Immunotherapy 101 in the Radiation Context

Jonathan Schoenfeld, M.D. M.P.H.
Associate Professor of Radiation Oncology, Harvard Medical School
Director Melanoma Radiation Oncology, Dana-Farber Cancer Institute
Director of Clinical Trial Development,
Department of Radiation Oncology, Brigham and Women’s Hospital
Disclosures

• Research support paid to institution: BMS, Regeneron, Merck
• Consulting/SAB/DMB for LEK, Catenion, ACI Clinical, Debiopharm, Immunitas
Outline

• What makes immunotherapy unique?
• Why are radiotherapy combinations appealing?
• Toxicity and response
Outline

• What makes immunotherapy unique?
• Why are radiotherapy combinations appealing?
• Toxicity and response
Understanding of T-cell biology and identification of “immune checkpoints” paved the way for modern tumor immunotherapy

- Activating receptors
  - Respond to danger signals

- Inhibitory receptors
  - Immune Checkpoints

doi:10.1038/nature10673
Cancer exploits immune checkpoints such as PD-1

https://www.ncbi.nlm.nih.gov/books/NBK65917

PD-L1 expression (brown) in squamous cell head and neck cancer
Schoenfeld et al. IJROBP 2018
Immune checkpoints have been targeted by blocking antibodies.

Hodi et al. NEJM 2010

Improvement in survival with CTLA-4 inhibitor ipilimumab in melanoma

I Mellman et al. Nature 480, 480-489 (2011) doi:10.1038/nature10673

Ipilimumab arms

Hodi et al. NEJM 2010
Immune checkpoints have been targeted by blocking antibodies.

Immune checkpoint inhibitors have led to improved outcomes across multiple different malignancy types (including melanoma, RCC, NSCLC, SCCHN, Merkel cell carcinoma, MSI high tumors, urothelial ca, cervical ca, gastric ca, TNBC, lymphoma, and others).

Nobel Prize for medicine awarded in 2018

James P. Allison (USA) and Tasuku Honjo (JPN) have won the 2018 Nobel Prize in Medicine for their discovery that the body’s immune system can be harnessed to attack cancer cells.

Hodi et al. NEJM 2010

Improvement in survival with CTLA-4 inhibitor ipilimumab in melanoma

I Mellman et al. Nature 480, 480-489 (2011)
doi:10.1038/nature10673
Immunotherapy impacts long-term survival

In contrast to other therapies, only a minority of patients demonstrate any response. However, responding patients can respond for long periods of time, or indefinitely.
Immunotherapy impacts long-term survival

In contrast to other therapies, only a minority of patients demonstrate any response. However, responding patients can respond for long periods of time, or indefinitely.

Goal: To increase the number of responding patients and maximize response.
Outline

• What makes immunotherapy unique?
• Why are radiotherapy combinations appealing?
• Relevant study endpoints
Improving systemic response rates in patients with metastatic disease

Tumor Immunity Cycle

1. Cancer antigen presentation (dendritic cells/APCs)
2. Release of cancer cell antigens (cancer cell death)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Radiation

Immune checkpoint blockade

Chen and Mellman, Immunity 2013

Ngwa, Irabor, Schoenfeld et al. Nature Reviews Cancer 2018
Improving Outcomes in Locally Advanced Disease
PACIFIC Trial – Stage 3 NSCLC
Patients Treated with Chemoradiation +/- PD-L1 Inhibition

Durvalumab Associated with Hazard Ratio for Progression of 0.53
(Response rate 10-20% in unselected metastatic NSCLC population)

Antonia, Villegas, Daniel et al. NEJM 2018
Why might the benefit of PD-L1 blockade be greater in locally advanced disease following chemoradiation?

Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients

Alexander, Schoenfeld, Trippa NEJM 2018.
Why might the benefit of PD-L1 blockade be greater in locally advanced disease following chemoradiation?

Deviation from proportional hazards, with a population of early progressors that don’t derive benefit from immunotherapy

Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients

Alexander, Schoenfeld, Trippa NEJM 2018.
Why might the benefit of PD-L1 blockade be greater in locally advanced disease following chemoradiation?

Deviation from proportional hazards, with a population of early progressors that don’t derive benefit from immunotherapy

Immunosuppressive disease burden?
Huang et al. Nature 2017

Landmark Immunotherapy Trials Demonstrate Durable Benefit in a Limited Percentage of Patients

Alexander, Schoenfeld, Trippa NEJM 2018.
Immunosuppressive tumor burden (ants)
Immunosuppressive tumor burden (ants) plus T-cells (ant traps)
Immunosuppressive tumor burden (ants) plus T-cells (ant traps) minus irradiated immunosuppressive tumor burden
= Durable Response
Emerging Data Suggests Lower Burden of Disease is Associated with Greater Benefit for Immune Checkpoint Blockade


Outline

• What makes immunotherapy unique?
• Why are radiotherapy combinations appealing?
• Toxicity and response
Clinical Data: Safety Concerns Regarding Overlapping Toxicities

Toxicities of Immune Checkpoint Blockade
Postow, Sidlow and Hellman. NEJM 2017

Common Toxicities Associated with Radiation Therapy
Toxicity Endpoints

• Initial data from clinical practice and multiple studies suggests that radiation and immune checkpoint blockade are generally well tolerated administered together (Bang and Schoenfeld Ann Pall Med 2018)

• There remain concern about long-term toxicities (including recall) and specific and overlapping toxicities (e.g. pneumonitis, lymphopenia)

• It is important but can be challenging to try to identify the etiology of toxicity in patients treated with immunotherapy radiation
Challenging to Attribute Toxicity with Combined Treatment

Right axillary radiotherapy for melanoma

Symptomatic pneumonitis 5 months following RT and 1.5 months following nivolumab therapy

Evolving change demonstrates consolidation and ground glass opacities outside of the radiation treatment field confined to the ipsilateral lung

Schoenfeld et al. JITC 2019
Response Underestimates Benefit

Hodi et al. NEJM 2010
Efficacy Parameters in Radiation Immunotherapy Studies

- Systemic Response (may be hard to interpret and correlate with clinical benefit in all cases)
  - RECIST, irRECIST, irRC
- Local response
- Overall survival

“Abscopal” responses following radiation in a patient progressing on anti-CTLA-4 therapy
Summary

- Immunotherapy provides durable improvement in survival in a limited number of solid tumor patients
- Radiation / immunotherapy combinations are being explored to help improve local or systemic responses and generate anti tumor immunity
- Immunotherapy response can be unique, and patterns of response and toxicity are important considerations with combined radiation / immune therapy
Thank you!!

jdschoenfeld@partners.org
@jdschoenfeld1