Radiation and Immunotherapy
What’s it All About?

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DISCLAIMER

The information contained in this presentation is not intended as a substitute for professional medical advice, diagnosis or treatment. It is provided for educational purposes only. You assume full responsibility for how you choose to use this information.
Proportion of U.S. Population Dying of Cancer Has Not Changed Since 1960
What Is Cancer Immunotherapy?

• Standard cancer therapy (chemotherapy, radiation) attacks the tumor cell directly

• Immunotherapy is a treatment that activates the immune system to fight cancer
The Immune System Has a Natural Ability
to Recognize and Kill Cancer

NORMAL MARKERS
("Self", "Safe")

ABNORMAL CANCER MARKERS
("Foreign", "Dangerous")

Normal Cell

Immune System

Cancer Cell

IGNORE

ATTACK

Adapted from Cancer Research Institute

Weill Cornell Medicine

New York Presbyterian
Killer T Cells Attacking a Cancer Cell
But Sometimes the Immune System Shuts Down Prematurely or the Attack is Insufficient

"Don’t Attack Me, I’m You!!"

Adapted from Cancer Research Institute

But Sometimes the Immune System Shuts Down Prematurely or the Attack is Insufficient
Breast cancer:
The Immune System is Present at the Tumor Site But Incapable of Rejecting Cancer

Immunologic phenotypes of tumor/host in 481 TNBC patients from ECOG trials E2197/E1199

for every 10% increase in TILs, a 14% reduction of risk of recurrence or death

Breast Cancer

• The immune system is present at the tumor site but incapable of rejecting cancer; immunosuppression dominates in established tumors

• For every 10% increase in tumor infiltrating immune cells, a 14% reduction of risk of recurrence or death

CAN RADIOTHERAPY RESET THE IMMUNOLOGIC PHENOTYPES OF A TUMOR?

How is Radiotherapy Delivered in the Modern Era?
Can Radiation Therapy Help the Immune System to Reject Cancer?

Abscopal effects
(ab-scopus = away from the target)
1969-2014: only 46 abscopal cases

WHY ARE ABSCOPAL EFFECTS SO RARE?
IMMUNOSUPPRESSION DOMINATES IN ESTABLISHED TUMORS

Of Mice and Men
Pioneers in Translating Radiation and Immunotherapy from the Lab to the Clinic

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Radiation Stimulates the Immune System to Attack and Shrink a Distant Tumor
RADIATION AND FLT-3L INDUCE AN ABSCOPAL EFFECT
Radiation with Immunotherapy, can stimulate the Immune System to Attack and Shrink a Distant Tumor

• A proof-of-principle trial: Local radiotherapy and GM-CSF—an immunotherapy—to generate abscopal responses in patients with metastatic solid tumors

• 26.8% abscopal responses

• Median overall survival: 20.98 months versus 8.33 months

Golden et al Lancet Oncology 2015
ABSCOPAL RESPONSE AFTER RADIATION AND GM-CSF

RT: 3.5 GyX10

GM-CSF: 125 µg/m²
Daily X 14 days
Unleashing the Immune System to Fight Cancer

James P. Allison, Ph.D.
2015 Lasker-DeBakey Clinical Medical Research Award
Instead of Pressing on the Accelerator, Release the Brakes

Tumor Cell

Inhibitory Receptor

= Brake

T Cell
Immune Checkpoint Blockade + Radiotherapy

- Immune checkpoint blockade is a type of immunotherapy that uses antibodies against the brakes in T cells, activating them and killing cancer cells.

- We have shown that radiotherapy and immune checkpoint blockade complement each other.

- Only with the combination of the two did we see improved survival, due to T cell-mediated control of the irradiated tumor and metastases.
Strategies to Establish Patient-Specific Anti-tumor Immunity

A
Induce tumor cell destruction
Provide checkpoint blockade

B
Identify potential neoantigens
Create synthetic vaccine (RNA, DNA, peptide)
Provide in combination with adjuvant and checkpoint blockade

C
Identify potential neoantigens
Induce or expand neoantigen specific T cells
Provide in combination checkpoint blockade
Mr. P: Patient with Lung Cancer Metastasized To Liver, Lung and Bone achieves a complete response

Treated with **Radiation Plus Checkpoint Blockade**

![Radiation to one lesion]

August 2012

January 2013

Currently at 4 years without any other therapy and with no evidence of disease
Un-irradiated distant sites
Key Points

• Cancer kills by metastatic spread
• Cancer is the result of a failure of the immune system to reject it
• Cancer often “blinds” the immune system
• Radiation therapy can un-blind the immune system and restore an immune response
• Radiation and checkpoint blockade or other immunotherapies can lead to tumor rejection in patients with metastatic disease
• Radiation is a new class of immunotherapy
> 80 Clinical Trials are Now Testing the Combination of Radiotherapy and Immunotherapy

“OPENING THE FLOOD GATES”
Thank You!