Radiation plus Immunotherapy to improve systemic immune response

Disclosures

- Employment: University of Texas MD Anderson
- Founder: Healios Oncology, MolecularMatch.com, OncoResponse
- Research Support: BMS, Incyte, GSK, Merck, Nanobiotics, Mavu, CheckMate
- Patents: MP470 (amuvatinib), MRX34 regulation of PDL1
- Scientific Advisor Board: RefleXion Medical, MolecularMatch, OncoResponse, CheckMate, Mavu, Alpine

XRT as systemic therapy

1) XRT ability to turn tumor into “in-Situ” vaccine
2) Ways of using XRT to address the inhibitory stroma
3) How automation of XRT can further improve immune response
Radiation needs an immune response

B16-SIY: 200Gy or B16: 200Gy x 2

Weichselbaum et al
Radiation needs CD8+ cells

Why XRT needs an Immune Response
Conclusion:
Potential Immunologic Benefits of XRT:

Focus on the Donut, Not the Hole

PD1/PDL1
A Historic Academic Battle

Ewing believed Radiation would be the future

Coley believed Immunology would be the future

VS

Ironically XRT is an immuno agent

DNA → cGAS → STING → type I IFN

What Dose of XRT?

DNA exonuclease Trex1 regulates radiotherapy-induced tumor immunogenicity

Silvia Formenti & Sandra Demaria

Nature Communication Jun 9, 2017

Sandra Demaria
Is Radiation an "in situ" vaccine?


Phase I/II Trial of Ipilimumab (Immunotherapy) and Hypofractionated Stereotactic Radiation Therapy in Patients with Advanced Solid Malignancies

Aung Naing MD, David Hong MD, Erminia Massarelli MD, Rodabe Amaria MD, Adi Diab, MD, Chad Tang, MD

Questions
1) Dose
2) Sequencing
3) Tumor location

Adverse Events (G3, no G4-5) (n=100)

<table>
<thead>
<tr>
<th>AE</th>
<th>Lung</th>
<th>Liver</th>
<th>Seq Lung</th>
<th>Seq Liver</th>
<th>Seq GIT</th>
<th>Seq Endocrine</th>
<th>Seq Chest</th>
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<tr>
<td>GIT:</td>
<td>Colitis</td>
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<td>2 (2%)</td>
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<td>AST/ALT increase</td>
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<td>Bilirubin Increase</td>
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<td>Endocrine:</td>
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FFe 11/2014: 50 Gy/4 SBRT Liver

FFe 12/2014: 20 Gy/5 SBRT R Sacrum

FFe 11/2014 – 12/2015: Ipilimumab x 4 cycles (q3 weeks)

Progression Feb 2015

FFe Feb 2015 - March 2015

Concurrent Liver Sequential Liver Concurrent Lung Sequential Lung

irSD 18 (95%)
irPR/irCR 1 (5%)
irPD 0 (0%)

12 (71%)
1 (6%)
4 (23%)

15 (79%)
2 (11%)
2 (11%)

11 (58%)
2 (11%)
6 (32%)

14 (67%)
3 (14%)
4 (19%)

1 (5%)
5 (29%)
7 (33%)
8 (42%)

4 (21%)

C linical Benefit

Response
Response rate

Clinical benefit SD+PR+CR
74/95 = 78%

Clinical benefit SD+PR+CR
48/95 = 51%

All Patient Tumors
Non-XRT Tumors

Complete Leukotrichia in 3 days

Receiving first infusion of ipi
3 days later

Lymphopenia Association With Gross Tumor Volume and Lung V5 and Its Effects on Non-Small Cell Lung Cancer Patient Outcomes
Moving beyond PD1: PD1 Resistant NSCLC Model

XRT Increases IFN β → MHC-I
XRT Overcomes PD1 Resistance

Wang, Welsh et al, Cancer Research, 2016
OX40 only works AFTER radiation

Niknam and Barsoumian et al., 2017

X Wang & J Welsh
Feb 15, 2017

Progression on OX40 agonist

Abscopal after progression on OX40
Conclusion:

Potential Immunologic Benefits of XRT:

**PRECISE:**

Preoperative Radiotherapy to Elicit Critical Immune Stimulating Effects

Co-Pi: S. Shattilman & E. Mittendorf

Stroma Blocks T cells
Using low dose scatter XRT to “Pull” in T cells

Lesion with low dose scatter

Lesion with no low dose scatter

Melanoma resistant to anti-PD1

4-21-17

6-12-17

This tumor got low dose scatter of 50cGy

Melanoma resistant to anti-PD1

6-8-16

1-17-17

Confidential do not share
Low dose scatter XRT

Low dose XRT “Pulls” and activates CD4+ and CD8+

RadScopal
Adoptive T cell Therapy

First Clinical of RadScopal in PD1 resistant melanoma
(RadScopal= high dose XRT to prime and low dose XRT to pull in T cells)

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First Clinical of RadScopal in PD1 resistant melanoma
(RadScopal= high dose XRT to prime and low dose XRT to pull in T cells)
PACIFIC trial: Compelling new data

Ablate inhibitory stroma

Trial Design

No Local Consolidative Therapy

Step 1: Enrollment

First Line Systemic Therapy

Staged Enrollment Non-PD Event Exclusion

Local Consolidative Therapy

Surgery and RT Allowed

Growth factor and chemotherapy

Crossover Allowed at Progression

PFS Outcomes (updated data)

One patient invaluable (24 in each group)
Median PFS times:
No-LCT arm: 3.9 months (95% CI 2.2-6.6 months)
LCT arm: 11.9 months (95% CI 5.4 months-NA)
My Car can drive itself why not my Linac?

BGRT: Biologically Guided Radiation Therapy

Reflexion is developing a novel radiation therapy system that harnesses signals originating from tumors continuously to guide the treatment beam.
Abscopal, RadScopal™ & XScopal strategies

Conclusion:
Potential Immunologic Benefits of XRT:

Metastatic Pancreatic cancer progressing on immunotherapy
Vaginal metastatic abscopal after liver XRT

Pre RT - 3/17/18
Post RT - 3/17/18

1 day after completing RT

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