Clinical Development of Drug-Radiotherapy Combinations

February 22-23, 2018 | Bethesda, MD

@FDAOncology @AACR @ASTRO_org @CR_UK

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Introduction

Phuoc T. Tran, MD, PhD
David G. Kirsch, MD, PhD
Targeting Molecular Pathways to Optimize Radiation and Drug Combinations

David Kirsch MD, PhD
Barbara Levine University Professor
Disclosures

• Scientific Advisory Board: Lumicell Inc.
• Stockholder in: Lumicell Inc., X-RAD Therapeutics
• Research Support from: Eli Lilly, X-RAD Therapeutics, and Merck
• Patent: co-inventor (US patent 8,983,581) of an imaging device
Bringing Science to
The City That Works
The Historic Hilton Chicago — September 23-26, 2018

Plenary Speakers:
Sandra Demaria, MD
Tyler Jacks, PhD
Cristian Tomasetti, PhD
Harald Paganetti, PhD
• Approximately 60% of cancer patients receive radiation therapy as part of their treatment
• 40% of cancer cures include the use of radiotherapy
• Can be one of the most cost-effective cancer therapies
Enhancing the Efficacy of Radiation Therapy: Premises, Promises, and Practicality

C. Norman Coleman, National Cancer Institute, Bethesda, MD
Theodore S. Lawrence, University of Michigan School of Medicine, Ann Arbor, MI
David G. Kirsch, Duke University School of Medicine, Durham, NC

Premises

- Radiation therapy is a spatially focused therapy
- Accurate radiation dosimetry to tumor and normal tissues
- Radiation is very potent in killing cancer cells
- Success is measured by increasing local control or survival

In Vitro

Coleman CN et al, Journal of Clinical Oncology 2014
Curing Cancer Requires Killing Many Logs of Cells

Figure 10.5a The Biology of Cancer © Garland Science 2007

Number of 2.0 Gy Fractions

<table>
<thead>
<tr>
<th>Total Dose (Gy)</th>
<th>Number of Tumor Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>$10^{10}$</td>
</tr>
<tr>
<td>20</td>
<td>$10^{7}$</td>
</tr>
<tr>
<td>30</td>
<td>$10^{4}$</td>
</tr>
<tr>
<td>40</td>
<td>$10^{1}$</td>
</tr>
<tr>
<td>50</td>
<td>$10^{2}$</td>
</tr>
<tr>
<td>60</td>
<td>$10^{1}$</td>
</tr>
<tr>
<td>70</td>
<td>$10^{0}$</td>
</tr>
</tbody>
</table>

Partial Response

Complete Response

Cures Possible

Courtesy of Elaine Zeman, PhD
Areas of Current and Future Focus for Radiation Research

- Modulating DNA Damage Response to Increase Radiosensitivity of Tumors
- Minimizing Radiation Toxicity to Normal Tissues/Stem Cells
- Metabolism
- Cancer Stem Cells
- Tumor Microenvironment
  - Combining Radiotherapy with Immunotherapy
  - Hypoxia, Tumor Vasculature
  - Extracellular Matrix and Physical-Mechanical Properties of Tumors
- Predictive Biomarkers
Improving the Predictive Value of Preclinical Studies in Support of Radiotherapy Clinical Trials


Coleman CN et al, Clinical Cancer Research 2016
Strategies for optimizing the response of cancer and normal tissues to radiation

Everett J. Moding¹, Michael B. Kastan¹ and David G. Kirsch¹,²

Moding EJ et al, Nature Reviews Drug Discovery 2013
Rationale for Radiation Therapy + MDM2 Inhibitor
Rationale for Radiation Therapy + MDM2 Inhibitor

NRG-DT01 (NCT03217266)
A Phase IB Trial of Neoadjuvant AMG 232 Concurrent with Preoperative Radiotherapy in Wild Type p53 Soft Tissue Sarcomas

NCI Experimental Therapeutics Clinical Trials Network (ETCTN)

PI: Meng Welliver MD, PhD
Targeting Kinases that Regulate the Response to DNA Damage

Moding EJ et al, Nature Reviews Drug Discovery 2013
SARC028 Results

- Multicenter phase II study of **pembrolizumab** for advanced soft tissue sarcoma
  - n = 40 patients (10/subtype)

<table>
<thead>
<tr>
<th>Soft-tissue sarcomas (n=40)</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (3%)</td>
<td>6 (15%)</td>
<td>15 (38%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td>Leiomyosarcoma (n=10)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>6 (60%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma (n=10)</td>
<td>1 (10%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Liposarcoma (n=10)</td>
<td>0 (0%)</td>
<td>2 (20%)</td>
<td>4 (40%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Synovial sarcoma (n=10)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>2 (20%)</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>

**UPS**: 40% response  
**LPS**: 20% response

Tawbi et al, Lancet Oncology 2017
SARC028 Results

Pre-Treatment  Post-Treatment

Tawbi et al, Lancet Oncology 2017
SU2C-SARC032 (NCT03092323)

**Aim 1:** Multi-institutional clinical trial to test the safety and efficacy of pembrolizumab and pre-operative radiotherapy to reduce the development of metastatic disease in sarcoma patients

- 1° endpoint: 2-year disease-free survival

**Aim 2:** Characterize immune response to radiotherapy with or without pembrolizumab and identify predictors of pembrolizumab response in patients with soft tissue sarcoma

PI: David Kirsch MD, PhD
SU2C-SARC032 Trial Schema

Group 1: Standard of Care Arm
- Image-guided XRT (50 Gy/25 fractions)
- 4-6 wk
- Surgery
- Follow up

Group 2: Experimental Arm
- Image-guided XRT (50 Gy/25 fractions)
- 4-6 wk
- Surgery
- Adjuvant pembrolizumab (200 mg Q3 week; up to 14 cycles for 1 yr total therapy)
- Follow up

PI: David Kirsch MD, PhD
Summary

• Tremendous Opportunity for Translation of Cancer and Radiation Research by Combining Molecularly Targeted Drugs with Radiotherapy

• To maximize success of clinical trials:
  • Rationale should be based on solid understanding of basic radiation biology
  • Pre-clinical models should be carefully selected
  • Pre-clinical data should provide compelling data for translation into clinical trials

• MDM2 inhibitor (AMG232 + RT) for p53 wild type sarcomas
• ATM inhibitor (AZD1390 + RT) for glioblastomas
• PD-1 inhibitor (Pembrolizumab + RT) for UPS and LPS
Acknowledgments

The Kirsch Lab
Katherine Castle
Amy Wisdom
Yvonne Mowery

Collaborators
Oren Becher
Meng Welliver
Dian Wang

NATIONAL CANCER INSTITUTE

SARC
STAND UP TO CANCER
MERCK
Deletion of p53 in Endothelial Cells Sensitizes Mice to Whole Heart Irradiation

Lee et al, Science Signaling 2012
Loss of *Atm* in Endothelial Cells Does Not Sensitize Mice to Whole Heart Irradiation

Moding et al, Journal of Clinical Investigation 2014
Loss of Atm Sensitizes p53 Null Endothelial Cells to Radiation

Moding et al, Journal of Clinical Investigation 2014
SESSION III:
Immunotherapy

Session Cochairs: Marka Crittenden, MD, PhD, and Andrew B. Sharabi, MD, PhD

Speakers:
Marka Crittenden, MD, PhD
Andy J. Minn, MD
Steven J. Chmura, MD, PhD
Jonathan D. Schoenfeld, MD, MPhil, MPH
Demystifying the abscopal effect

Marka Crittenden MD, PhD
EACRI, Providence Cancer Center
Portland Oregon
Disclosures

- Institutional support from BMS, Medimmune.
- Laboratory support from BMS, Jounce, Nanobiotix, NCI, NIAID
Outline

• Mechanisms of immune radiation interactions

• Dose, timing and fractionation

• Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses

• Optimizing RT as a vaccine to enhance abscopal responses
Mechanisms of interactions for radiation and immune response

- Interaction 1: Radiation can function as an *in situ* vaccine and enhance immune control of distant disease (Abscopal response)

- Interaction 2: The immune system can function to enhance control of irradiated tumors because of changes in the cancer cell and microenvironment induced by radiation (Immunogenic modulation)
Radiation therapy as an endogenous vaccine
Radiation therapy as an endogenous vaccine
Mechanisms of interactions between radiation and immune response

• Tumor antigen release and increased priming
• Tumor adjuvant release (DAMPS)
• Deletion of anergic and regulatory T cells and activation of T cells
• Antigen processing machinery and death receptor upregulation
• Cytokine and chemokine induction
• Enhanced immune cell trafficking
Radiation as an *in situ* vaccine

Two fundamental components for vaccination.

- **Antigen**—without adjuvant can lead to tolerance.
  - Has to get into Dendritic cells for priming of T cells. Low level chronic antigen release tends to lead to tolerance or anergy

- **Adjuvent**—without antigen can lead to an immune refractory period
  - DAMPS (uric acid, HMGB1, Calreticulin, dsDNA) and PAMPS (CpG, pIC, LPS)
Radiation as an *in situ* vaccine

- Priming versus Boosting
  - Priming requires higher threshold and is dendritic cell dependent. Also requires secondary lymphoid tissue. (7-10 days)
  - Boosting does not require dendritic cells, starts sooner but may require overcoming anergy and can occur in the tumor. (3-5 days)
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Release of DAMPS following radiation-Dose

B

C

ATP

HMGB1

ATP (nM/10^6 cells)

HMGB1 (ng/10^6 cells)

Dose (Gy)

Dose (Gy)

Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing

Soledad Ferrone, Monnadi L. Jannneh, Max M. Wattenberg, Kwong Y. Tsang, Selda Ferrone, and James W. Hodge
Release of DAMPS Following Radiation-Dose

Radiation fosters dose-dependent and chemotherapy-induced immunogenic cell death.

Golden EB1, Frances D1, Pellicciotta I1, Demaria S2, Helen Barcellos-Hofmann1, Formenti SC1.
Tumor antigen release and enhanced priming in preclinical mouse models-Dose
dsDNA degradation at high radiation doses

Vanpouille-Box Nat Comm 2017
Co-stimulation and Checkpoint Regulation

Best concurrent or immediate post radiation since expression is tightly regulated with antigen presentation

Best post radiation since that is when it is upregulated of T cells
Timing matters when treating with anti-OX40

Young et al PLOSone 2016
Timing dependent improvement in control of residual disease by anti-CTLA4

Young et al PLOSone 2016
T cell co-inhibition molecules and timing

- Patients with metastatic melanoma
- Treated with RT during maintenance Ipilimumab increased survival compared to during induction
- Non-randomized

Barker et al CIR, 2013
Radiation Therapy and Immunotherapy in Patients With Pancreatic Cancer
Hypofractionation preserves immune cells

![Graph](image.png)

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>ICRT</th>
<th>CRIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of patients with normal ALC for 2 consecutive measurements post RT</td>
<td>40% (4/10)</td>
<td>70% (7/10)</td>
</tr>
<tr>
<td>Mean time to normal ALC for patients that normalize</td>
<td>272 days (108-523 days)</td>
<td>50 days (all patients)</td>
</tr>
</tbody>
</table>

Crocenzi et al JITC 2016
Dose, timing and fractionation

- Dose-for endogenous vaccine effect higher is better but in some tumors the may be an inflexion point

- Timing of radiation and immunotherapy combinations will depend on agent used and preclinical may help guide testing

- Fractionation is good but too much may be bad
Outline

• Mechanisms of immune radiation interactions

• Dose, timing and fractionation

• Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses

• Optimizing RT as a vaccine to enhance abscopal responses
# Prospective Clinical Trials

<table>
<thead>
<tr>
<th>IO Agent</th>
<th>Tumor</th>
<th>Patient number</th>
<th>RT dose</th>
<th>RT site</th>
<th>ORR</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose IL-2</td>
<td>Melanoma, RCC, bladder, sarcoma</td>
<td>28</td>
<td>5Gy x 2-4</td>
<td>Multiple</td>
<td>7%</td>
<td>Lange et al Journal of Immunotherapy 1992</td>
</tr>
<tr>
<td>High dose IL-2</td>
<td>RCC</td>
<td>16</td>
<td>8Gy x 1</td>
<td>Multiple</td>
<td>12.50%</td>
<td>Redman et al CCR 1998</td>
</tr>
<tr>
<td>High dose IL-2</td>
<td>Melanoma, RCC</td>
<td>12</td>
<td>20Gy x 1-3</td>
<td>Lung and Liver met</td>
<td>66.60%</td>
<td>Seung et al Sci Tr Med</td>
</tr>
<tr>
<td>Anti-CTLA4</td>
<td>Melanoma</td>
<td>22</td>
<td>6-8Gy x 2-3</td>
<td>Multiple</td>
<td>18%</td>
<td>Tyman-Saint Victor Nature 2015</td>
</tr>
<tr>
<td>Anti-CTLA4</td>
<td>Melanoma</td>
<td>22</td>
<td>2.5-25Gy x1-15</td>
<td>Multiple</td>
<td>27%</td>
<td>Hiniker et al IJORBP 2016</td>
</tr>
<tr>
<td>Anti-CTLA4</td>
<td>Solid tumors</td>
<td>35</td>
<td>6-12.5 Gy</td>
<td>Lung and Liver met</td>
<td>10%</td>
<td>Tang et al CCR 2016</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Solid tumors</td>
<td>41</td>
<td>3.5Gy x10</td>
<td>Multiple</td>
<td>Not reported</td>
<td>Golden et al Lancet Oncology 2015</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>Solid tumors</td>
<td>73</td>
<td>10-15Gy x3-5</td>
<td>Multiple</td>
<td>13.20%</td>
<td>Luke et al JCO 2018</td>
</tr>
<tr>
<td>Anti-CTLA4</td>
<td>Melanoma</td>
<td>315</td>
<td>None</td>
<td>None</td>
<td>19%</td>
<td>Wolchok et al NEJM 2017</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td>Melanoma</td>
<td>316</td>
<td>None</td>
<td>None</td>
<td>44%</td>
<td>Wolchok et al NEJM 2017</td>
</tr>
</tbody>
</table>
Clinical Trials

- Most trials have been single arm phase I-II studies of IO agents with immunotherapy.
- Suggestion of higher response rates when combined with high-dose IL-2 if RT is given in ablative doses.
- Response rates with checkpoint inhibitors have not shown the degree of combined benefit as preclinical studies have suggested.
Outline

• Mechanisms of immune radiation interactions

• Dose, timing and fractionation

• Prospective clinical trials of radiation and IO in metastatic setting-searching for abscopal responses

• Optimizing RT as a vaccine to enhance abscopal responses
Radiation alone is a second rate vaccine
Anti-CTLA4 does not expand T cells

Shelly Bambina
Original sin and the fall of tumor

Fall of man.
Michelangelo
Figure 1. The generation and subsequent decay of concomitant immunity to growth of a tumor implant in mice bearing a progressive meth A tumor. (Top) Growth of the primary meth A tumor growing from an intradermal implant in the belly region. (Bottom) Growth of an intra-footpad implant of 10⁶ meth A cells given to control mice and to tumor-bearing mice on day 3, 6, 9, 12, or 16 of tumor growth (numbers on individual graphs). Means of five mice per group.

Figure 10. Diagrammatic representation of the immune response to a progressive immunogenic tumor of the type represented by the meth A fibrosarcoma. After the tumor reaches a critical minimum size it provides enough antigen to evoke the generation of Ly-1⁻²⁻ effector T cells. However, a short period of additional tumor growth provides antigenic conditions that favor the generation of Ly-1⁻²⁻ suppressor T cells that function to down-regulate the production of Ly-1⁻²⁺ effector T cells. Consequently, not enough effector T cells are made to destroy the tumor.
Anti-CD40L prior to challenge blocks responses
Reduced efficacy in antigen tolerant animal
Final Thoughts

• Strong rationale for radiation and IO combinations to enhance abscopal responses.
• Dose, timing of combination and fractionation should be addressed.
• We need to exercise caution in the interpretation of some of our preclinical data
• If the abscopal response depends on generating new immune responses, there may be a number of IO agents other than checkpoints that we need to be testing in the clinic.
THANK YOU
Toxicities of Radiation-Immunotherapy Combinations

Jonathan Schoenfeld MD MPH
Melanoma Radiation Oncology Director,
Center for Head and Neck Oncology
Department of Radiation Oncology, Harvard Medical School
Disclosures

Employer: Brigham and Women’s Physicians Organization

Potential Conflicts of Interest: research funding paid to the institution (BMS, Merck), Previous paid SAB (AstraZeneca, BMS, Debiopharm, Nanobiotix), Consulting (Tilos)
Introduction: Potential Synergy Can Be Accompanied by Increased Toxicity

Checkmate 067, Wolchok et al. NEJM 2017
Outline

• Toxicity concerns

• Existing and emerging clinical data

• Path forward, challenges
Outline

• Toxicity concerns

• Existing and emerging clinical data

• Path forward, challenges
Toxicities of Immune Checkpoint Blockade

- Increased immunity can lead to inflammatory side effects
- Most commonly involves: skin, GI tract, lung, endocrine glands, liver
- Rare but serious effects also reported (e.g. fatal myocarditis)
- Frequency and distribution depends on immunologic agent used
- Early identification and appropriate treatment important
- Difficult to study in animal models

Postow, Sidlow and Hellman. NEJM 2017
Toxicities of Radiation Therapy

- Impacts on more common / severe overlapping toxicities of particular interest
  - Dermatitis
  - Pneumonitis
  - Colitis
  - Hepatitis
- Important impact of dose/fractionation, field location/size, treatment technique, and concurrent therapy.
Potential for Enhancement of Local Radiation Effects with Immunotherapy

- Clinical reports of local toxicity following radiation / interferon treatment
  - Hazard et al. IJROBP 2002: neuropathy, radiation necrosis
  - Nguyen et al. Melanoma Res 2003: grade 3-4 mucositis, dermatitis
  - Perera et al. IJROBP 1997: neuropathy, stricture

Preclinical Data: Control of fibrosarcoma tumors, Stone et al. JNCI 1979
Outline

• Toxicity concerns

• Existing and emerging clinical data

• Path forward, challenges
Tolerability of Radiation / Immune Checkpoint Blockade, Bang et al. IJROBP 2017

- Retrospective analysis of 133 consecutive patients with metastatic melanoma, renal cell cancer, and lung cancer treated at 5 affiliated centers
- Patients received standard of care 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*

- Overall rates of ir-AEs similar to patients 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.
Tolerability of Radiation / Immune Checkpoint Blockade (ICB), Martin et al. JAMA Oncol 2018

• Analysis of 480 patients treated with stereotactic radiosurgery to the brain, 115 of whom were also treated with ICB

• Receipt of ICB was associated with symptomatic radiation necrosis after adjusting for tumor histology (HR 2.6, 95% CI 1.4-4.9), and particularly melanoma patients who received ipilimumab (HR 4.7, 95% CI 1.4-16.2)
Prospective Studies with PD-1 Directed Therapy: PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017

![Graph showing progression-free survival](image)

### Table 3. Adverse Events of Any Cause.

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N = 475)</th>
<th>Placebo (N = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade*</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>460 (66.8)</td>
<td>142 (29.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (15.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Pneumonitis or radiation pneumonitis†</td>
<td>161 (13.9)</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (23.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (23.3)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>87 (18.8)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (14.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (13.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (13.1)</td>
<td>21 (4.4)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>55 (11.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>58 (12.2)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (12.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>38 (22.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>36 (11.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>55 (11.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>52 (10.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>51 (10.7)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (10.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39 (8.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>36 (7.6)</td>
<td>14 (2.9)</td>
</tr>
</tbody>
</table>

*Any Grade: Grade 1, 2, 3, or 4
†Grade 4 Pneumonitis
Prospective Studies with PD-1 Directed Therapy: PD-L1 Inhibition Following Chemoradiation in Stage III NSCLC (PACIFIC), Antonia et al. NEJM 2017
Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

• Retrospective:
  – Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  – Ahmed et al. Annals Onc 2015 (anti-PD-1)
  – Anderson et al. JITC 2018 (anti-PD-1)
  – Barker et al. CIR 2013 (anti-CTLA-4)
  – Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  – Fang et al. J. Neuroonc 2017 (anti-PD-1)
  – Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  – Hwang et al. JAMA Onc 2017 (anti-PD-1)
  – Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  – Kiess et al. IJROBP 2015 (anti-CTLA-4)
  – Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  – Qin et al. IJROBP 2016 (anti-CTLA-4)
  – Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

• Prospective:
  – Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
  – Katz et al. ASCO 2017 (anti-PD-1 with neoadjuvant chemoRT in pancreatic cancer)
  – Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  – Papadopoulos et al. ASCO 2016 (anti-PD-1 with hypofractionated RT)
  – Powell et al. ASCO 2017 (anti-PD-1 with definitive chemoradiation in head and neck cancer)
  – Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  – Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  – Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)
Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- **Retrospective:**
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
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  - Anderson et al. JITC 2018 (anti-PD-1)
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  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  - Diao et al. J Neurosurg 2018 (anti-CTLA-4)
  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
  - Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  - Hwang et al. JAMA Onc 2017 (anti-PD-1)
  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

- **Prospective:**
  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
  - Katz et al. ASCO 2017 (anti-PD-1 with neoadjuvant chemotherRT in pancreatic cancer)
  - Luke et al. JCO 2018 (anti-PD-1 with SBRT)
  - Papadopoulos et al. ASCO 2016 (anti-PD-1 with hypofractionated RT)
  - Powell et al. ASCO 2017 (anti-PD-1 with definitive chemoradiation in head and neck cancer)
  - Tang et al. CCR 2016 (anti-CTLA-4 with SBRT)
  - Tywan St. Victor et al. Nature 2015 (anti-CTLA-4 with hypofractionated RT)
  - Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Conventionally fractionated chemoradiation
Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

• Retrospective:
  – Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  – Ahmed et al. Annals Onc 2015 (anti-PD-1)
  – Anderson et al. JITC 2018 (anti-PD-1)
  – Barker et al. CIR 2013 (anti-CTLA-4)
  – Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  – Fang et al. J. Neuroonc 2017 (anti-PD-1)
  – Hubbeling et al. J. Thoracic Oncol. 2018 (anti-PD-1)
  – Hwang et al. JAMA Onc 2017 (anti-PD-1)
  – Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  – Kiess et al. IJROBP 2015 (anti-CTLA-4)
  – Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  – Qin et al. IJROBP 2016 (anti-CTLA-4)
  – Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

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  – Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
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  – Welsh et al. ASTRO 2017 (anti-CTLA-4 with SBRT)
  – Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

Higher dose stereotactic body radiotherapy (SBRT) treatment
Limited Rates of Toxicities Observed in other Retrospective / Prospective Studies

- **Retrospective:**
  - Aboudaram et al. Melanoma Res 2017 (anti-PD-1)
  - Ahmed et al. Annals Onc 2015 (anti-PD-1)
  - Anderson et al. JITC 2018 (anti-PD-1)
  - Barker et al. CIR 2013 (anti-CTLA-4)
  - Colaco et al. J Neurosurg 2016 (anti-CTLA-4 or PD-1)
  - Diao et al. J Neurosurg 2018 (anti-CTLA-4)
  - Fang et al. J. Neuroonc 2017 (anti-PD-1)
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  - Kaidar-Person et al. AntiCancer Drugs 2017 (anti-CTLA-4 or PD-1)
  - Kiess et al. IJROBP 2015 (anti-CTLA-4)
  - Liniker et al. Oncoimmunology 2016 (anti-PD-1)
  - Patel et al. Am J Clin Oncol 2015 (anti-CTLA-4)
  - Qin et al. IJROBP 2016 (anti-CTLA-4)
  - Shaverdian et al. Lancet Oncol 2017 (anti-PD-1)

- **Prospective:**
  - Hiniker et al. IJROBP 2016 (anti-CTLA-4 with palliative RT)
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  - Williams et al. IJROBP 2017 (anti-CTLA-4 with SRS/WBRT)

**Hypofractionated radiation**
Attention is Needed in Future Studies and With Longer Follow up

- Nivolumab induced radiation recall pneumonitis (Shibaki et al. Annals Oncology 2017)
Outline

• Toxicity concerns

• Existing and emerging clinical data

• Path forward, challenges
Combining Standard of Care Radiation and Immunotherapy: Clinical Practice

- Concerns regarding theoretical and observed toxicity must be balanced by clinical benefit
  - Pike et al. Radiother Oncol 2017, median overall survival in melanoma patients treated with brain radiation/PD-1 inhibitors > 4 years
  - No evidence to support arbitrary time cutoffs between therapies

Outstanding Questions

• Fewer data in regards to:
  – Combinations in the definitive setting (e.g. with definitive chemoradiation, larger field radiation, etc.)
  – High dose radiation – SBRT

• Novel combinations currently being explored in the clinic
  – E.g. CTLA-4/PD-1 inhibitors; CAR-T cells, IDO inhibitors, other immune checkpoint inhibitors, intratumoral immune therapies

Lung SBRT given in combination with PD-1 inhibition on protocol.

Fractionated RT for Hodgkin’s Lymphoma. Image courtesy of Andrea Ng MD.
Challenges

• Time course of side effects can be delayed (both with immunotherapy and radiation)
  – Importance of multidisciplinary and extended follow-up after initiating combined therapy

• Attribution of side effects can be difficult (e.g. pneumonitis, elevated liver function tests, etc.)
Attributing Lung Toxicity


Summary

• Immunotherapy has unique toxicities, many of which overlap with potential radiation effects

• Initial data suggests standard of care and experimental approaches that combine radiation and immune checkpoint blockade are generally safe but more data are needed

• Challenges moving forward include lack of mechanistic understanding / biomarkers, the variability and time course with which side effects develop, rapid development of new drugs and therapies
Considerations Moving Forward

• Need for evaluation of toxicity in randomized clinical trials evaluating radiation (e.g. impact of radiation dose)

• Importance of collecting radiation data on trial and also of using multi-institutional registries / databases to evaluate toxicities and rare side-effects
  – ePRO pilot to be integrated on ETCTN protocol 10021 (Durvalumab/tremelimumab +/- low or high dose RT)

• Value for education of the multidisciplinary team as more patients receive immunotherapy in the definitive setting
SESSION III Panel Discussion:  
Immunotherapy  

**Moderators:** Marka Crittenden, MD, PhD, and Andrew B. Sharabi, MD, PhD  

**Panelists:**  
David M. Berman, MD, PhD  
Michael Yellin, MD  
Margaret K. Yu, MD  
Andy J. Minn, MD  
Steven J. Chmura, MD, PhD  
Jonathan D. Schoenfeld, MD, MPhil, MPH
SESSION IV:
Other Targeted Therapies

Session Cochairs: Theodore S. Lawrence, MD, PhD, and Ester M. Hammond, PhD

Speakers:
Kyle Cuneo, MD
Meredith A. Morgan, PhD
Ester M. Hammond, PhD
Andrew Wang, MD
Combining Chemoradiation with Novel Kinase Inhibitors

Kyle C. Cuneo, MD
Department of Radiation Oncology
University of Michigan
Disclosures

• Employee at University of Michigan
• Grant funding from NCI/NIH
Chemoradiation treatment for locally advanced cancers

Chemoradiation is standard of care for most locally advanced cancer.

Long term outcomes remain suboptimal for most sites.

Potential areas for improvement:

- Improve cure rates
- Organ preservation
- Reduce toxicity
Timeline of the development of chemoradiation regimens.

Sensitizing regimens have changed minimally since introduced.

5-FU and Related Compounds

- First described by Heidelberger et al. in 1957
- FdUMP inhibits thymidylate synthase
  - Decreases dTTP leading to:
    - Inhibition of DNA synthesis
    - Accumulation in early S phase
- FdUTP misincorporates into DNA
  - Initiates a futile repair cycle

Key:
- 5-FU: 5-fluorouracil
- dUMP: deoxyuridine monophosphate
- dUTP: deoxyuridine triphosphate
- dTTP: deoxythymidine triphosphate
- TS: Thymidylate synthase

Cisplatin

• Discovered in 1845
• Licensed for medical use in 1979
• Interferes with DNA replication
• Crosslinks DNA
• Mechanism of radiation sensitization not fully understood
Improving chemoradiation with targeted therapies

- Signal transduction
  - EGFR
  - PI3K/AKT
  - MEK/ERK
  - MET
- Cell cycle checkpoints
  - WEE1
  - CHK1
- Microenvironment
  - VEGF
  - Immunotherapy

EGFR inhibition in Head and Neck Cancer

- Cetuximab improves OS when combined with radiation alone
- Adding cetuximab to cisplatin has no benefit with more toxicity


<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Treatment arms</th>
<th>N</th>
<th>Results (red indicates statistically significant result)</th>
</tr>
</thead>
</table>
| RTOG 0522 Ang et al., 2014 Phase III | Head and neck cancer All sites | 1. Radiation with cisplatin  
2. Radiation with cisplatin + cetuximab                                         | 895 | 3 y OS: 73% chemoRT vs. 76% chemoRT + cetuximab 
3 y PFS: 61% chemoRT vs. 59% chemoRT + cetuximab 
3 y DM: 13% chemoRT vs. 10% chemoRT + cetuximab |
|                                   |                               |                                                                              |     | Grade 3-4 mucositis higher with cetuximab  
More skin toxicity with cetuximab  |
| TREMPLIN Lefebvre et al., 2013 Randomized Phase II | Head and neck cancer Larynx Hypopharynx | Induction docetaxel/cisplatin, if response:  
1. Radiation with cisplatin  
2. Radiation with cetuximab | 116 | 3 mo larynx preservation: 95% RT + cisplatin vs. 93% RT + cetuximab  
18 mo OS: 92% RT + cisplatin vs. 89% RT + cetuximab |
|                                   |                               |                                                                              |     | Treatment compliance higher in cetuximab arm  
Similar results with induction chemo followed by RT alone  |
| Italian Study Group Ghi et al. 2012, 2013 Randomized Phase II | Head and neck cancer All sites | 2 x 2 factorial design  
A. Plus or minus induction docetaxel/cisplatin/5-FU  
B. Radiation with cisplatin/5-FU or cetuximab | 421 | Complete response: 36% chemoRT vs. 39% cetuximab-RT  
Median PFS: 21.6 mo chemoRT vs. 20.7 mo cetuximab-RT  
Median OS: 44.7 mo chemoRT vs. 44.7 mo cetuximab-RT |
|                                   |                               |                                                                              |     | Primary endpoint was in field grade 3-4 toxicity:  
Mucositis 29% chemoRT vs. 23% cetuximab-RT  
Skin reaction: 11% chemoRT vs. 14% cetuximab-RT  |
| CONCERT-1 Mesia et al., 2015 Randomized phase II | Head and neck cancer All sites | 1. Radiation with cisplatin  
2. Radiation with cisplatin + panitumumab | 153 | 2 y locoregional control:  
68% chemoRT vs. 61% chemoRT + panitumumab |
|                                   |                               |                                                                              |     | Serious toxicity rate:  
32% chemoRT vs. 43% chemoRT + panitumumab  |
Nonsmall cell lung cancer: RTOG 0617

All patients

High EGFR expression
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Treatment arms</th>
<th>N</th>
<th>Results (red indicates statistically significant result)</th>
<th>Toxicity/Notes</th>
</tr>
</thead>
</table>
| RTOG 0324 Blumenschein et al., 2011 Phase II | Nonsmall cell lung cancer           | Radiation with carboplatin/paclitaxel + cetuximab                           | 93 | Response rate: 62%  
Median OS: 22.7 months  
2 y OS: 49%                                                                 | Grade 4 hematological toxicity: 22%  
Grade 3 esophagitis: 8%; G3-4 pneumonitis: 7%  
5 treatment related deaths                                                                 |
| CALGB 30407 Govindan et al., 2011 Randomized Phase II | Nonsmall cell lung cancer           | 1. Radiation with carboplatin/pemetrexed  
2. Radiation with carboplatin/pemetrexed + cetuximab | 101 | 18 mo OS: 58% chemoRT vs. 54% chemoRT + cetuximab                                                            | Grade 3+ toxicity: 76% ChemoRT vs. 85% ChemoRT + cetuximab                                                                 |
| Netherlands van den Heuvel et al., 2014 Randomized Phase II | Nonsmall cell lung cancer           | 1. Radiation with cisplatin  
2. Radiation with cisplatin + cetuximab                                      | 102 | Local control: 84% chemoRT vs. 92% chemoRT + cetuximab  
1 y OS: 82% chemoRT vs. 71% chemoRT + cetuximab                                          | Toxicity similar between groups                                                                                      |
| RTOG 0617 Bradley et al., 2015 Phase III | Nonsmall cell lung cancer           | 1. Radiation with carboplatin/paclitaxel  
2. Radiation with carboplatin/paclitaxel + cetuximab                           | 544 | Median OS: 24 mo chemoRT vs. 25 mo chemoRT + cetuximab  
High EGFR expression subset:  
Median OS: 21 mo chemoRT vs. 42 mo chemoRT + cetuximab                                                 | Grade 3+ toxicity increased with cetuximab: 86% vs. 70%                                                             |
EGFRi with chemoradiation in Rectal Cancer

### No patient selection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm 1 (n=49)</th>
<th>Arm 2 (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>TRG 0</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>TRG 1</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>TRG 2</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>TRG 3</td>
<td>35%</td>
<td>47%</td>
</tr>
<tr>
<td>TRG 4</td>
<td>33%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Most frequent G3-4 toxicities:

- Diarrhea: 16% in Arm 1, 24% in Arm 2
- Rash: 0% in Arm 1, 10% in Arm 2
- Mucositis: 5% in Arm 1, 6% in Arm 2
- Dehydration: 5% in Arm 1, 6% in Arm 2

### EXPERT-C Trial

- 90 patients
- KRAS/BRAF WT rectal cancer
- Randomized to CAPOX then CAP-RT +/- cetuximab
- Improved response rate and OS


### US Oncology Study

- 98 patients
- Randomized to 5-FU RT +/- cetuximab
- No difference in RR or PFS/OS
- Increased toxicity

# Factors Associated with EGFR Response

<table>
<thead>
<tr>
<th>Disease</th>
<th>Factors Associated with Sensitivity</th>
<th>Factors Associated with Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>Accelerated radiation fractionation</td>
<td>HPV negative tumor</td>
</tr>
<tr>
<td></td>
<td>Acneiform rash (cetuximab)</td>
<td>Smoker</td>
</tr>
<tr>
<td></td>
<td>Oropharynx primary</td>
<td>Non-oropharynx primary</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>EGFR mutation: exon 19 and 12 (L858R, L861), exon 18 (G719X, G719), exon 20 (S768I)</td>
<td>EGFR T790M mutation</td>
</tr>
<tr>
<td></td>
<td>KRAS wild type</td>
<td>EGFR exon 20 insertion</td>
</tr>
<tr>
<td></td>
<td>EGFR overexpression</td>
<td>KRAS mutation</td>
</tr>
<tr>
<td></td>
<td>Non-squamous cell histology</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Non-smoker</td>
<td>MET amplification/overexpression</td>
</tr>
<tr>
<td></td>
<td>Asian heritage</td>
<td>Epithelial to mesenchymal transition</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>RAS wild type</td>
<td>KRAS mutation</td>
</tr>
<tr>
<td></td>
<td>BRAF wild type</td>
<td>NRAS mutation</td>
</tr>
<tr>
<td></td>
<td>Increased EGFR gene copy number</td>
<td>BRAF mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MET amplification/overexpression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2 amplification/overexpression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EGFR mutation in cetuximab binding domain (rare)</td>
</tr>
</tbody>
</table>
Scheduling of Chemoradiation with targeted therapies

- Drug schedule affects radiosensitivity
- Delivering the optimal sequence in patients is challenging
- Suboptimal sequencing may lead to missed opportunities for patients

Cuneo et al. Unpublished data.
Scheduling Cetuximab with Chemoradiation

Drug Concentration

Cetuximab loading week 0 (blue)
Weekly cetuximab during radiation (blue)
Cisplatin every 3 weeks (orange)
Radiation 5 days/week

Positive Effects of EGFR inhibition:
- Blocks repopulation
- Inhibits RT induced signaling (AKT/ERK)
- Attenuates DNA repair

Negative effects of EGFR inhibition:
- Antagonizes cisplatin
- Blocks redistribution
- Compensatory heterodimerization

Potential issues:
- Loading dose antagonizes chemotherapy
- Long half life affect cell cycle redistribution

Potential solutions:
- Eliminate loading dose
- EGFR inhibitor with shorter half life

VEGFi in Rectal Cancer: Impact of Scheduling

• **Rationale:**
  - VEGF/VEGFR inhibition normalizes vasculature
  - Increases delivery of systemic therapy
  - Improves oxygenation

• **Clinical Data**
  - 14 reported phase II studies in rectal cancer
  - CR rates range from 11-34%
  - Concern for postoperative complications

Impact of Scheduling

Complete regression rate: Schedule A 12% vs. Schedule B 50%

Conclusions

• Chemoradiation regimens have evolved very slowly
• Novel targeted therapies can change current treatment paradigms
• Previous studies limited by scheduling and patient selection
• Optimizing scheduling and target selection is essential for success
• Need for improved preclinical models
• Need for biomarker based patient selection
The potential of DNA damage response (DDR) inhibitors in combination with radiation treatment

Meredith Morgan, PhD
• I receive research funding from AstraZeneca.
• I will not discuss any off-label uses.
Rationale for combining DDR inhibitors with radiation

Strategies for development of DDR inhibitors with radiation:
- Integration with chemoradiation
- DDR-DDR inhibitor combinations with radiation
- DDR-immunotherapy combinations with radiation
Radiation is the most prescribed cancer therapy. Major technological advancements in radiation delivery have maximized tumor radiation doses given in combination with full systemic doses of chemotherapy for most locally advanced cancers. Chemoradiation escalated to maximum tolerated dose; more radiation or additional chemotherapy is not feasible. Further improvements in treatment will require tumor cell selective agents.
DNA is the principal target of radiation.

Radiation-induced cell death is caused by unrepaired DNA double-strand breaks.

Inhibition of the DNA damage response improves radiation therapy efficacy and has the potential to improve survival in patients with clinically advanced cancer\(^1, 2\).

--

Molecular responses to radiation

Stop proliferation

Pause DNA synthesis

Tumor cell survives radiation treatment
Poly ADP ribose polymerase (PARP) inhibitors prevent protective cellular responses. They inhibit major repair pathways, leading to unrepaired damage and replication stress. Tumor cell death occurs after radiation treatment due to cell division with DNA damage, aberrant origin firing, replication stalling, and fork instability. Examples of PARP inhibitors include Olaparib, Veliparib, and Talazoparib.
Mutations present in cancer cells but not normal cells cause replication stress and defective DNA damage responses.

These tumor cell defects can be exploited therapeutically. DDR inhibitors are *synthetically lethal* with these tumor defects.

Radiation induces damage specifically in tumor cells that differentiates this process. Radiation may broaden the therapeutic efficacy of DDR inhibitors to tumor cells without defined mutations.
• DDR inhibitors used to sensitize tumor cells to chemotherapy and radiation
• Potential to simultaneously improve systemic and local disease control
• As sensitizers, lower doses (relative to monotherapy) can be effective
• AZD1775 (WEE1 inhibitor) is most extensively studied

Current clinical trials

<table>
<thead>
<tr>
<th>DDR inhibitor</th>
<th>Chemo-RT</th>
<th>Tumor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD1775</td>
<td>Gem-RT</td>
<td>Pancreatic</td>
<td>1</td>
</tr>
<tr>
<td>AZD1775</td>
<td>Tem-RT</td>
<td>GBM</td>
<td>1</td>
</tr>
<tr>
<td>AZD1775</td>
<td>Cis-RT</td>
<td>HNSCC</td>
<td>1</td>
</tr>
</tbody>
</table>
Improvements in pancreatic cancer therapy are urgent.

Median survival:
- Metastatic: <1 year
- Locally advanced: 1 year
- Resectable: 2 years

Locally advanced refers to surgically unresectable, but not overtly metastatic.

Chemoradiation is standard-of-care.

Both local and systemic control are important.

Effective control is the only hope for surgery and potential cure.
36 patient trial

Objectives:
Determine target dose and toxicity of AZD1775 in combination with gemcitabine-radiation
Determine WEE1 inhibition by AZD1775 in surrogate biomarkers and evaluate efficacy

Reference & Kyle Cuneo
Treatment of a pancreatic cancer patient with AZD1775

Pretreatment 6 months after treatment with AZD1775 and GemRT

went on to have resection with negative margins.

Still alive with no evidence of disease 2.5 years after diagnosis
01775 with Gem-RT for locally advanced pancreatic cancer

Median overall survival: 22.6 months
Historical control median overall survival: 11 months
Strategic combinations of DDR inhibitors may have greater therapeutic benefit.

Most combinations induce profound radiosensitization (e.g. WEE1-PARP)\(^1\)

Only some combinations are therapeutic without radiation (e.g. ATR-PARP)

These DDR-DDR inhibitor combinations may alleviate the need for cytotoxic chemotherapy in chemoradiation regimens and thus reduce toxicity.

---

**Strategy 2: DDR-DDR inhibitor combinations**

<table>
<thead>
<tr>
<th>DDR inhibitor combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNAPK</td>
</tr>
<tr>
<td>ATR</td>
</tr>
<tr>
<td>WEE1</td>
</tr>
</tbody>
</table>
E1-PARP inhibitor combination proficient MiaPaCa2 cells

Surviving Fraction of cytotoxic activity but robust potentiation of radiosensitization
Inhibition overcomes PARP inhibitor resistance

HR proficient MiaPaCa2 cells

HR deficient MiaPaCa2 cells

Surviving Fraction

Surviving Fraction

Olaparib (μM)

Olaparib (μM)

Con + Dox\(^{(72h)}\)

Control
100 nM AZD6738
300 nM AZD6738
1 μM AZD6738
PARP inhibition has synergistic cytotoxic and radiosensitizing activity.
Strategy 2: DDR-DDR inhibitor combinations with radiation

Clinical trials underway with several DDR-DDR inhibitor combinations
Integration of radiation should increase the therapeutic benefit of these combinations

**Current clinical trials**

<table>
<thead>
<tr>
<th>Agent 1</th>
<th>Agent 2</th>
<th>RT</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD6738 (ATR)</td>
<td>Olaparib (PARP)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AZD1775 (WEE1)</td>
<td>Olaparib (PARP)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AZD0156 (ATM)</td>
<td>Olaparib (PARP)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>
Radiation causes release of damaged DNA or chromosomes from the nucleus.

DNA in cytoplasm is recognized as foreign and activates an innate immune response.

Inhibitors of the DDR may increase this response.

Increased innate immunity should synergize with immune checkpoint therapy.

[Reference: Nature Immunology, 17:1142-49, 2016]
Radiation enhances immunotherapy efficacy\textsuperscript{1} 
Preclinical data show potential benefit of PARP inhibition\textsuperscript{2} 
In contrast, DNA-PK inhibition may be antagonistic\textsuperscript{3} 
DDR and immunotherapy agents are being tested clinically 
Integration of radiation will be important in future trials

Current clinical trials

<table>
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<th>RT</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>AZD6738 (ATR)</td>
<td>MEDI4736 (PD-L1)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Olaparib (PARP)</td>
<td>MEDI4736 (PD-L1)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AZD1775 (WEE1)</td>
<td>MEDI4736 (PD-L1)</td>
<td>-</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Twyman-Saint Victor et al., Nature 520:373-7, 2015
\textsuperscript{2}Jiao et al., Clin Cancer Res 23:3711-20, 2017
\textsuperscript{3}Harding et al. Nature, 2017
Looking to the future

Historically very difficult to develop experimental agents as radiosensitizers

WHAT IS CHANGING!

As treatment of metastatic cancer improves, therapy for locally advanced cancers will become increasingly important. The demand for new combination radiation treatment regimens will increase.

The biology of DDR (and immunotherapy) agents warrants radiation combination studies

Integration with standard-of-care chemoradiation or radiation is the most logical path to approval
Acknowledgements

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Immunology
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University of Michigan Health System
National Cancer Institute
Hypoxia – Success and Failure

Ester M. Hammond

FDA-AACR-ASTRO Workshop on Radiotherapy Combinations, February 2018
Hypoxia – insufficient oxygen

**Normoxia**
Atmospheric O₂ pressure (20.9 %). The pO₂ where most pre-clinical testing is carried out.

**Physioxia, Physioxia, Tissue normoxia**
The normal pO₂ in specific tissues/organs.
- e.g. Brain 4.6% O₂, Intestine 8.0% O₂,
- Skin 2.8% O₂, liver 4.1% O₂

**Hypoxia**
Low O₂ levels, indicating that the tissue/organ has insufficient O₂. Associated with HIF-1 stabilisation.

**Radiobiological hypoxia**
The level of hypoxia where significant resistance to radiation is observed (<0.13% O₂)

Hammond/Williams Clinical Oncology 2014
Why do we care about hypoxia?

**Chemotherapy**
Effective drug delivery and activity is compromised in hypoxic/acidic tumour regions. Adaption to hypoxia promotes chemoresistance.

*Most chemotherapies are less effective*

**Surgery**
The biological response to hypoxia includes increased motility and invasion and therefore metastasis.

*Tumour is more likely to have spread at time of treatment*

**Radiotherapy**
In the presence of oxygen, radiation leads to the formation of reactive radicals which damage DNA.

*Hypoxic tumour cells receive up to 3 times less DNA damage during radiotherapy*

**Increased genomic instability and decreased DNA repair**

**RESISTANCE TO THERAPY AND POOR PATIENT PROGNOSIS**

Hammond/Williams Clinical Oncology 2014
Why do we care about hypoxia?

Hockel et al., 1999 Cancer Research

Toustrup et al., Radiother and Oncol 2012
Should we target tumour hypoxia?

• Many studies have demonstrated that hypoxia correlates with poor prognosis
• Hypoxic/anoxic cells are radiation resistant
• Hypoxic cells are more motile/invasive
• Hypoxia is one of the most significant differences between tumour and normal tissue

*At the very least we should verify that therapies work in hypoxia*
What strategies have we come up with for targeting hypoxia?

- Hyperbaric oxygen (HBO)
  - Increased radiotherapy related toxicity, oxygen seizures
  - Cumbersome and difficult to provide for all patients

- Oxygen mimics
  - Some toxicity problems but nimorazole is tolerated and used in the treatment of HNSCC in Denmark
  - NIMRAD currently testing nimorazole + IMRT in HNSCC (UK)

- CARBOGEN (95% O₂: 5% CO₂ or 98% O₂:2% CO₂)
  - BCON, phase III improved overall survival in bladder cancer
  - ARCON, phase III significant gains in regional control rates HNSCC

- Hypoxia activated prodrugs/cytotoxins
  - e.g. Tirapazamine, Evofosfamide
Hypoxia activated prodrugs – a beautifully simple concept

Drug delivery
Level of hypoxia required
Relevant enzymes must be expressed
High expression of reductases in liver
Should only work in patients with hypoxic tumours

Hunter et al., British Journal of Cancer 2016
Tirapazamine
TROG 02.02, HeadSTART – no evidence of benefit of adding TPZ in HNSCC
- Poor radiotherapy delivery (25% of patients had noncompliant plans)
- Poorly managed drug toxicity
- No selection of patients based on tumour hypoxia

Evofosfamide (TH302)
MAESTRO trial – little to no advantage in pancreatic and soft tissue sarcoma
- No selection of patients based on tumour hypoxia

Peters et al., J Clin Oncol 2010
For a medal position – we need to pick the right patients

- Needle electrodes
- Hypoxia signatures
- Serological markers
- Imaging
- Tissue based biomarkers
Has our preclinical testing been good enough?

Mouse to Human
- Pharmacology
- Biology
- Are we hitting the target?
- Do we have reliable biomarkers?

Is the drug in the right place at the right time, at the right concentration?

CAIX (hypoxia)
All NSCLC xenografts 100-200 mm3
Overall indications are that hypoxia modification works but...

<table>
<thead>
<tr>
<th>Endpoint: Loco-regional failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Hypoxic modification Control</td>
</tr>
<tr>
<td>Normobaric oxygen</td>
</tr>
<tr>
<td>1970</td>
</tr>
<tr>
<td>1973</td>
</tr>
<tr>
<td>1979</td>
</tr>
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<td>2005</td>
</tr>
<tr>
<td>2010</td>
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<tr>
<td>Subtot</td>
</tr>
<tr>
<td>Hyperbaric oxygen</td>
</tr>
<tr>
<td>1971</td>
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<tr>
<td>1973</td>
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<td>1979</td>
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<td>1980</td>
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<td>1999</td>
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<td>Hypoxic sensitizer</td>
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<tr>
<td>1982</td>
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<td>1995</td>
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<td>1996</td>
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<tr>
<td>1999</td>
</tr>
<tr>
<td>2006</td>
</tr>
<tr>
<td>Subtotal (hypoxic sensitizer)</td>
</tr>
<tr>
<td>All trials with hypoxic modification</td>
</tr>
</tbody>
</table>

Meta Analysis - Hypoxic modification of radiotherapy in HNSCC

Overgaard J 2011 Radiotherapy and Oncology
New approaches: Reduce oxygen consumption
Atovaquone alleviates hypoxia in spheroid and xenograft models

Ashton et al., Nat Commun 2016
Atovaquone leads to increased radiosensitivity
ATovaquone as Oxygen Modifier

‘Window of opportunity trial’ in NSCLC patients prior to surgical resection

• **NOT** an efficacy study in unselected patients

• Biomarker driven proof of concept study

• Does atovaquone reduce tumour hypoxia in patients?

• Can we stratify patients who will respond?

• Robust, affordable biomarker?
Cohort 1 (Atovaquone group)

- Surgical outpatient visit. Cohort 1 Patient Information Sheet given
- Consent obtained. Medical history
  - **Baseline hyp-PET-CT, pCT, DWI-MRI and DCE-MRI. Baseline bloods including osteopontin, miR210, VEGF, CAIX. Start atovaquone.**
  - **Repeat hyp-PET-CT, pCT, DWI-MRI and DCE-MRI. Repeat bloods including osteopontin, miR210, VEGF, CAIX, plasma atovaquone measurement.**
- Pimonidazole administered and atovaquone stopped
- Tumour resected, fixed with formalin, and orientated to correlate with hyp-PET-CT imaging. In cases where orientation is difficult, MRI of the resected tumour will be performed.
- Tumour sectioned after discussion with pathology. GCP lab [IHC analysis will include CAIX, pimonidazole, CD31 and CD146. Tumour mRNA extraction for gene expression quantification, tumour DNA extraction for mutational analysis, HPLC analysis of tumour atovaquone concentration.](#)
How do we get a hypoxic cell sensitiser for use with radiation?

**Better drugs** – *must confirm activity in patients*

**Better trials** – *must stratify patients*

Have to **overcome negative perceptions**

**Clinical champions** to carry out the trials

Government and/or industrial **investors** to pay for the trials

Acknowledgments

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Oxford Institute for Radiation Oncology
Manchester 1824
The University of Manchester
ICRR 2019
Manchester 25-29 Aug

@Hammond_Lab
@The_OIRO
SESSION IV Panel Discussion:
Other Targeted Therapies

Moderators: Theodore S. Lawrence, MD, PhD, and Ester M. Hammond, PhD

Panelists:
Gideon M. Blumenthal, MD
Özlem Ataman, MD, PhD
Kyle Cuneo, MD
Meredith A. Morgan, PhD
Andrew Wang, MD
SESSION IV: Discussion Questions

• Why are there no novel agents registered in combination with radiotherapy in recent years despite the increase in clinical studies?

• Could the first registration of a novel agent be in combination with radiotherapy?

• Are there any specific surrogate endpoints (i.e. loco-regional control, pCR) to accelerate registration in combination with radiotherapy?

• Is there a need for guidelines from regulatory agencies on the elements/design of registration for radiation combinations studies?
Prognostic and Predictive Biomarkers in (Radiation) Oncology

Daniel Spratt, MD
Associate Chair, Clinical Research
Chair, Genitourinary Division Clinical Research
Director, Spine Oncology Program
No relevant disclosures
Objectives

- Understand the difference in a prognostic and predictive biomarkers
- Understand methods to use these biomarkers for drug approval combinations with radiotherapy
Biomarkers

- **Prognostic**: Real world personalized medicine

- **Predictive**: Ultimate personalized medicine
How do you “prove” a biomarker is predictive?

• To determine whether a biomarker is potentially predictive or prognostic, a formal **test for an interaction** between the biomarker and treatment group needs to be performed.

• Basically:
  – You are testing an interaction between the **treatment group**, **biomarker**, and **outcome**, and it should be statistically significant.
Validated Biomarkers

- **Examples of prognostic biomarkers:** *Thousands*
  - Prostate cancer: Decipher, Oncotype, Prolaris
  - Breast: Ki-67
  - GBM: MGMT

- **Examples of predictive biomarkers:** *Very few*
  - Colon: Ras
  - Lung: EGFR, ROS, Alk
  - Breast: ER, Her2
  - Melanoma: Braf
  - Mismatch repair
  - DNA damage repair
Predictive Biomarker - Colorectal Cancer and Ras

**Ras wildtype**
- CT + cetuximab (n = 178)
- CT (n = 189)
- No. of events: 130 vs. 154
- Median, months: 28.4 vs. 20.2
- 95% CI: 24.7 to 31.6 vs. 17.0 to 24.5
- HR: 0.69, 95% CI: 0.54 to 0.88

**Ras mutant**
- CT + cetuximab (n = 246)
- CT (n = 214)
- No. of events: 216 vs. 182
- Median, months: 16.4 vs. 17.7
- 95% CI: 14.9 to 18.4 vs. 15.4 to 19.6
- HR: 1.05, 95% CI: 0.86 to 1.28

**TESTING MATTERS!**
### Biomarkers used for FDA Drug Approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker gene</th>
<th>Indication</th>
<th>Original (O) or supplemental (S) approval</th>
<th>Accelerated Approval or regular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-Trastuzumab Emantansine</td>
<td>ERBB2</td>
<td>Breast cancer</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Afatinib</td>
<td>EGFR</td>
<td>Lung cancer</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>ESR1, PGR</td>
<td>Breast cancer (early stage)</td>
<td>S</td>
<td>accelerated</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>ESR1, PGR</td>
<td>Breast cancer (advanced stage)</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>KRAS</td>
<td>Colorectal cancer</td>
<td>S</td>
<td>NA</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK</td>
<td>Lung cancer</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>BRAF</td>
<td>Melanoma (single agent)</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>BRAF</td>
<td>Melanoma (with trametinib)</td>
<td>S</td>
<td>accelerated</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>BCR/ABL1</td>
<td>Blood cancer</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Denileukin Diftitox</td>
<td>IL2RA</td>
<td>Other</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>Lung cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Everolimus</td>
<td>ERBB2</td>
<td>Breast cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Everolimus</td>
<td>ESR1</td>
<td>Breast cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Exemestane</td>
<td>ESR1</td>
<td>Breast cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>ESR1</td>
<td>Breast cancer</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Imatinib</td>
<td>KIT</td>
<td>Blood cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Imatinib</td>
<td>BCR/ABL1</td>
<td>Blood cancer (Ph + ALL, adult patients)</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Lapatinib (with capecitabine)</td>
<td>ERBB2</td>
<td>Breast cancer</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Lapatinib (with letrozole)</td>
<td>ERBB2</td>
<td>Breast cancer</td>
<td>S</td>
<td>accelerated</td>
</tr>
<tr>
<td>Letrozole</td>
<td>ESR1, PGR</td>
<td>Breast Cancer (early stage)</td>
<td>S</td>
<td>accelerated</td>
</tr>
<tr>
<td>Letrozole</td>
<td>ESR1, PGR</td>
<td>Breast cancer (advanced stage)</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>Colorectal cancer</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>KRAS</td>
<td>Colorectal cancer</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>ERBB2</td>
<td>Breast cancer (Metastatic)</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>ERBB2</td>
<td>Breast cancer (Neo-adjuvant)</td>
<td>S</td>
<td>accelerated</td>
</tr>
<tr>
<td>Trametinib</td>
<td>BRAF</td>
<td>Melanoma</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2</td>
<td>Metastatic Breast cancer</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2</td>
<td>Breast cancer, adjuvant</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>ERBB2</td>
<td>metastatic gastric adenocarcinoma</td>
<td>S</td>
<td>regular</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>Melanoma</td>
<td>O</td>
<td>regular</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>ALK</td>
<td>Lung cancer</td>
<td>O</td>
<td>accelerated</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>del (5q)</td>
<td>Blood cancer</td>
<td>O</td>
<td>regular</td>
</tr>
</tbody>
</table>

Biomarkers used for FDA Drug Approvals

<table>
<thead>
<tr>
<th>Drug/biomarker</th>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>N_bm</th>
<th>n</th>
<th>Outcome</th>
<th>HR or OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole/ESR1-PGR</td>
<td>Phase 3 RCT</td>
<td>9366</td>
<td>8607</td>
<td>7839</td>
<td>768</td>
<td>TTP (HR)</td>
<td>0.78 (0.63–0.93)</td>
<td>1.12 (0.80–1.58)</td>
</tr>
<tr>
<td>Celuximab/KRAS</td>
<td>Study 10152</td>
<td>Phase 3 RCT</td>
<td>337</td>
<td>233</td>
<td>134</td>
<td>PFS (HR)</td>
<td>0.57 (0.36–0.91)</td>
<td>1.83 (1.10–3.10)</td>
</tr>
<tr>
<td>CRYSRAL</td>
<td>Phase 3 RCT</td>
<td>1198</td>
<td>540</td>
<td>192</td>
<td>348</td>
<td>PFS (HR)</td>
<td>0.68 (0.50–0.94)</td>
<td>1.07 (0.71–1.61)</td>
</tr>
<tr>
<td>Study 3</td>
<td>Phase 3 RCT</td>
<td>572</td>
<td>394</td>
<td>230</td>
<td>164</td>
<td>OS (HR)</td>
<td>0.55 (0.41–0.74)</td>
<td>0.98 (0.70–1.37)</td>
</tr>
<tr>
<td>Everolimus/ESR1</td>
<td>IES</td>
<td>Phase 3 RCT</td>
<td>4724</td>
<td>4702</td>
<td>4042</td>
<td>DFS (HR)</td>
<td>0.75 (0.64–0.87)</td>
<td>0.79 (0.55–1.14)</td>
</tr>
<tr>
<td>Fulvestrant/ESR1</td>
<td>Studies 20 &amp; 21 Phase 3 RCT</td>
<td>924</td>
<td>734</td>
<td>655</td>
<td>79</td>
<td>Response (CR)</td>
<td>1.18 (0.78–1.79)</td>
<td>0.63 (0.18–2.12)</td>
</tr>
<tr>
<td>Lapatinib/ERBB2</td>
<td>EGFR300039</td>
<td>Phase 3 RCT</td>
<td>1286</td>
<td>1171</td>
<td>219</td>
<td>PFS (HR)</td>
<td>0.71 (0.53–0.96)</td>
<td>0.90 (0.77–1.05)</td>
</tr>
<tr>
<td>Panitumumab/KRAS</td>
<td>Study 1</td>
<td>Phase 3 RCT</td>
<td>463</td>
<td>427</td>
<td>243</td>
<td>PFS (HR)</td>
<td>0.45 (0.34–0.59)</td>
<td>0.99 (0.73–1.36)</td>
</tr>
<tr>
<td>PMR</td>
<td>Phase 3 RCT</td>
<td>1186</td>
<td>597</td>
<td>486</td>
<td>PFS (HR)</td>
<td>0.73 (0.59–0.90)</td>
<td>0.89 (0.68–1.16)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Validated Biomarkers in Radiation Oncology

• **Examples of prognostic biomarkers**: Thousands
  – Prostate cancer: Decipher, Oncotype, Prolaris
  – Breast: Ki-67
  – GBM: MGMT

• **Examples of predictive biomarkers**: NONE
There is not a single prospectively validated clinical grade biomarker that has been shown to determine who selectively benefits from radiotherapy or to guide radiotherapy dose.

The complexity of interactions of RT with tumor cells, immune cells, microenvironment, circulating disease, host, limitations of preclinical models, have been a formidable opponent.

Bottom line: Tumor cell radiosensitivity is not enough.
• Another method for use of biomarkers in radiation oncology for drug approval is to leverage:
  – Prognostic biomarkers or
  – Develop predictive biomarkers for the combination agents that may have unique biological synergy with radiotherapy.
**Side note:** ADT may be the best example of a near pure radiosensitizer that is proven clinically AND provides synergy

Persistently viable disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT</td>
<td>100%</td>
</tr>
<tr>
<td>RT</td>
<td>40%</td>
</tr>
<tr>
<td>RT+ADT</td>
<td>20%</td>
</tr>
</tbody>
</table>

Is this synergy?
Side note: ADT may be the best example of a near pure radiosensitizer that is proven clinically AND provides synergy

HR for PCSM

Observation vs ADT 1.0
ADT vs RT + ADT 0.44
Surgery vs Surgery + ADT 1.0
RT vs RT + ADT ~0.3-0.5

Addition of ADT to RT does not increase radiation side effects (GI/GU)
- In contrast to chemo
• A story of prognostic and predictive biomarkers in prostate cancer and how they could be used for drug approval...
• The most common treatments in prostate cancer include:
  – Radiotherapy
  – Androgen deprivation therapy (ADT)
  – Taxane chemotherapy

We have no predictive biomarkers to guide their use.
Complex interplay between DNA repair and Androgen signaling

Polkinghorn W, et al, Cancer Discovery 2013
Complex interplay between DNA repair and Androgen Signaling

Opportunity to develop a predictive biomarker for ADT to benefit men receiving radiotherapy
The Decipher test, aka 22-gene expression classifier is one of the most well validated prognostic biomarkers in localized and recurrent prostate cancer.
Decipher is a robust prognostic biomarker to predict metastatic outcome.

Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

**Cumulative Incidence of Metastasis (%)**

- **Decipher Risk**
  - Low
  - Intermediate
  - High

**Time (years post-RP)**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
<th>Weights, % (random effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kernes et al</td>
<td>235</td>
<td>1.59 (1.34 to 1.88)</td>
<td>30</td>
</tr>
<tr>
<td>Den et al</td>
<td>139</td>
<td>1.7 (1.12 to 2.58)</td>
<td>4.9</td>
</tr>
<tr>
<td>Ross et al</td>
<td>260</td>
<td>1.48 (1.3 to 1.69)</td>
<td>49.5</td>
</tr>
<tr>
<td>Glass et al</td>
<td>224</td>
<td>1.48 (1.14 to 1.95)</td>
<td>11.8</td>
</tr>
<tr>
<td>Freedland et al</td>
<td>117</td>
<td>1.46 (0.91 to 2.35)</td>
<td>3.8</td>
</tr>
<tr>
<td>Overall</td>
<td>975</td>
<td>1.82 (1.39 to 1.67)</td>
<td></td>
</tr>
</tbody>
</table>

**F² = 0%**

**P = .95**

Spratt DE et al, JCO 2017
Decipher independently predicts metastatic outcome

Individual Patient-Level Meta-Analysis of the Performance of the Decipher Genomic Classifier in High-Risk Men After Prostatectomy to Predict Development of Metastatic Disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>MVA (decipher as continuous)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log2 preoperative PSA level, ng/mL</td>
<td></td>
<td>1.10 (0.88 to 1.38)</td>
<td>.417</td>
</tr>
<tr>
<td>RP Gleason score ≤ 3 + 4</td>
<td></td>
<td>ref</td>
<td>1</td>
</tr>
<tr>
<td>RP Gleason score 4 + 3</td>
<td></td>
<td>2.40 (1.22 to 4.72)</td>
<td>.011</td>
</tr>
<tr>
<td>RP Gleason score ≥ 8</td>
<td></td>
<td>2.97 (1.60 to 5.51)</td>
<td>.001</td>
</tr>
<tr>
<td>Positive surgical margins</td>
<td></td>
<td>1.57 (0.96 to 2.58)</td>
<td>.075</td>
</tr>
<tr>
<td>Extraprostatic extension</td>
<td></td>
<td>1.92 (0.99 to 3.75)</td>
<td>.054</td>
</tr>
<tr>
<td>Seminal vesicle invasion</td>
<td></td>
<td>1.91 (1.18 to 3.11)</td>
<td>.009</td>
</tr>
<tr>
<td>Lymph node invasion</td>
<td></td>
<td>1.78 (0.98 to 3.26)</td>
<td>.06</td>
</tr>
</tbody>
</table>
| Decipher*                        |                              | 1.30 (1.14 to 1.47)   | < .001
Integrating prognostic biomarkers with clinicopathologic staging

Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

**Total cohort**

(N = 6,928)

**Retrospective training cohort**
- Pretreatment clinical data
- RP genomic data
- Years: 1997-2004
  (n = 756)

**Retrospective validation cohort**
- Pretreatment clinical data
- Biopsy genomic data
- Years: 1995-2005
  (n = 235)

**Prospective cohort I**
- Pretreatment clinical data
- RP genomic data
- Years: 2014-2016
  (n = 4,960)

**Prospective cohort II**
- Pretreatment clinical data
- Biopsy genomic data
- Year: 2016
  (n = 977)

- Assessing prognostic performance of NCCN risk groups
- Development and validation of clinical-genomic risk groups
- Discriminatory analyses

- Genomic characterization of NCCN risk groups and clinical-genomic risk groups
- Reclassification analyses
Biomarker derived risk groups are highly prognostic

Development and Validation of a Novel Integrated Clinical-Genomic Risk Group Classification for Localized Prostate Cancer

**RT + ADT**
Prognostic biomarkers can be used in clinical trials to potentially identify the patient subset that will benefit most from therapy.

**Prognostic biomarkers**

- Prognostic biomarkers can be used in clinical trials to potentially identify the patient subset that will benefit most from therapy.

**Schema**

**Step 1 Registration**
Submission of tissue for Decipher Post-OP analysis

**Note:** Decipher analysis results must be completed before STEP 2 randomization can occur***

**Androgen deprivation therapy**

**Step 2 Randomization**

**Stratify**

<table>
<thead>
<tr>
<th>Decipher risk category</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Average</td>
<td>1.0</td>
</tr>
<tr>
<td>High</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Randomize 1:1**

- **Arm 1**
  - External Beam Radiation
  - Starting 8 weeks after initiation of ADT
  - 68.4 Gy/1.8 Gy/fraction
  - **Plus**
    - Androgen Deprivation Therapy*
      - LHRH Agonist/antagonist
    - **Plus**
      - Non-Steroidal Anti-androgens
      - 6 months duration

- **Arm 2**
  - External Beam Radiation
  - Starting 8 weeks after initiation of ADT
  - 68.4 Gy/1.8 Gy/fraction
  - **Plus**
    - Androgen Deprivation Therapy*
      - LHRH Agonist/antagonist
    - **Plus**
      - Non-Steroidal Anti-androgens
      - 6 months duration
  - **Plus**
    - Docetaxel starting 4-6 weeks after completion of radiation
    - Day 1 of each 21-day cycle x 6 cycles**

**Graph**

- Cumulative incidence of metastasis (%)
- Year to metastasis
- Decipher Risk
  - Low/Intermediate
  - High

**P-value < 0.001**
Predictive biomarkers in Prostate Cancer

Luminal and Basal Subtyping of Prostate Cancer

Felix Feng, MD, Shuang Zhao, MD, Laura Chang, PhD, Nicholas Erho, MS, Menggang Yu, PhD, Jonathan Lehrer, BA, Mohammed Alshalalfa, PhD, Matthew Cooperberg, MD, Won Kim, MD, Charles Ryan, MD, Robert Den, MD, Stephen Freedland, MD, Edwin Posadas, MD, Howard Sandler, MD, Eric Klein, MD, Peter Black, MD, Roland Seiler, MD, Scott Tomlins, MD PhD, Arul Chinnaiyan, MD PhD, Robert Jenkins, MD PhD, Elai Davicioni, PhD, Ashley Ross MD PhD, Edward Schaeffer MD PhD, Paul Nguyen MD, Peter Carroll, MD, Jeffrey Karnes, MD, Daniel Spratt, MD
Luminal and Basal Subtyping in Prostate Cancer

- The cell of origin of prostate cancer is unknown.

- Prostate cancer was first thought to originate from glandular luminal cells.

- More recent evidence suggests that basal cells may play a role in prostate carcinogenesis.
• The PAM50 test is the only clinically-utilized classifier of luminal versus basal cell-derived disease.

• The test measures the expression of 50 classifier genes and 5 control genes to identify the intrinsic subtypes of breast cancer (luminal A, luminal B, basal, and Her2)

• We hypothesized that, similar to breast cancer, subtyping can be used to guide treatment selection in prostate cancer.
Luminal and Basal Subtyping in Prostate Cancer

Breast Cohort
N=232
Expression data and PAM50 algorithm obtained from Parker et al.

Prostate Cohort
N=1567
Prostatectomy samples on a CLIA-certified platform
Studies included: MCI, MCII, DVA, TJU, JHMI, CCF
Luminal and Basal Subtyping in Prostate Cancer

Cohorts for Matching  
N=780

2:1 matching on  
ADT  
Covariates:  
Gleason, PSA,  
RT, LNI, ECE,  
SVI, SM

Final Matched Cohort  
N=315

Predict response to post-operative ADT

Test for interaction was highly significant p=0.0057
Transcriptomic heterogeneity of androgen receptor activity in primary prostate cancer: Identification and characterization of a low AR-active subclass

Daniel Spratt, MD
Assistant Professor
Vice Chair, Clinical Research
Chair, Genitourinary Division of Clinical Research
Department of Radiation Oncology
University of Michigan

NRG GU-006
A PHASE II, DOUBLE-BLINDED, PLACEBO CONTROLLED RANDOMIZED TRIAL OF SALVAGE RADIOTHERAPY WITH OR WITHOUT ENHANCED ANTI-ANDROGEN THERAPY WITH APALUTAMIDE

STEP 2 REGISTRATION

STRATIFY
Surgical Margins: Positive vs. Negative
Pre-SRT PSA: <0.5 ng/mL vs ≥0.5-1.0 ng/mL
PAM50 Molecular Subtype per Decipher analysis: Luminal B vs (Luminal A or Basal)

Randomize 1:1

Arm 1 (Blinded)
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions
Plus
Blinded placebo daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

Arm 2 (Blinded)
External Beam Radiation:
64.8 to 70.2, 1.8 Gy/36-39 fractions
Plus
Blinded apalutamide daily for 6 months (~180 days) to start on Day 1 of radiation therapy (+/- 2 weeks)

Co-PIs: Spratt, Feng
Predictive biomarker driven trials: Biomarker validation phase I trial

NCCN High Risk Prostate Cancer

DNA: DNA repair alterations
RNA: AR activity

SBRT + ADT + PARPi

Time-to-event continual reassessment method (TITE-CRM) design

N=38

Analyze response by biomarkers to determine if biomarker enhanced trial preferred for phase II design.

PI: Spratt
Conclusions

• There has been success in developing CLIA grade prognostic tests for many malignancies.

• There has been isolated success stories of developing predictive biomarkers for systemic therapies.

• There have been no success stories YET for a prospectively validated predictive biomarker for radiotherapy.
Both prognostic and predictive biomarkers can be used to personalize treatment and to design trials to select a patient subset most likely to derive benefit from combination therapy.

These biomarkers would be ideal candidates to be used in combination therapy trials and could increase the success of the trial and speed drug approval.
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Hopkins
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NYU
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Mount Sinai
Ashutosh Tewari
Kaiser
Sheila Weinmann

Funding support

Prostate Spore

NIH
Questions

#DrSpratticus
The Debate:
The Next Drug Approved in Combination With Radiation Will Be...

Debaters:
“An IO Agent” - James W. Welsh, MD
“Something Else (not IO)” - Theodore S. Lawrence, MD, PhD
This House believes that the next agent to be FDA-approved with radiation therapy will be immunotherapeutic AGAINST

Ted Lawrence, MD, PhD
University of Michigan
Sadly, I have no financial relationships to disclose that are relevant to this talk

– and –

I will mention the following off-label use and/or investigational use in my presentation:

The WEE1 inhibitor AZD1775
The views expressed in this talk do not represent those of AACR, ASTRO, the FDA or, frankly, the speaker himself. They should be received in the spirit of stimulating discussion and, hopefully, a few smiles.
Although immunotherapy (IT) will be found to cure every problem of mankind in the coming years, it has no approval path in combination with radiation therapy (RT)

Fundamental problem for IT
- The focus is on RT stimulating the elusive abscopal effect: i.e. getting a response where we are not pointing the beam
  - How to differentiate the abscopal effect from the systemic effect of IT?
- Responses are rare
- Because mechanisms are mysterious, there are too many different approaches
Drugs work by increasing the response or producing protection where we are pointing the beam

- Responses are easily measurable
- Responses are common
- Because mechanisms are clearer, easier to get agreement on dosage and schedule

Our side has successes
- And more in the wings
Immunootherapy Cures- Hope and Hype

Better than...
Immunotherapy Cures- Hope and Hype

Bad breath
Immunotherapy Cures- Hope and Hype
Immunotherapy Cures - Hope and Hype

Bad taste
IT is counting on the “Elusive Abscopal Effect”

The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site.

to get FDA approval in combination with RT
The patient was treated with two cycles of ipilimumab, followed by stereotactic radiotherapy to two of eight hepatic metastases and two additional cycles of ipilimumab. Remarkably, subsequent positron-emission tomography–computed tomography showed that all metastases, including the nonirradiated liver lesion and a nonirradiated axillary lesion, had completely resolved…”

He was treated with intracranial stereotactic radiosurgery (SRS) and immunotherapy with ipilimumab…This patient received palliative radiation to primary melanoma, yet there was a delayed but robust response in all untreated cutaneous metastases. This type of response in distant tumors after local radiotherapy is known as the abscopal effect.”

Hinniker et al NEJM 366: 2035, 2012
The patient was treated with two cycles of ipilimumab, followed by stereotactic radiotherapy to two of eight hepatic metastases and two additional cycles of ipilimumab. Remarkably, subsequent positron-emission tomography–computed tomography showed that all metastases, including the nonirradiated liver lesions and a nonirradiated axillary node, had completely resolved…"

He was treated with intracranial stereotactic radiosurgery (SRS) and immunotherapy…This patient received palliative radiation to his primary melanoma, yet this was a delayed but robust response in all untreated cutaneous metastases. This type of response in distant tumors after local radiotherapy is known as the abscopal effect.”

**NO IT DOES NOT!!**

**IT SHOWS A SYSTEMIC EFFECT OF IMMUNOTHERAPY**

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnajatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.
How many radiation oncologists does it take……

Over a 1000!

Schipper, M soon to be published observations.
00 Unhappy Radiation Oncologists
trials are incredibly disorganized!

Overview of ongoing clinical trials combining RT with IT

<table>
<thead>
<tr>
<th></th>
<th>Vaccination</th>
<th>CTLA-4</th>
<th>PD-1</th>
<th>Others*</th>
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<td>9</td>
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<td>7</td>
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<td>Year of initiation</td>
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<td>Dose per fraction¹</td>
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<td>2</td>
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<td>6-10 Gy</td>
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<td>8</td>
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<td>&gt;10 Gy</td>
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<td>7</td>
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<td>7</td>
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<td>Fractionation¹</td>
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<tr>
<td>1 fraction</td>
<td>4</td>
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<td>2</td>
<td>5</td>
<td>16</td>
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<tr>
<td>2-5 fractions</td>
<td>6</td>
<td>11</td>
<td>7</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>6-10 fractions</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>10-27 fractions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;27 fractions</td>
<td>22</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>30</td>
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<tr>
<td>RT timing¹</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RT &gt;1 wk before IT</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>RT within 1 wk of IT</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>RT &gt;1 wk after IT</td>
<td>7</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; GBM = glioblastoma multiforme; IT = immunotherapy; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; RT = radiation therapy.

We queried ClinicalTrials.gov for ongoing trials involving IT and RT.

* The "Others" category includes immunotherapies such as interleukin 2, toll-like receptor agonists, tumor necrosis factor receptor superfamily, member 4 agonists, and transforming growth factor β-targeted agents, as well as other immune modulators.

† Row totals are lower than the sum of the trials because 2 trials combining CTLA-4 and PD-1 blockade were included in both columns.

‡ Studies co-sponsored by industry were not included.

§ The sums of these categories may not equal the actual number of trials reported because trials using multiple dose, fractionation, or timing schemes were included in the totals for each category and/or some trials did not report exact schemes.

fostine Protects Against Xerostomia

Comparison of mean scores on PBQ during treatment and during the posttreatment follow-up period; patients receiving amifostine plus radiotherapy had a significantly higher mean score ($p=0.008$).

Brizel, DM et al J. Clin. Oncology 18: 3339,
Amifostine Protects Against Xerostomia

Amifostine with RT FDA Approved!

Panitumumab + Radiation is Superior to Radiation for HN Cancer

Overall survival by treatment: 5-year update (median follow-up 60 months)

Bonner JA et al Lancet Oncology 11: 21, 2010
Cetuximab + Radiation is Superior to Radiation for HN Cancer

Bonner JA et al Lancet Oncology 11: 21, 2010

Cetuximab with RT FDA Approved!
ONCOLOGY

1775 with Gem/RT may increase OS in Pancreatic Cancer

Cuneo K, et al (preliminary results of an ongoing clinical trial)
Immunotherapy Cures - Hope and Hype

Better than...
# Cool but Drugs will Rule!

<table>
<thead>
<tr>
<th>Category</th>
<th>Immunotherapy</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of assessing response</td>
<td>Hard: is it a systemic response or the elusive abscopal effect?</td>
<td>Easy: Look inside in the beam!</td>
</tr>
<tr>
<td>Responses rate</td>
<td>Rare: needs 1000 physicians</td>
<td>Common</td>
</tr>
<tr>
<td>Getting agreement on the right trial</td>
<td>Hard: every cytokine and T cell has its own fan club</td>
<td>Easy: Targeted therapies are….targeted</td>
</tr>
<tr>
<td>Successes</td>
<td>None</td>
<td>Drugs are already FDA approved with RT</td>
</tr>
</tbody>
</table>
## Cool but Drugs will Rule!

### Category Immunotherapy Drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Immunotherapy</th>
<th>Drugs</th>
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</thead>
<tbody>
<tr>
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<td>None</td>
<td>Drugs are already FDA approved with RT</td>
</tr>
</tbody>
</table>

The next agent that will be FDA approved combined with RT will be: A DRUG
Final Panel Discussion:

Moderator: Amanda Walker, MD

Panelists:
Paul G. Kluetz, MD
Helen Bulbeck, PhD
Robert Iannone, MD
Quynh-Thu Le, MD, FACR, FASTRO
Ricky Sharma, MD, PhD
Summary & Future Directions

Speaker:
Amanda Walker, MD