Immunotherapy and Radiation

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Disclosure

Employer: Brigham and Women’s Physicians Organization

Potential Conflicts of Interest: funded clinical trials (BMS, Merck, Regeneron), SAB (AstraZeneca, BMS, Debiopharm, Nanobiotix), Consulting (Tilos)

I will discuss investigational uses of immunotherapy and radiation.
Objectives

• To discuss the rationale for combining radiation with immunotherapy

• To review clinical data relevant to radiation / immunotherapy combination treatment

• To discuss ongoing/planned trials and considerations in clinical trial design such as potential correlative biomarkers
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Rationale for combining radiation and immunotherapy

• The immune system likely contributes to the local impacts of focal radiotherapy

• Targeted radiation can lead to immunogenic cell death and/or allow for more effective immune responses

• Synergy observed between radiation and immunotherapy in preclinical models
Importance of the immune system: Radiation is less effective in immunosuppressed preclinical models

**Text-Figure 4.**—Dose-response curves for local control of the highly immunogenic FSa in normal and TlxIR mice (replotted without individual data points from text-fig. 1) compared to curve for C3H mammary carcinoma MDAH-MCa-4, a tumor of little or no immunogenicity in these mice (16).

Stone et al. JNCI 1979

Lee et al. Blood 2009
Advancements in targeted radiotherapy

• Significant advancement over the last several decades
  – Improved accuracy
  – Decreased toxicity
  – Fewer treatments
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  – Stimulate initial immune response?
Limited response rates for immune checkpoint blockade in solid tumors: Initial immune response matters

Immune Checkpoint Blockade

How to generate an initial immune response?
Radiation leads to immunologic cell death

Dranoff et al. PNAS 1993
Radiation as “In situ vaccination”
Radiation as “In situ vaccination”

Sharabi et al. Lancet Oncology 2015
Preclinical evidence for synergy between radiation and PD-1 pathway inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Benefit</th>
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<tr>
<td>Deng et al. JCI 2014</td>
<td>TUBO (breast)</td>
<td>- Tumor growth</td>
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<td>Dovedi et al. Can Res 2014</td>
<td>4T1 (breast)</td>
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<td>Nature 2015</td>
<td>TSA (breast)</td>
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<td></td>
<td>PDA (pancreatic)</td>
<td>- Contralateral tumor growth</td>
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<tr>
<td>Zeng et al. IJROBP 2013</td>
<td>GL261 (glioma)</td>
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Zeng et al. IJROBP 2013

- Implantable glioma (GL261) luciferase model treated with small animal radiation research platform (SARRP)

- Only combination of radiation and anti-PD-1 antibody improved survival with increased infiltrating CD8+ T-cells and decreased regulatory CD4+/FoxP3+ cells
Summary: There is preclinical rationale for testing radiation and immunotherapy

- Immunotherapy enhances the LOCAL effects of radiation
- Radiotherapy potentiates the SYSTEMIC effects of immunotherapy

Adapted from Smyth et al. Nat Reviews Clin Oncol 2016
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• To discuss ongoing/planned trials and considerations in clinical trial design such as potential correlative biomarkers
Safety considerations

• Importance: Increasing numbers of patients may benefit from immune checkpoint blockade and palliative radiation
  – Expanding indications for immune checkpoint blockade
  – Indications for radiation: painful lesions, brain metastases, isolated progression (oligoprogression), locally advanced disease, etc.

• Concern: Radiation and immune checkpoint blockade have overlapping toxicities: dermatitis, pneumonitis, colitis, etc., especially with radiation fields that include lung or bowel
Retrospective analysis of 133 consecutive patients with metastatic melanoma, RCC, and NSCLC

Patients received palliative radiation and CTLA-4 and/or PD-1 blockade (105 patients received PD-1 inhibitors)

Tolerability of Radiation / Immune Checkpoint Blockade: Bang et al. IJROBP 2017
Tolerability of Radiation / Immune Checkpoint Blockade: *Bang et al. IJROBP 2017*

- Retrospective analysis of 133 consecutive patients with metastatic melanoma, RCC, and NSCLC

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Tolerability of Radiation / Immune Checkpoint Blockade: Bang et al. IJROBP 2017

- Overall rates of ir-AEs similar to those historically treated with immune checkpoint blockade alone

- Few severe (grade 3 or higher) irAE; no associations between these and site, dose or timing of radiation
Limited Rates of AE’s observed in other Retrospective / Prospective Studies

• Retrospective:
  – Ahmed et al. Annals Onc 2015 (anti-PD-1)
  – Barker et al. CIR 2013 (anti-CTLA-4)
  – Fang et al. J. Neuroonc 2016 (anti-PD-1)
  – Hwang et al. JAMA Onc 2017 (anti-PD-1)
  – Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  – Qin et al. IJROBP 2016 (anti-CTLA-4 or PD-1)

• Prospective:
  – Hiniker et al. IJROBP 2016 (anti-CTLA-4)
  – Papadopoulos et al. ASCO 2016 (anti-PD-1)
  – Powell et al. ASCO 2017 (anti-PD-1 + definitive chemoradiation in head and neck cancer)
  – Tang et al. CCR 2016 (anti-CTLA-4)
  – Williams et al. IJROBP 2017 (anti-CTLA-4, SRS/WBRT)
Attention is Needed in Future Studies and With Longer Follow up

- Nivolumab induced radiation recall pneumonitis (Shibaki et al. Annals Oncology 2017)
Safety considerations for palliative treatment

• Preliminary retrospective and prospective data suggests radiation and immune checkpoint blockade generally well tolerated – including patients treated with radiation prior to, during and after drug therapy.

• Attention is needed to monitor for associations with: rare but potentially severe side effects (e.g. myocarditis Johnson et al. NEJM 2016), delayed side effects (e.g. pneumonitis Shibaki et al. Ann. Oncol. 2017), and also enhanced radiation effects (e.g. radionecrosis Kaidar-Person et al. Anti-Cancer Drugs 2017)

• Palliative radiation and/or immune checkpoint blockade should not be deferred when of potential clinical benefit
Clinical Data: Immunotherapy may be particularly effective following radiation.

Subset analysis of Keynote-001 trial.
Shaverdian et al. Lancet Oncology 2017

PACIFIC trial: consolidation PD-L1 inhibition in stage III NSCLC.
Antonia et al. NEJM 2017
Palliative Radiation and PD-1 Inhibition

*Pike et al. Radiother & Oncol, 2017*

- Favorable results after brain radiation: melanoma, NSCLC, RCC
  - Historical controls (SEER, 2010-2013):
    - Median OS 4-6 months (Cagney et al. Neuro-Onc 2017)
  - Radiation + PD-1 inhibition:
    - Median OS 634 days (all patients)
      - Median OS = 4.3 years in melanoma patients
Palliative Radiation following PD-1 Inhibition

*Pike et al. Radiother & Oncol, 2017*

- Brigham & Women’s / Dana-Farber experience:
  - 25/52 NSCLC and melanoma patients (42%) remained on PD-1 inhibitors for a median of 179 days following radiation
  - Median survival not reached in 17 patients with isolated intracranial progression
Biologic rationale for isolated intracranial progression on immune checkpoint blockade?

Mansfield et al. Annals of Oncology 2017

CD3+ immune cells in lung metastasis

Lack of CD3+ immune cells in brain metastasis
### Prospective Studies with Radiation + Ipilimumab (CTLA-4 inhibitor)

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<td>RT given 5 days after starting ipilimumab</td>
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Development of numerous radiation / immunotherapy combination trials

- Johnson and Jagsi IJROBP 2016:
  - At least 81 ongoing trials testing radiation-immunotherapy combinations
  - Many more in development

Adapted from Johnson and Jagsi IJROBP 2016
# Ongoing & Planned Radiation + Immunotherapy Trials

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PACIFIC Trial: PD-L1 inhibition following chemoradiation in stage III NSCLC

Antonia et al. NEJM 2017
Adding immunotherapy to radiation standard of care approach

• Locally advanced SCCHN, Javelin 100 study: standard chemoradiation with cisplatin concurrent with placebo versus avelumab

• Newly diagnosed GBM, Checkmate-498 and Checkmate-548: radiation with temozolomide versus nivolumab (MGMT unmethylated) or radiation with temozolomide and nivolumab versus placebo (MGMT methylated)

• Newly diagnosed and recurrent pediatric high grade glioma and diffuse intrinsic pontine glioma, PNOC-013: Standard or hypofractionated radiation with REGN2810
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• Combining radiation with novel immunotherapy agents  
• Biomarker driven trials |
Adding radiation to immunotherapy standard of care

• Phase II Randomized Study of High Dose Interleukin-2 Versus Stereotactic Body Radiation (SBRT) and High Dose Interleukin-2 (IL-2) in Patients With Metastatic Melanoma

• DF-HCC 16-604, Targeting PD-1 Resistance with Focused High or High and Low Dose Radiation in SCCHN

Phase 1 results of SBRT + high dose IL-2
Seung et al. Science Translational Medicine 2012
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CTEP PD-L1 Team: ETCTN 10021

Rationale:
Preclinical synergy observed with the combination of PD-L1 and CTLA-4 inhibition across various models.

Low dose radiation may have clinically relevant immunologic effects (Monjazeb and Schoenfeld Lancet Oncol. 2016)


NSCLC Cohort- Cohort 1

Arm A
8Gy x 3 + durvalumab/tremelimumab

Arm B
Low-dose RT*+ durvalumab/tremelimumab

Arm C
durvalumab/tremelimumab

Continue durvalumab to progression

Colorectal Cohort- Cohort 2

Arm A
8Gy x 3 + durvalumab/tremelimumab

Arm B
Low-dose RT*+ durvalumab/tremelimumab

Continue durvalumab to progression

Initial response assessment week 7-8 then every 12 weeks.

Integrated biopsies / correlative studies to examine the impact of radiation on the TME, circulating biomarkers

Metastatic NSCLC that failed to respond to prior PD-1 or PD-L1 inhibitor

Metastatic CRC, progressive on >=1 chemotherapy regimens (exclude MSI tumors)

*0.5 Gy BID x2 days repeated q4weeks with durvalumab / tremelimumab
Translational Endpoints

• Potential predictive biomarkers for patients treated with PD-1 / PD-L1 inhibitors
  - PD-L1 expression
  - tumor infiltrating lymphocytes
  - inflammatory gene signature
  - mutational burden

• Need to study the effects of radiation +/- immune therapy on these and other factors

PD-L1 expression in glioblastoma, Berghoff et al. Neuro-Oncology 2015
Radiation impacts local and circulating immune factors

- Changes seen during and after treatment
  - Cytokines
  - Antibodies
  - T-cells
  - Immune checkpoints
  - T-cell repertoire, clonality

References:
- Hiniker et al. IJROBP 2016
- Postow et al. NEJM 2012
- Sridharan et al. Journal of Immunotherapy for Cancer 2016
- Tang et al. CCR 2016
Immune impact of chemoradiation: Adenoid Cystic Carcinoma

Local immune effects

Systemic immune effects

Sridharan et al. Cancer Immunology Research 2016
# Biomarkers in Radiation + Ipilimumab Studies

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<td>Tang et al. CCR 2016 (NSCLC, CRC, sarcoma, RCC) n=35</td>
<td>CD8/CD4 ratio, % 4-1BB+ and PD1+ T-cells. Liver RT led to increased T-cell activation</td>
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<td>Tywan-St.Victor et al. Nature 2015 (melanoma) n=22</td>
<td>Reinvigorated T-cells (&lt;= avg % of PD1/Eomes+ CD8+ T-cells with increased % of Ki67/GzmB) PD-L1 negative tumors</td>
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Summary

• Supported by preclinical data, an increasing number of prospective clinical trials are testing radiation-immunotherapy combinations
  – Radiation can play traditional (locoregional control, palliation) and potentially novel roles (immune stimulation) when combined with immunotherapy
  – Data extends beyond synergy with PD-1 inhibitors

• Incorporation of correlative studies can help examine the impact of radiation on anti-tumor immunity
• Radiation Oncology (BWH/DFCI):
  – Ayal Aizer MD
  – Brian Alexander MD MPH
  – Tracy Balboni MD MPH
  – Andrew Bang MD
  – Daniel Cagney MD
  – Daphne Haas-Kogan MD
  – Monica Krishnan MD
  – Ray Mak MD
  – Harvey Mamon MD PhD
  – Paul Nguyen MD
  – Luke Pike MD D.Phil
  – Alex Spektor MD PhD
  – Vishwajith Sridharan BS
  – Tyler Wilhite MD

• Center for Immuno Oncology & Melanoma, DFCI:
  – Elizabeth Buchbinder MD
  – Gordon Freeman PhD
  – Evisa Gjini PhD
  – Steve Hodi MD
  – Patrick Ott MD
  – Scott Rodig MD PhD
  – Mariano Severgnini PhD

• Pacific Pediatric Neuro-Oncology Consortium (PNOC):
  – Daphne Haas-Kogan MD
  – Cassie Kline MD
  – Sabine Mueller MD PhD
  – Michael Prados MD

• CTEP PD-L1 Project Team
  – Monsoor Ahmed PhD
  – Steve Hodi MD
  – Arta Monjazeb MD PhD
  – Scott Rodig MD PhD