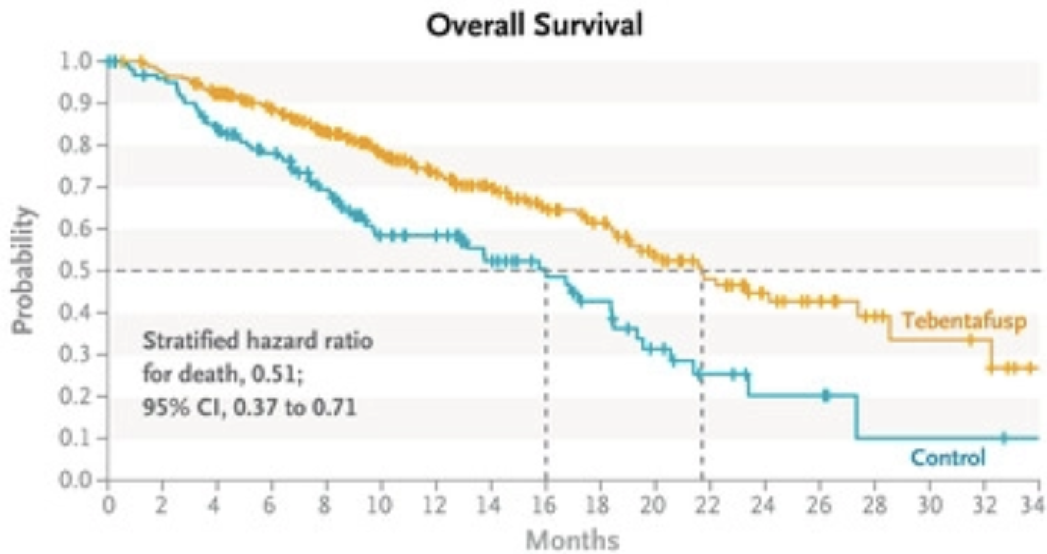
> nice response for BRAF MEK, but it's going to be a short response" - Dr. Daud

- **Triple Therapy [16:00]**
  - One major point that is brought up is:
    - Combining drugs previously used in sequence will lead to an improvement in PFS
      - But then the question is, what are you left with when the patient undergoes progression?
        - Additionally, there will be some individuals who will take benefit from a checkpoint inhibitor
          - But they will also have the BRAF/MEK inhibitors on board (which are not doing the heavy lifting) that may cause unwarranted toxicity
    - Other considerations to take note of are impacts on quality of life
      - For example, Vemurafenib, leads to extreme sun sensitivity
- **Tebentafusp [22:00]**
  - Mechanism of action



Source

- Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma
  - Nathan et al., NEJM, 2021
- Drawbacks
  - Surprisingly, tebentafusp does not function well for non-uveal melanoma
- Results



1-Year Survival		
Tebentafusp Group	73%	95% CI, 66 to 79
Control Group	59%	95% CI, 48 to 67

Treatment-Related Adverse Events

	Tebentafusp Group (N=245)	Control Group (N=111)
	number of patients (percent)	
Any Event	243 (99)	91 (82)
Grade 3 or 4 Event	109 (44)	19 (17)

CONCLUSIONS

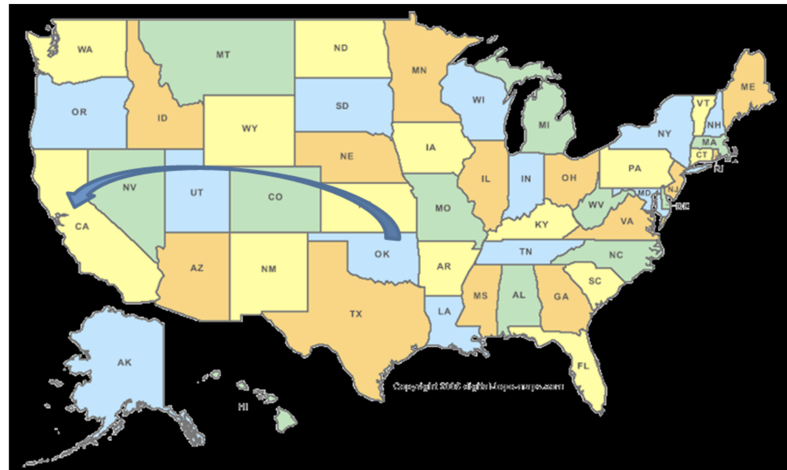
Tebentafusp provided an overall survival benefit in previously untreated patients with metastatic uveal melanoma.

Source

- **Localized melanoma [28:41]**
  - Nodal dissection

> "I think I thought of sentinel lymph node biopsy initially as as a staging tool, not as a survival enhancing kind of tool. So, to me, it is not surprising that just a nodal dissection itself doesn't improve survival" - Dr. Daud

- **Will Rogers Effect [31:41]**



"When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."

Will Rogers

Source

  - The connection to cancer staging
    - As you get better imaging, there's going to be somebody who – in 1992 – were a stage 3 patient
      - Now you the same person with a better imaging in 2012 and you're gonna find some very occult metastatic disease and they will be diagnosed as a stage 4 patient

> "It's kind of like this joke that you can get vast improvements in survival over time, merely through better stage classification" - VP

- **IO [37:00]**
  - Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)
    - Luke et al., Future Oncology, 2020
- **Academic Medicine [44:00]**
  - How is Dr. Daud able to strike a balance between his personality and the fact that he is doing something incredibly tough, and at times sad, and preserving who he is while still being able to be there for his patients?
    - Dr. Daud doesn't have any particular insight, other than the difficulties and complexities that the field requires and that it is handled on an individual basis
      - His views are also in line with VP's

> "I feel like the way I judge myself on a daily basis, even though it's always hard to lose somebody, especially somebody I've known for years, and the way I judge myself on a daily basis is: "if it weren't me in that room that day, or for that person's cancer journey, would their cancer journey have been the same?"" - VP

  - Training
    - One benefit of the apprenticeship style of teaching is that it permits you to justify your treatment choices and, and in some ways helps you clarify your thinking
      - Hopefully for the next generation of students, this learning technique is not lost to academic seminars
- **Other literature mentioned:**
  - Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation
    - Chapman et al., NEJM, 2011

- Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma
    - DREAMseq
  - KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in *BRAF*mutant melanoma
    - Ferrucci et al., Journal for Immunotherapy of Cancer
  - MSLT-2 trial
- **Other people mentioned:**
  - George Sledge, Jr.
  - Alan Houghton
  - Jedd Wolchok
  - Gilbert Ryle
  - Lawrence Einhorn
  - Jason Luke
  - David H. Lawson
  - Alexander M.M. Eggermont
  - Atul Gawande

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