The melanoma treatment landscape: past, present and future

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February 2020
Disclosures

Research Support: BMS, Novartis

Consultant: Tango Therapeutics
Cancer Death Rate in U.S. Sees Sharpest One-Year Drop

Breakthrough treatments for lung cancer and melanoma have driven down cancer mortality overall — and from 2016 to 2017 spurred the largest-ever decline.
Why have treatments been successful?

Dacarbazine


“Drought”

Ipilimumab
Vemurafenib

Encorafenib + binimetinib
Adjuvant dab + tram
Ipi + nivo

Adjuvant pembrolizumab
Nivolumab
Pembrolizumab
Dabrafenib
Trametinib
Vemurafenib +
Cobimetinib
T-VEC

Adjuvant nivolumab

High dose IL-2

Dana-Farber Cancer Institute
Pre-clinical work

- Discovery of CTLa-4
- Function of CTLa-4 in mice
- Discovery of PD-1
- Function of PD-1 in mice
- Discovery of BRAF mutations
- CTLa-4 blockade for cancer treatment in mice

1975
Dacarbazine
1980
Discovery of CTLa-4
1985
Function of CTLa-4 in mice
1990
Discovery of PD-1
1995
Function of PD-1 in mice
2000
Discovery of BRAF mutations
2005
CTLa-4 blockade for cancer treatment in mice
2010
Adjuvant nivolumab
2015
Adjuvant pembrolizumab
2020
Adjuvant dab + tram
Ipilimumab + nivo
Encorafenib + binimetinib
Ipilimumab
Vemurafenib
High dose IL-2
How does targeted therapy work?

- BRAF mutations found in ~half of melanomas
- Now three combination therapies that have demonstrated efficacy
- Other half without approved targeted options
Pros and Cons of Targeted Therapy

**Pros**
- Rapid improvement in symptoms
- Tumor shrinkage in almost all patients
- Largely tolerable
- Oral delivery

**Cons**
- Only available for BRAF-mutant melanoma patients
- Acquired resistance in most patients
How does immunotherapy work?

Adapted from: https://www.smartpatients.com/targets/pd-1
Pros and Cons of Immunotherapies

**Pros**
- Durability
- Broad activity
- Largely tolerable

**Cons**
- Influenced by tumor factors, host immune factors, and microbiome
- No clear biomarker
- Intravenous delivery
- May have delayed response

Wolchok et al, NEJM 2019
Longstanding responses to immunotherapy are possible, whereas less likely with targeted therapies.

Adapted from Luke JJ, et al.
1. How to overcome resistance to targeted therapies?

2. How to enhance immunotherapies?

   = How to determine the optimal treatment for an individual patient?

3. How to prevent/treat side effects?

4. How to treat rare, less responsive melanoma subtypes?

5. How to prevent melanoma?
Challenge 1: How do we overcome resistance to targeted therapy?

• More potent inhibitors of existing targets

• Combinations

• Intermittent dosing

• Broadening the mutations that can be targeted (other targets)
Example of combination, alternative dosing eradicates melanoma in mice

Challenge 2: How do we enhance immunotherapy?

- Combinations: 2006-2019: 3,362 clinical trials, recruiting > 500,000 patients
- Optimal combination will likely differ between patients
- Highlights need for understanding of the underlying biology and for the need for predictive biomarkers

Combination IO + targeted therapy

• Promising efficacy
• Long-term benefit still has to be proven
• 'Manageable' safety profiles, but increased toxicity of either therapy alone
• Can the same benefit be achieved with sequencing of the therapies without toxicity?

Brain metastasis

• Now some therapies that are effective with brain metastasis

Tawbi HA et al, *NEJM* 2019
Challenge 1+2: Personalizing treatment

Need to identify biomarkers associated with treatment efficacy and resistance

- **Tumor-based markers**: Mutational burden, gene mutations, gene expression
- **Host-derived markers**: Germline DNA, plasma-based markers, stromal elements
- **Environmental influences**: Gut microbiome
Challenge 3: How do prevent/treat side effects?

• Most cases we don't understand the underlying reason for the side effects

• Understanding why a side effect occurs might enable effective therapy
Challenge 3: How do prevent/treat side effects?

Exfoliative dermatitis

Challenge 4: Treat rare melanoma subtypes

Ocular Melanoma
- ~50% of patients develop metastatic disease
- 15% one-year survival for patients with metastatic disease
- Distinct biologically from cutaneous melanoma
  - No BRAF mutations
  - GNAQ, GNA11 mutations
- No standard of care therapy
- Clinical trial highly encouraged!
Challenge 5: Prevention of melanoma

- Sun avoidance or barriers, while essential, cannot be the only ways to prevent melanoma
- Intrinsic risk of melanoma in red-headed individuals may be partially UV-independent
- Mechanisms of melanomagenesis is crucial to advance this field!
Challenge 5: Prevention of melanoma

Red-headed individuals have a significantly higher risk of melanoma

Could activating the tanning pathway using drugs protect these individuals from melanoma?

Conclusions

1. Understand mechanisms of resistance and side effects

2. Rational therapy combination and sequencing regimes, predictive biomarkers

3. Guiding therapy selection for specific patients/broadening the responding patient population

4. Improving clinical outcomes for patients

RESEARCH IS THE ENGINE THAT WILL DRIVE THESE ADVANCES
Acknowledgements

Haq Lab
Cecile Gstalder, Ph.D
Priya Pancholi, M.Sc.
Dorota Sadowicz, M.Sc.
Julia Wojdylo, M.Sc.
Sascha DeVine, B.Sc.
Megha Shettighar, Ph.D
Bart Lutterbach, Ph.D

F. Stephen Hodi
G. Freeman
S. Rodig

And my patients!

Post-doctoral positions available