What’s New in Immunotherapy and Targeted Therapy?

18th Focus on Melanoma 2021 Conference

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Old Model of Cancer Care

One size fits all

Same diagnosis, same prescription
New approach that takes into account individual variability in genes, environment and lifestyle to allow doctors and researchers to predict more accurately which treatment and prevention strategy will work in which groups of patients.
One Size Does Not Fit All!
Distinct Genetic Changes in Melanoma

Superficial Spreading Melanoma
Abnormal gene: C-kit-2%
BRAF- 50%
NRAS- 20%

Lentigo Maligna Melanoma
Abnormal gene:
C-kit-2%
BRAF- 10%
NRAS- 10%

Acral Lentiginous Melanoma
Abnormal Gene:
C-kit-15%
BRAF- 15%
NRAS- 15%
Distinct Genetic Changes in Melanoma

Ocular Melanoma
Abnormal gene:
GNA11- 32%
GNAQ- 50%
BRAF < 1%

Mucosal Melanoma
Abnormal Gene:
C-kit- 20%
NRAS- 15%
BRAF- 5%
Many mutations in melanoma

- Difficult to predict which mutations will be present in a particular tumor

- Molecular profiling can help clinicians:
  - Enroll patients in clinical trials
  - Make informed therapeutic choices

Adapted from mycancergenome.org
Timeline of approvals

- **1980**: DTIC
- **2011**: Ipilimumab
- **2013**: Dabafenib (D), Trametinib (T)
- **2015**: Nivolumab
- **2020**: Cobimetinib + V

Key therapies:
- High-dose IL-2
- Vemurafenib (V)
- Encorafenib + Binimetinib
- Dabafenib (D), Trametinib (T)
- Nivolumab
- Pembrolizumab
- Cobimetinib + V
- Ipilimumab + Nivolumab
### Immunotherapy
- Interferon
- IL-2
- Ipilimumab (Yervoy)
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)
- Ipilimumab + Nivolumab
- Talimogene laherparevec, TVEC (imlygic)
- Atezolizumab + Cobimetinib + Vemurafenib

### Targeted Therapy
- Dabrafenib (Tafinlar)
- Trametinib (Mekinist)
- Vemurafenib (Zelboraf)
- Cobimetinib (Cotellic)
- Encorafenib (Braftovi)
- Binimetinib (Mektovi)
How we got here

Ipilimumab

Pembrolizumab
Nivolumab

Atezolizumab
Tumor Cell

Tumor antigens released by tumor cells

Tumor antigens presented to T cells

Tumor Cell

T cells are activated and proliferate

Activated T Cell

T cells recognize tumor antigens

Activated T Cell

T cells kill tumor cells
Immunotherapy
Immune checkpoint inhibitors

- Yervoy (ipilimumab)
- Keytruda (pembrolizumab)
- Opdivo (nivolumab)
- Tecentriq (atezolizumab)
Precision Immunotherapy

“Mutational Burden”
High numbers of mutations correlate with strong response to immunotherapy

PD-L1 expression on tumor cells
Neoantigens are more likely to occur in highly mutated tumors

Targeted therapies, including CAR/engineered T cell therapy (simple genomes, target specific therapeutic vulnerability)

Immunotherapies (complex genomes, target genetic diversity)

Lee et al Trends in Immunology May 2018
Updates in immunotherapy stage IV melanoma

Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study


Lancet Oncol 2019; 20: 1239–51

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma


N Engl J Med 381;16 NEJM.ORG October 17, 2019
Toxicity
BRAF/MEK inhibitor combinations

- Encorafenib + Binimetinib
- Cobimetinib + Vemurafenib
- Dabrafenib + Trametinib

Years:
- 1980
- 2014
- 2015
- 2018
BRAF mutations differ

Even mutations in commonly mutated genes vary between individuals.
Targeted therapy toxicity

- Pyrexia
- Rash
- Photosensitivity
- Nausea
- Arthralgias
- Abnormalities in liver enzymes
- Cardiac toxicities
- Increase in cuSCCs

ALL REVERSIBLE!!!
Triplet Therapy

Triplet Therapy involves targeting BRAF, MEK, and PD-L1/PD-1 pathways in melanoma cells. BRAF and MEK inhibitors are used to suppress proliferation, survival, invasion, and metastasis. PD-1 blockade suppresses anergy, exhaustion, and T-cell death. The activated T lymphocyte can then recognize and destroy the melanoma cell.
Triplet Therapy Trials

Vem/Cobi/Atezo vs Vem/Cobi
IMSpire150

Dab/Tram/Pembro vs Dab/Tram
Keynote-022

Dab/Tram/Sparta vs Dab/Tram
COMBI-i
What’s on the horizon

❖ Combination Trials
  • Combinations with radiation
  • Combinations with hydroxychloroquine

❖ New Targets: “Next Generation”
  • LAG-3, TIM-3, TIGIT

❖ Adoptive T Cell Therapy

❖ CAR T Cell Therapy

❖ Cancer Vaccines
Bristol Myers Squibb Announces LAG-3-Blocking Antibody Relatlimab and Nivolumab Fixed-Dose Combination Significantly Improves Progression-Free Survival vs. Opdivo (nivolumab) in Patients with Previously Untreated Metastatic or Unresectable Melanoma

MAY 19, 2021
What’s on the horizon

- **Combination Trials**
  - Combinations with radiation
  - Combinations with hydroxychloroquine

- **New Targets: “Next Generation”**
  - LAG-3, TIM-3, TIGIT

- **Adoptive T Cell Therapy**

- **CAR T Cell Therapy**

- **Cancer Vaccines**
<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
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<tbody>
<tr>
<td>RADVAX trial</td>
<td>Ipilimumab, nivolumab and radiation</td>
</tr>
<tr>
<td>LIMIT trial</td>
<td>Nivolumab and hydroxychloroquine</td>
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<tr>
<td>Umbrella trial</td>
<td>Includes rotating new drugs combined with pembrolizumab (TIGIT, CTLA-4, Lenvatanib)</td>
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<tr>
<td>BAMM trial</td>
<td>Dabrafenib, trametinib and hydroxychloroquine</td>
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In Summary

• Precision Medicine approach to cancer treatment
• Clinical Trials
• Biomarker research