Combining radiotherapy with immunotherapy in metastatic cancer

Silvia C Formenti, M.D.
New York University School of Medicine
and Langone Medical Center
Disclosures

- P.I. DOD Multi-Team Award
- P.I. BCRF grant
- P.I NIH R01
- 1 S10 RR027619-01 (NIH)
- P.I. peer-reviewed Varian research grant (No personal salary support)
- Scientific Advisory Board of Bristol Meyers Squibb, Oncoimmunology Division

Fresolimumab trial: drug gifted by Sanofi/Aventis (FDA-IND)
Ipilimumab NSCLC trial: drug gifted by Bristol Myers Squibb (FDA-IND)
How do standard anti-cancer treatments interfere with this landscape?
IN SITU VACCINATION HYPOTHESIS

RT

IMMUNITY AGAINST METASTASES

Tumor cell lysis

CD8 T cell

CTL activation

CD4 T cell

IL-12

IL-2

γIFN

Formenti & Demaria, IJROBP 2004; Lancet Oncology 2009
Cross-priming of anti-tumor T cells: immunogenic cell death

CRT, “eat me” signal, translocation to membrane induced by ER stress (Obeid et al., Nat Med 2007, 13:54-61)

ATP released by dying cells by autophagy binds to P2RX7 purinergic receptor leading to inflammasome activation and IL-1β production (Ghiringhelli et al., Nat Med 2009, 15:1170)

HMGB-1, a damage associated molecular pattern (DAMP) binds to TLR4 to promote cross-presentation of tumor-derived antigens (Apetoh et al., Nat Med 2007, 13:1050)

WIN 2014 Symposium • 23-24 June • Paris • France
In vitro assay for RT-induced ICD

(Golden et al. OncoImmunology 2014)
Abscopal Effect

Latin *ab* (position away from) and *scopus* (mark or target)

Mole RJ. Whole body irradiation - radiology or medicine? *Br J Radiol* 1953; 26:234

RELEVANCE TO METASTATIC CANCER
Why are abscopal effects of radiation rarely observed in the clinic?
IMMUNOSUPPRESSION DOMINATES IN ESTABLISHED TUMORS

Immunotherapy strategies to combine with radiation

- Priming phase:
  - FLT-3L/GM-CSF
  - TLR agonists

- Effector phase:
  - Anti-CTLA4
  - Anti-PD-1
  - Anti-TGFβ
Hypothesis:
Ionizing radiation can stimulate anti-tumor immunity –by generating an \textit{in situ} vaccine - and combination with immunotherapy may uncover this effect.

BALB/C mice injected at two separate sites with the syngeneic mammary carcinoma 67NR cell line

Day: 0
67NR
5x10^4 or 10^5 each sides,
primary R and secondary L

Day: 20
2 Gy
21
Flt3-L (0.5mg/kg)
Day: 31

WIN 2014 Symposium • 23-24 June • Paris • France
RT+Flt3-L: systemic anti-cancer effects

irradiated

non-irradiated
Abscopal Effect is tumor specific and abrogated in nude mice.
NYU 0258
Abscopal trial RT+GM-CSF in metastatic solid tumors

Within 2 weeks from study entry:
- Baseline measurements
- CT and PET

End of Week 3
- Assess clinical response

Week 7-8
- Assess clinical response and CT/PET response

RT
3.5Gy×10

GM-CSF
125 μg/m²
NYU 0258
Abscopal trial RT+GM-CSF in metastatic solid tumors

Lancet Oncology 2009
Abscopal effect 10/37 (27%)
Abscopal effect and survival, 37 patients (NYU 02-58)

Abscopal responders likely to be patients already more immunocompetent

ASTRO 2012
4T1 mouse model of metastatic breast cancer

Antigen-CTLA-4 mAb 9H10

Experimental Endpoints:
- Primary Tumor growth
- Lung metastasis
- Immune response evaluation

WIN 2014 Symposium • 23-24 June • Paris • France
Immune-Mediated Inhibition of Metastases after Treatment with Local Radiation and CTLA-4 Blockade in a Mouse Model of Breast Cancer

Sandra Demaria, Noriko Kawashima, Anne Marie Yang, Mary Louise Devitt, James S. Babb, James P. Allison, and Silvia C. Formenti

Departments of Pathology, Radiation Oncology, and Radiology, New York University School of Medicine, New York, New York; and Howard Hughes Medical Institute, University of California at Berkeley, Berkeley, California

* p < 0.01 from day 20 when compared to Ig-treated group. Differences between treatment groups were assessed using the Tukey’s honestly significant difference (HSD) procedure and p values reported are HSD adjusted.

Survival differences among treatment groups were analyzed using a Weibull model.
Characterization of T cell-tumor cell interactions by intravital two-photon laser scanning microscopy

Michael Dustin

WIN 2014 Symposium • 23-24 June • Paris • France
Radiation up-regulates ICAM-1 and Rae1 on 4T1 cancer cells \textit{in vivo}

\textbf{TUMOR CELLS}

\textbf{CD8 T CELLS (day 16)}

\begin{align*}
\text{NONE} & \quad \text{RT+9H10} \\
\text{TUMOR} & \quad \text{SPLEEN} \\
\text{NKG2D} & \quad \text{TDLN} \\
\text{CD69} & \quad \text{RT+9H10} \\
\end{align*}

\textbf{WIN 2014 Symposium \cdot 23-24 June \cdot Paris \cdot France}

\textit{Ruocco et al JCI 2012}
Blocking NKG2D abolishes immune-mediated tumor inhibition by combination of RT+anti-CTLA-4
Radiation-induced Rae-1/NKG2D interaction is required for stable immunological synapse of tumor and T cells.

**Clinical translation:**
NKG2D and its ligand MHC class I chain-related protein A (MICA)

**WIN 2014 Symposium** • 23-24 June • **Paris** • France

*Ruocco et al., J Clin Invest 2012*
12 ongoing trials testing RT and Ipilimumab:

At NYU:
- Melanoma randomized trial
- NSCLC Phase II trial

Postov et al 2012
Patient with Metastatic NSCLC

Progressing after 3 lines of chemo and chest RT: Multiple lung, bone and liver metastasis

RT to one liver met 6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT q3 weeks, X 4 cycles

WIN 2014 Symposium • 23-24 June • Paris • France
Golden et al Cancer Immunology Research, 2014
Metastatic NSCLC: Response to RT+ipilimumab
Comparison of SCV metastasis at diagnosis (2010) and after RT and Ipilimumab (2013)

H&E

CD8

TIA-1

Ratio CD8/FoxP3

Cancer Imm. Research, 2014
Clinical and radiological CR at one year (currently NED at 22 months from tx)
Pre-clinical to clinical testing of RT and immunotherapy in metastatic cancer

- Flt3L (Demaria et al., Int J Radiat Oncol Biol Phys, 2004)
- TLR7-agonist (Dewan et al. Clin Cancer Res 2012)
- anti-TGFβ (Bouquet et al Clin Cancer Res 2012)
- NYU 02-58 Proof of principle abscopal trial
- open trial in met melanoma (NCT01689974)
- open trial in met NSCLC
- Developing trial of in met breast cancer
- open trial in met BC (NCT01421017)
- open trial in met BC (NCT01401062)

WIN 2014 Symposium • 23-24 June • Paris • France
Preclinical efficacy of low dose CTX when added to IMQ/RT

Imiquimod (IMQ) is a synthetic, TLR-7 agonist. Aldara is an IMQ topical cream FDA approved for treatment of superficial basal cell carcinoma, actinic keratosis, and external genital warts.  

**3 ARMS CLINICAL TRIAL IN METASTATIC BREAST CANCER**

- **With skin mets:** RT + IMQ
- **CTX+RT+IMQ**
- **Without skin mets:** CTX+ RT

CTX 200mg i.v. 1 week before RT
TLR7 agonist Imiquimod: Abscopal response

Response at a distant site of disease

10/2012          01/2013          03/2013
Immunotherapy strategies to combine with radiation

Priming phase:
- FLT-3L/GM-CSF,
- TLR agonists

Effector phase:
- Anti-CTLA4
- Anti-PD-1,
- Anti-TGFβ
Winning combinations for precision cancer medicine

**Activation of latent TGFβ**

- TAA Release
- Decreased DDR
- Anti-TGFβ
- Latency Associated Peptide
- TGF-β

**Inhibition of effector T cells**

- CD8 T cell
- CD4 T cell

**Induction of regulatory T cells**

- Treg

**Inhibition of DC maturation**

- TAA Uptake by DC
- Cross-priming
- TDLN

**Cross-priming**

**Anti-tumor immunity**

**Immunosuppression**

WIN 2014 Symposium • 23-24 June • Paris • France
RT synergizes with TGFβ neutralizing Ab to in immunocompetent models of breast and lung tumors, but not in the immunocompromised model 4T1.
CLINICAL TRIAL IN METASTATIC BC
Accrued 22 patients: 11 per arm
Comparison of OS and PFS based on fresolimumab dose (arm A = 10mg, arm B = 1 mg)

Overall Survival

- Arm A: Median OS = 14.4 months
- Arm B: Median OS = 6.9 months
- Log-Rank P-Value = 0.14

Progression Free Survival

- Arm A: Median PFS = 12.1 months
- Arm B: Median PFS = 3.6 months
- Log-Rank P-Value = 0.07

16 out of 22 (73%) patients died. (7/11 in arm A, 9/11 in arm B)
Hazard Ratio = 2.174 (95% CI: 0.753 – 6.272)
Fresolimumab and radiation (7.5 GyX3) to one lesion

Patient #2

11/10/11 before tx
11/18/11 First Fresolimumab+RT to liver
12/19/11 a month after first TX
2/8/12 Second Freso+RT to breast skin
2/27/12 Last PET/CT
Response reported as irSD, 28% reduction, no new lesions,
Slide content not available for publication
CONCLUSIONS

Ionizing radiation can convert the tumor into an *in situ* vaccine

Promising partner with immunotherapy: localized/predictable toxicity approved, standard modality accessible at any cancer center easy to standardize for a consortium trial
RT and Immunity Team

MH Barcellos-Hoff Ph.D.
Encouse Golden M.D., Ph.D.
Mike Dustin Ph.D.
Sandra Demaria M.D.

Claire Vanpouille-Box Ph.D.
Karsten Pilones Ph D.
Keith DeWyngaert, Ph.D.
Maria Fenton-Kerimian, N.P.

WIN 2014 Symposium • 23-24 June • Paris • France