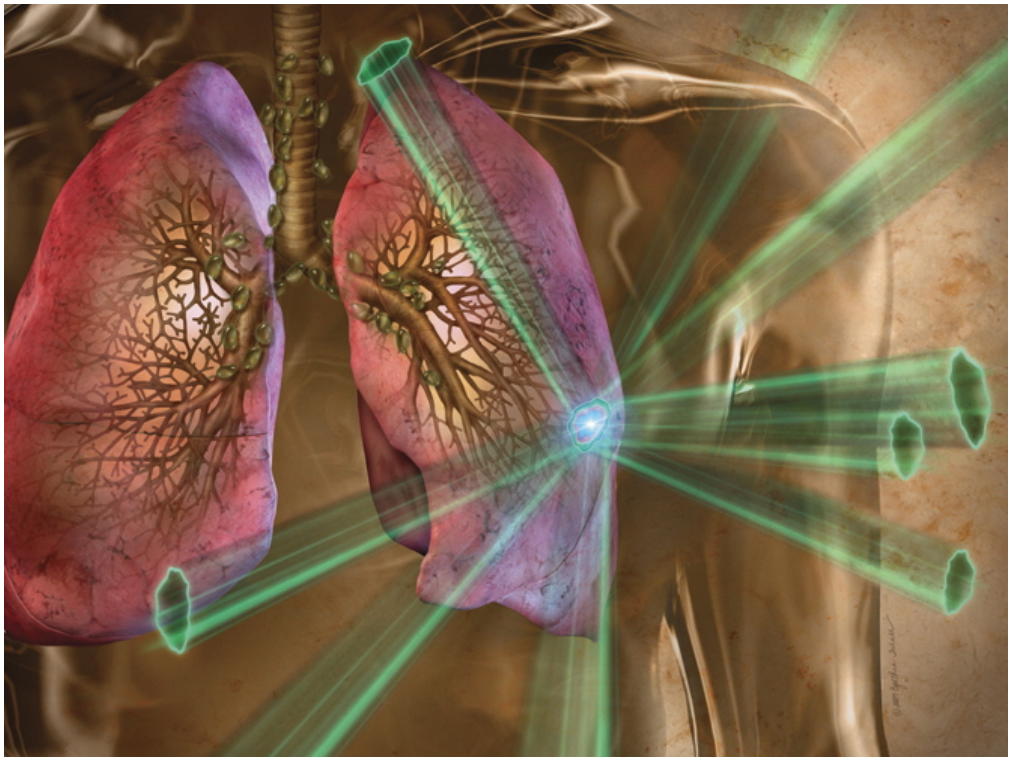
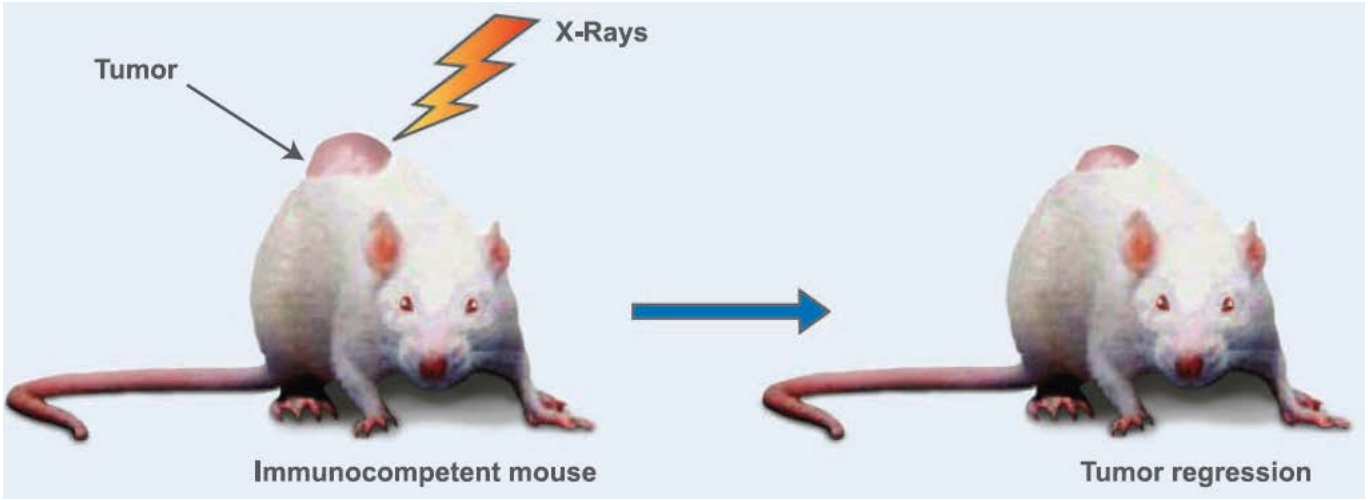
Exploiting the Immunomodulatory Properties of Radiation Therapy



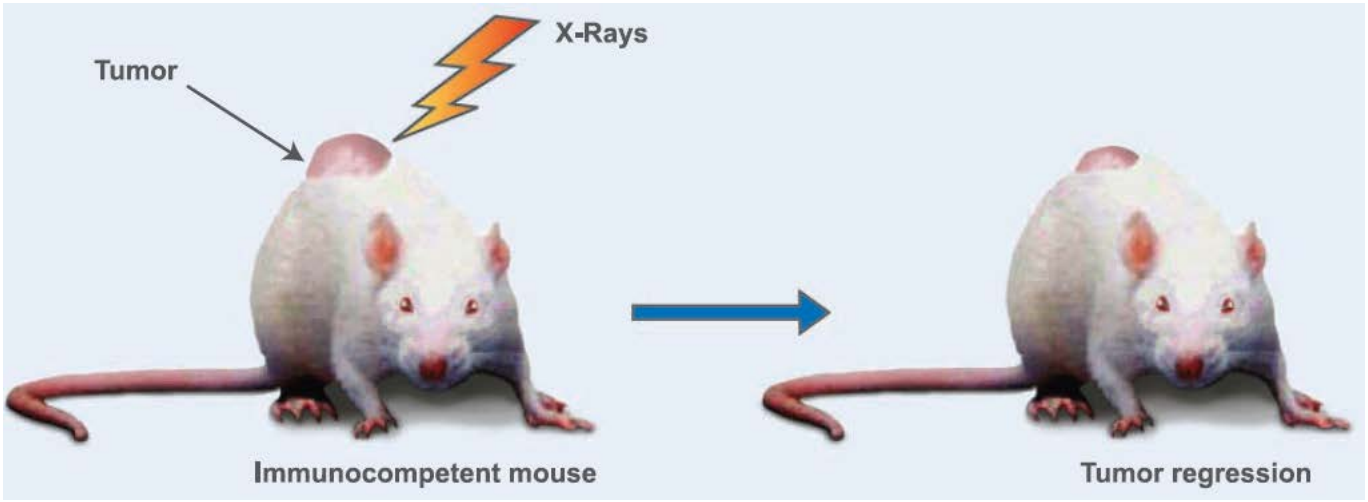
UT SOUTHWESTERN
THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

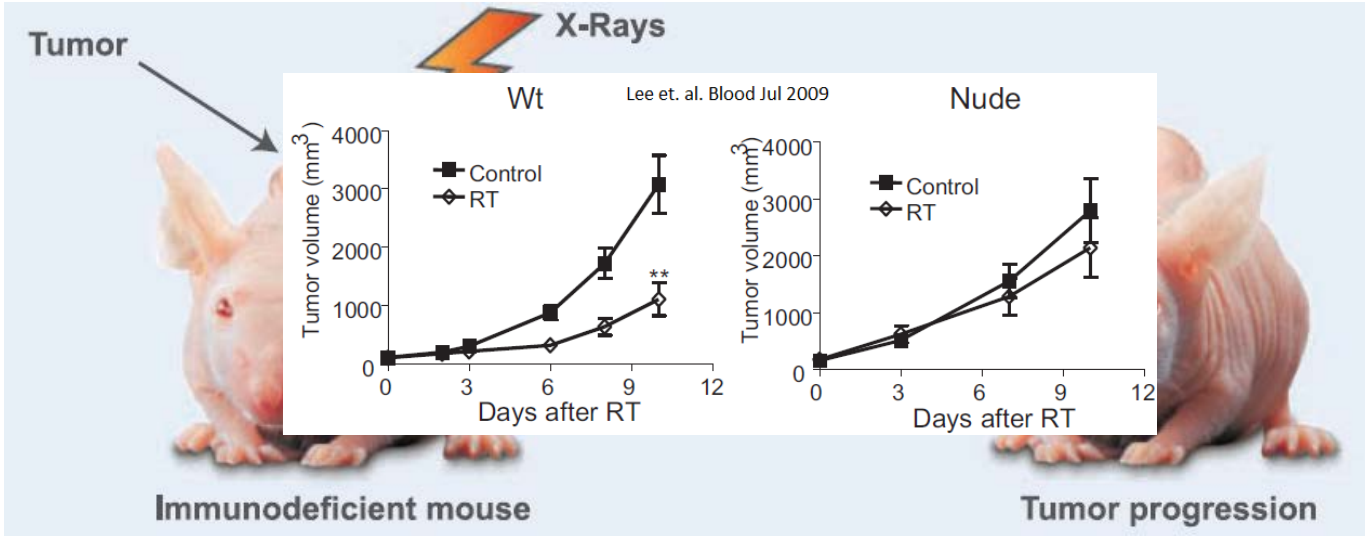
Puneeth Iyengar, MD, PhD
Assistant Professor
Thoracic Radiation Oncology Chief
Department of Radiation Oncology

Immunomodulation by Radiation Therapy



Immunomodulation by Radiation Therapy





Apoteh et al, Can. Res. 2008; Apoteh et al, Nat Med, 2007

Outline

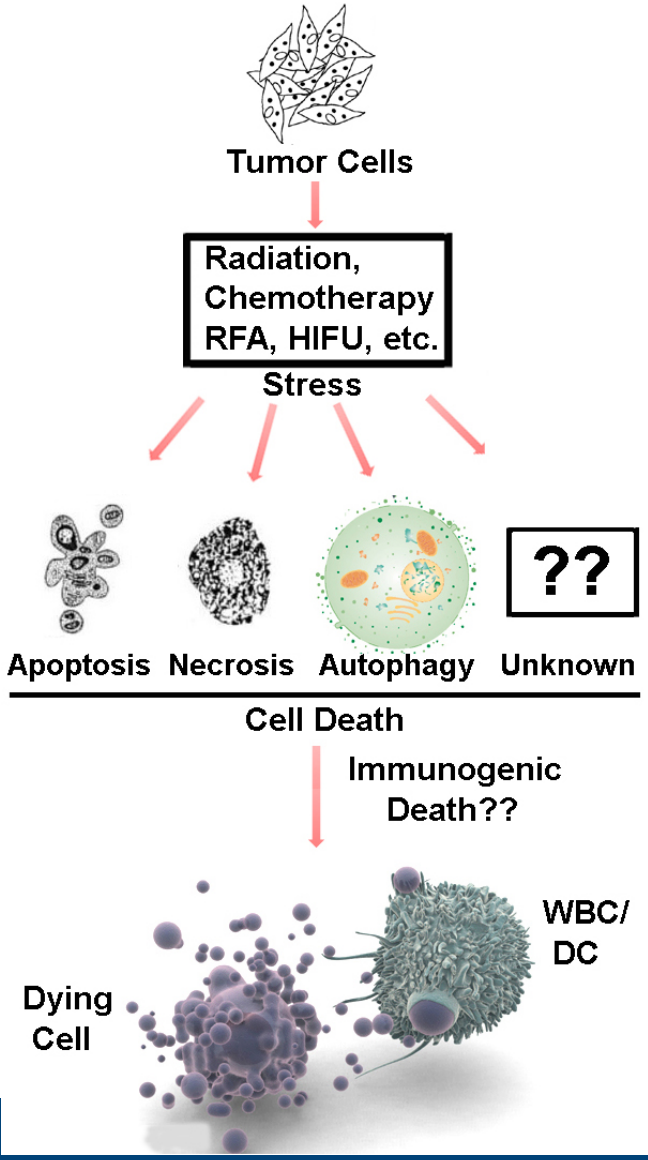
- Immunomodulation by radiation therapy (RT)
  - Pre-clinical evidence
  - Limited clinical evidence

- The i-SAbR approach at UTSW as a paradigm for IO and RT
  - Pre-clinical models
  - Clinical Trial Design
  - Translational studies

Immunomodulation by RT

- Cancers are Immunogenic
  - –Multiple TAAs described for different cancer sub-sites
  - –Tumors travel to LN—a primary immune organ
  - –Tumor immuno-editing hypothesis
- RT
  - –As a focal therapy, keeps the host completely immunocompetent
    - –Stereotactic Ablative Radiation (SAbR) also spares the regional draining lymph nodes
  - –Keeps the antigen depot within the host and induces an immunogenic cell death

Immunomodulation by RT

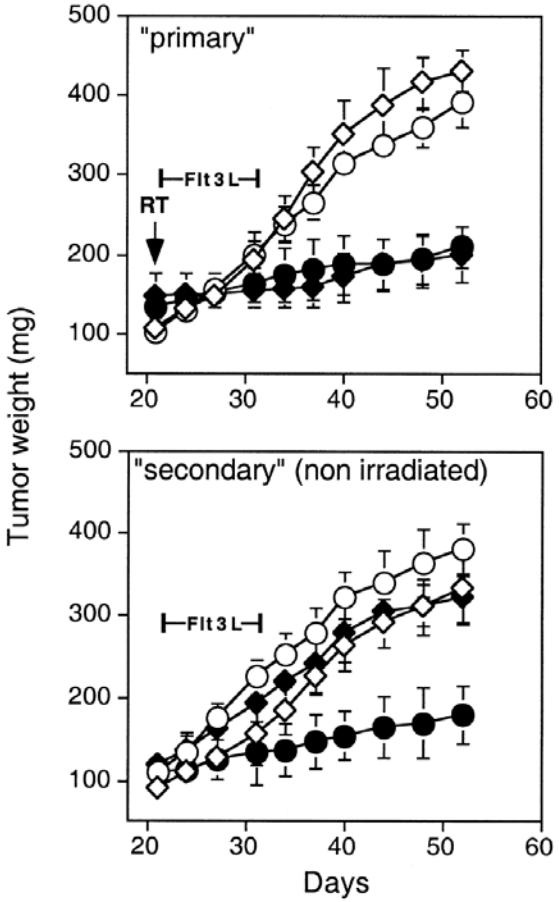


- RT leads to the translocation and release of Danger (or Damage)-Associated Molecular Patterns (DAMPS)
  - HMGB1, HSP70, Calreticulin, ATP
  - DAMPS recruit Dendritic Cells into the tumor-microenvironment
- RT increases pro-inflammatory cytokine release
- RT increases the permeability of the tumor -microenvironment

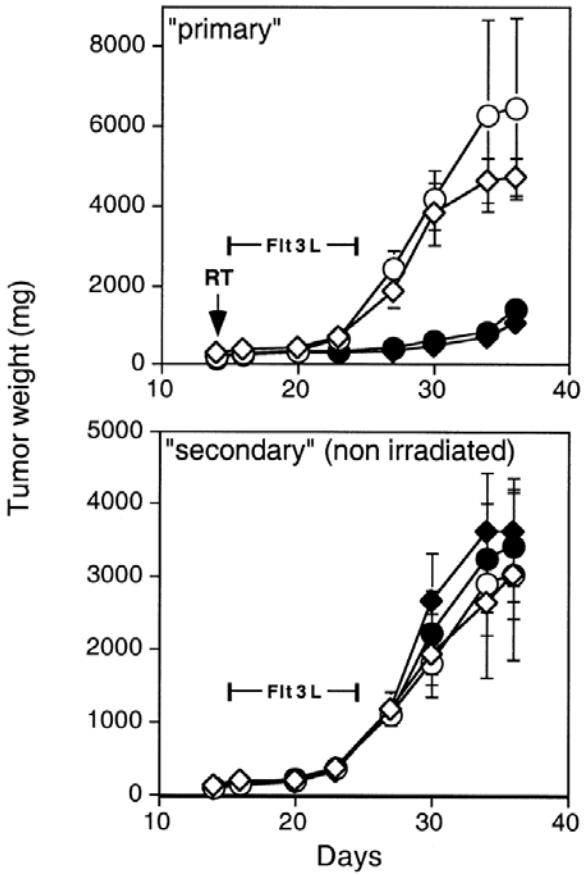
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

IJROBP 2004 Mar 1;58(3):862-70

SANDRA DEMARIA, M.D.,* BRUCE NG, M.S.,† MARY LOUISE DEVITT, A.A.S.,‡ JAMES S. BABB, PH.D.,§
NORIKO KAWASHIMA, M.S.,* LEONARD LIEBES, PH.D.,† AND SILVIA C. FORMENTI, M.D.‡



Normal



Immunocompromised

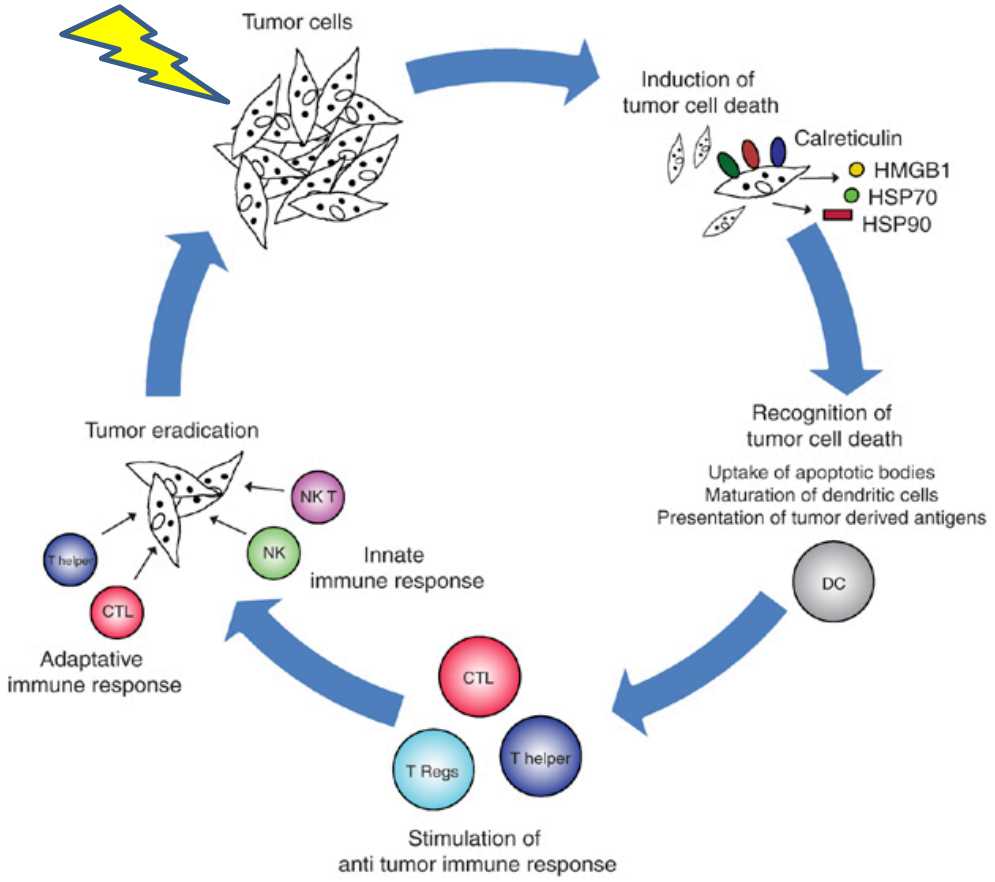
Empty diamonds= Untreated mice

Empty Circles= Flt3-L

Filled Diamonds=RT

Filled Circles= Flt3-L+RT

Immunomodulation by RT: Proposed mechanism



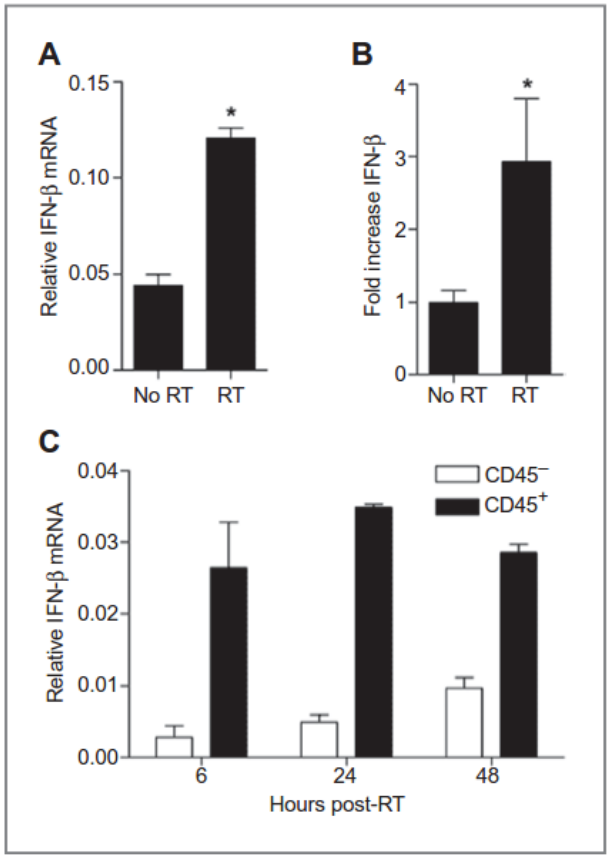
- Lugade et. al. J Immunol 2005

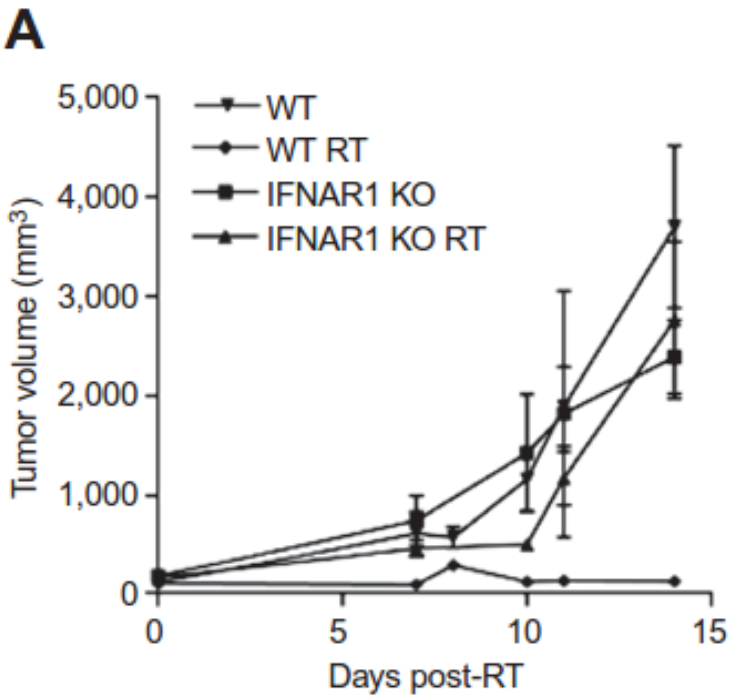
Cancer Res; 71(7) April 1, 2011

Cancer Research

The Efficacy of Radiotherapy Relies upon Induction of Type I Interferon–Dependent Innate and Adaptive Immunity

Byron C. Burnette[1], Hua Liang[2], Youjin Lee[1], Lukasz Chlewicki[1], Nikolai N. Khodarev[2], Ralph R. Weichselbaum[2], Yang-Xin Fu[1], and Sogyong L. Auh[1]

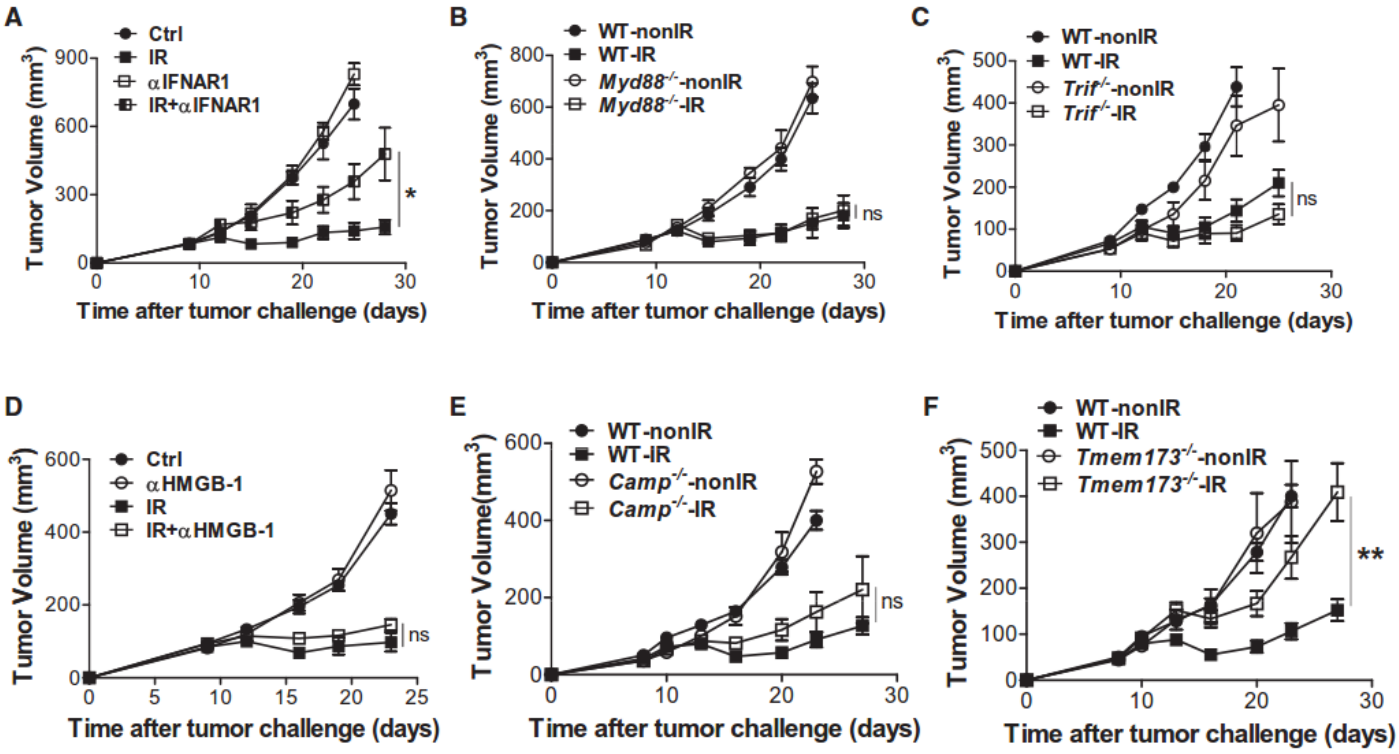




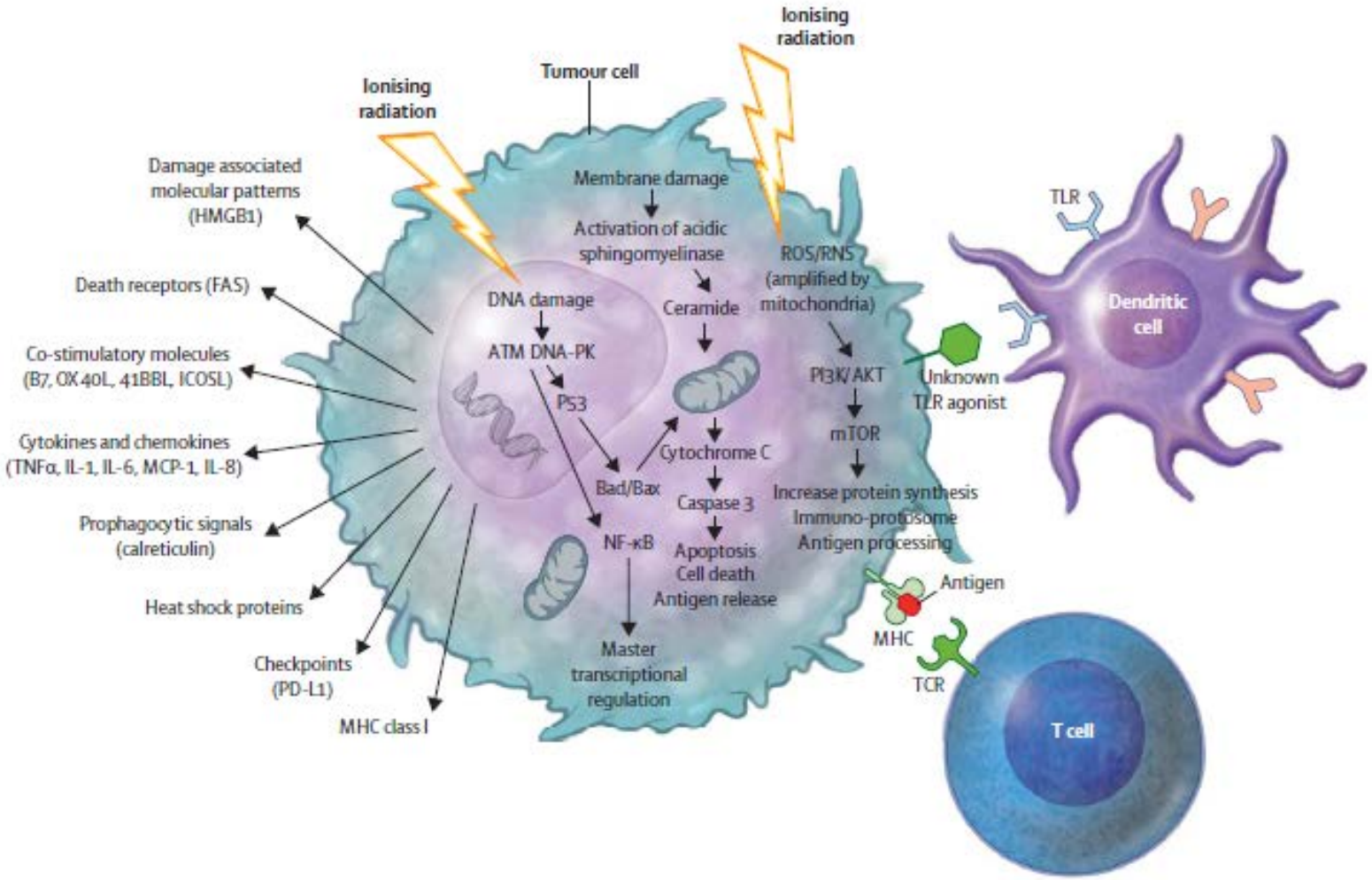
Immunity
Article
Immunity 41, 843–852, November 20, 2014 ©2014 Elsevier Inc.
CellPress

STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors

Liufu Deng,[1,3] Hua Liang,[1,3] Meng Xu,[2] Xuanming Yang,[2] Byron Burnette,[1,3] Ainhoa Arina,[1,3] Xiao-Dong Li,[4] Helena Mauceri,[1,3] Michael Beckett,[1,3] Thomas Darga,[1,3] Xiaona Huang,[1] Thomas F. Gajewski,[2] Zhijian J. Chen,[4,5] Yang-Xin Fu,[2,3,*] and Ralph R. Weichselbaum[1,3,*]



Immunogenic properties of SAbR



Sharabi et. al. Lancet Oncology Dec 2015

Immunomodulation by RT

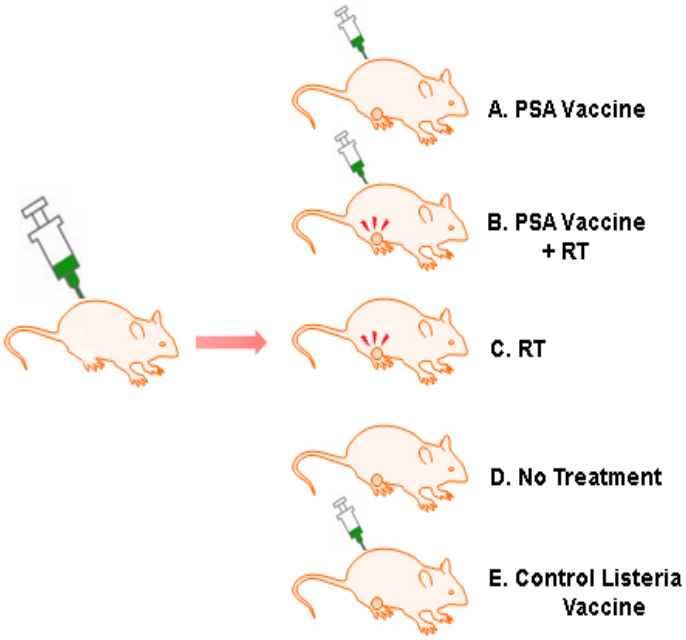
Can RT immunomodulation be exploited for therapeutic benefit?

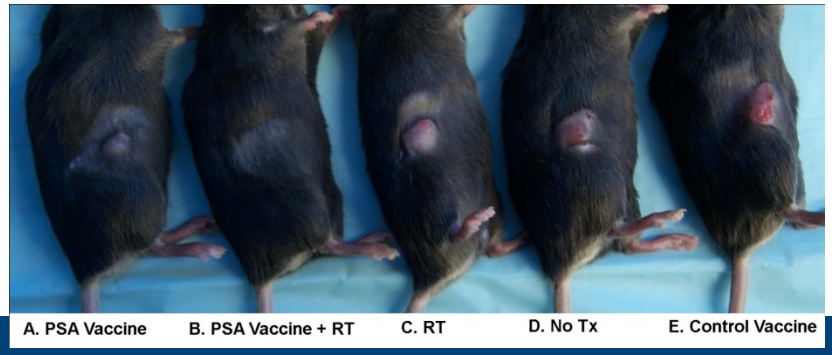
IT+RT Pre-Clinical Data

Tumor Model	RT Dose	Immunotherapy	Reference
Lung (LLC)	60 Gy	Flt3-Ligand	Chakravarty et. al. Can. Res. 1999
Fibrosarcoma	10-35 Gy	IL-3 gene therapy	Chiang et. al. Can Gen Ther 2000
Colon(MC38)	2-30 Gy	Vaccia/Avipox-CEA	Chakravarty et. al. Can Res 2004
Breast (67NR)	2-6 Gy	Flt3-Ligand	Demaria et. al IJROBP 2004
Fibrosarcoma (MCA-102), Lymphoma (EL4), Colon (CT-26)	15 Gy	DC	Kim et. al. Int. J. Cancer 2004
Breast (4T1)	12-24 Gy	Anti-CTLA-4	Demaria et. al. CCR 2005
Colon(MC38)	20-30 Gy	Anti-CTLA-4	Dewan et. al. CCR 2009
Gliosarcoma (9L)	10 Gy	DC+GM-CSF	Driessens et. al. CII, 2011
Breast (AT-3)	12-30 Gy	Anti-PD-1, Anti-CD137	Verbrugge, et. al. Can Res 2012
Lymphoma (EL4, EG7), Lung (LLC) Melanoma (B16)	2, 15 Gy	Th1 Cell Therapy	Takeshima et al. Can Res 2012
Prostate (TRAMP-C1)	10 Gy	Listeria –PSA Vaccine	Hannan et. al, CII 2012
Lymphoma (A20, EL4, EG7)	10, 25Gy	TLR-7 agonist	Dovedi et. al. Blood 2013
Breast (TUBO), colon (MC38)	12Gy	Anti-PD-L1	Deng and Fu et. al. JCI 2014

Pre-Clinical Data

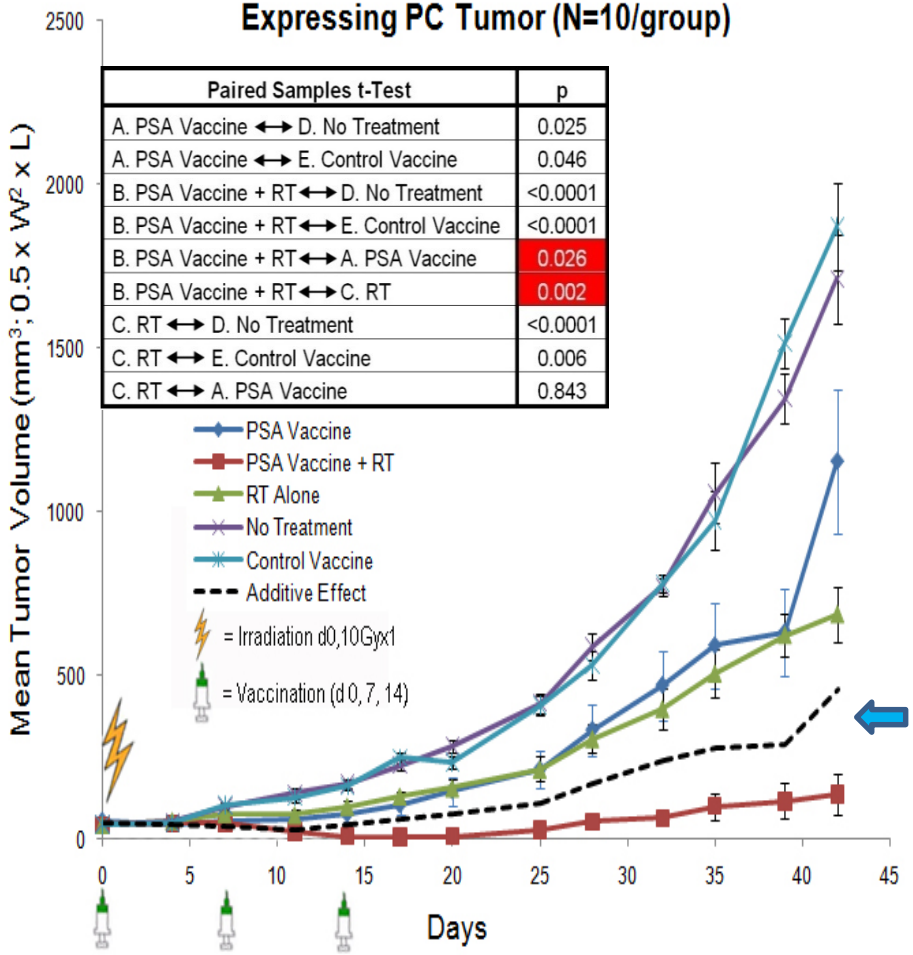
Synergy between RT and IT:





Tumor Growth in Mice w/ Syngeneic PSA Expressing PC Tumor (N=10/group)

Paired Samples t-Test	p
A. PSA Vaccine ↔ D. No Treatment	0.025
A. PSA Vaccine ↔ E. Control Vaccine	0.046
B. PSA Vaccine + RT ↔ D. No Treatment	<0.0001
B. PSA Vaccine + RT ↔ E. Control Vaccine	<0.0001
B. PSA Vaccine + RT ↔ A. PSA Vaccine	0.026
B. PSA Vaccine + RT ↔ C. RT	0.002
C. RT ↔ D. No Treatment	<0.0001
C. RT ↔ E. Control Vaccine	0.006
C. RT ↔ A. PSA Vaccine	0.843



Hannan et. al. , Cancer Immunol Immunother, May 2012

Outline

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- The i-SAbR approach at UTSW
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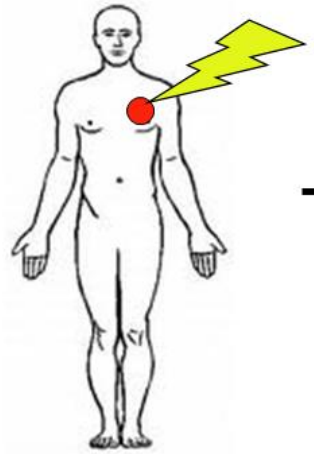
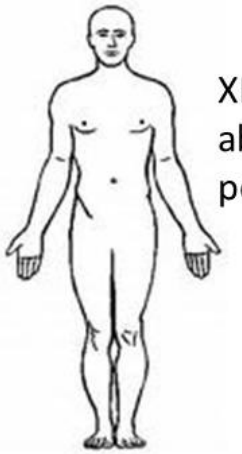
Abscopal Response



XRT

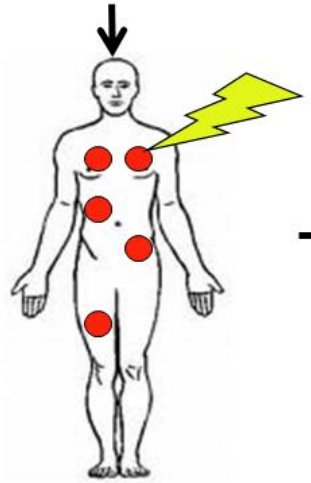


XRT has direct cell kill function; ablative effect during high dose per fraction radiation.

● = Tumor site

Immunotherapy

XRT = external beam radiation



XRT

+ systemic agent that promotes immune system activity

XRT stimulates immune action against all tumor sites, even those not irradiated.

Dendritic cell recruitment, T cell activation, Vascular permeability, Increased antigen presentation

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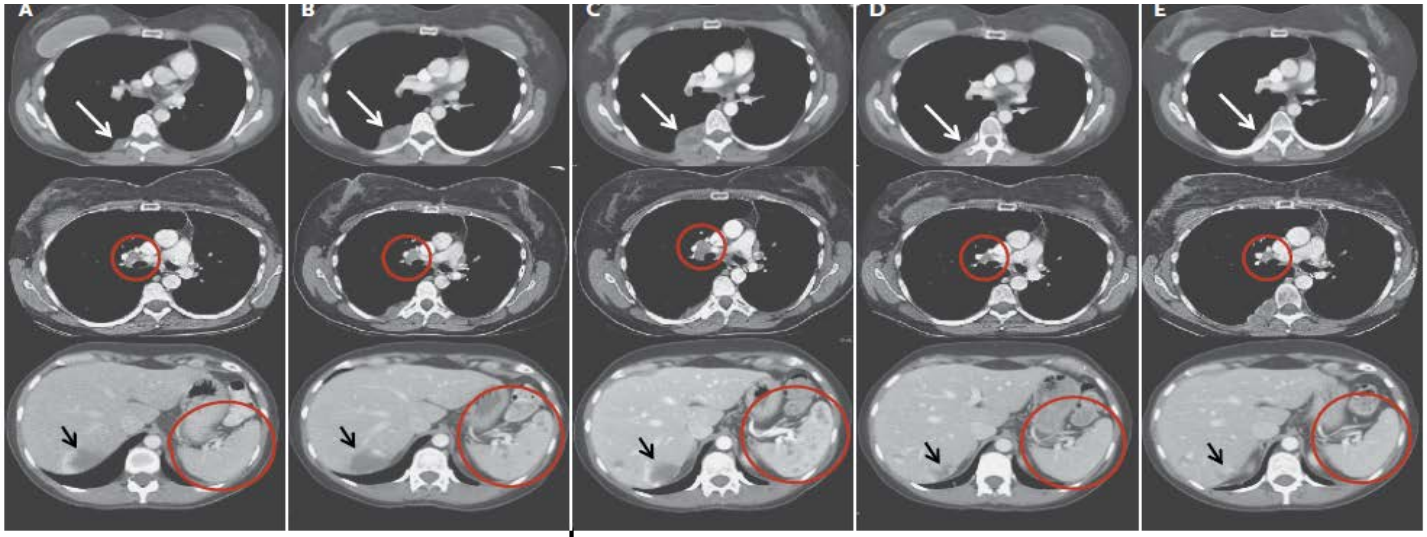
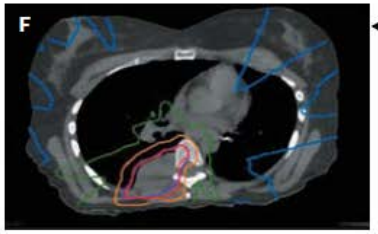
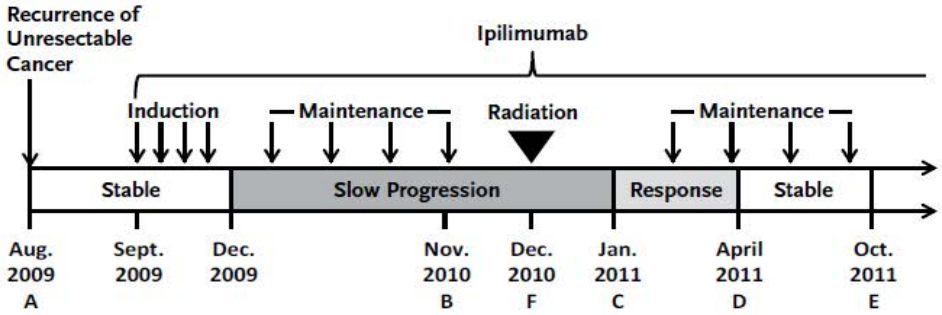
BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma





December 2010



Postow et. al. NEJM March 8th, 2012

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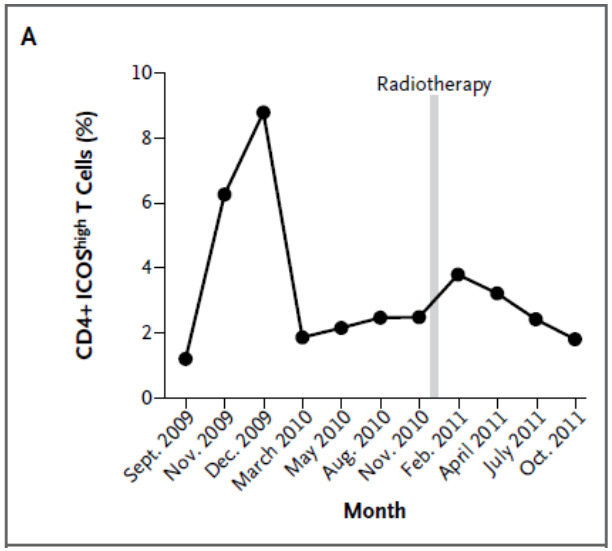

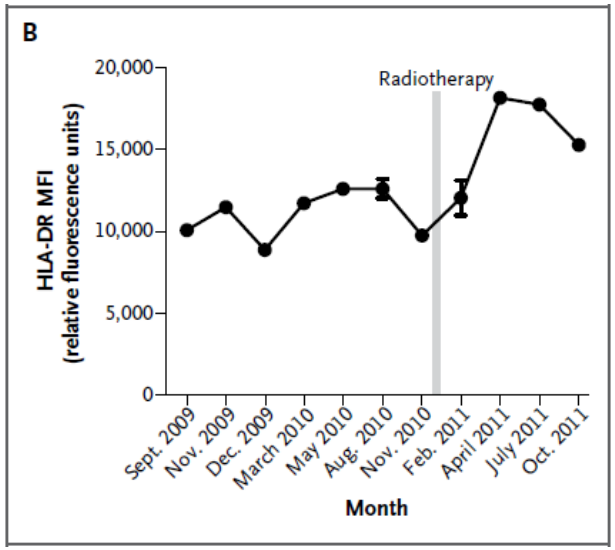

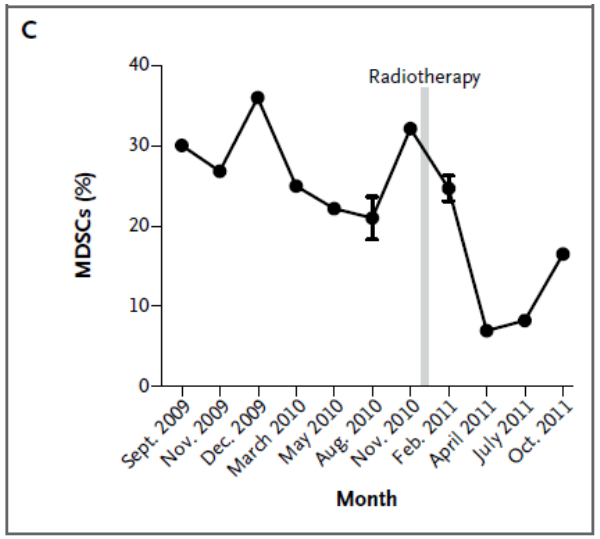

Postow et. al. NEJM March 8th, 2012

IT + RT Clinical Data: Abscopal Effect

Tumor-type	Treatment	Abscopal effect	Mediator of abscopal effect	Reference
CLINICAL REPORTS				
Hepatocellular carcinoma	RT of thoracic vertebral bone metastases, *dose:* 36 Gy	Regression of primary tumor	TNF-alpha	Ohba et al. (1998)
Hepatocellular carcinoma	RT of mediastinum, *dose:* 27 × 2.25 Gy	Regression of lung metastases		Okuma et al. (2011)
Renal cell carcinoma	RT of primary tumor, *dose:* 12 × 8Gy	Regression of enlarged lymph nodes and lung lesions		Wersall et al. (2006)
Mammary carcinoma	RT of primary tumor	Regression of metastatic lymph nodes	CD8+ and CD4+ T cells	Konoeda (1990)
NK-ENKL	RT of eyelid tumor	Regression of NK cell lymphoma	CD8+ T cells	Isobe et al. (2009)

Rubner et. al. Front Oncol 2012

Science Translational Medicine
AAAS

Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—Tumor and Immunological Responses

Steven K. Seung *et al.*

Sci Transl Med **4**, 137ra74 (2012);
DOI: 10.1126/scitranslmed.3003649

- Eligibility:
  - –Metastatic RCC or melanoma
  - –no previous medical therapy
- SAbR 20Gy/fx for 1-3 fractions
- IL-2 (600,000 IU/kg IV bolus) Q8h x 14 doses
  - –Started three days after last SABR
- Treated 12 patients (5 mRCC)
- Evaluate safety/feasability
- Evaluate for immune response

Science Translational Medicine
AAAS

Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—Tumor and Immunological Responses

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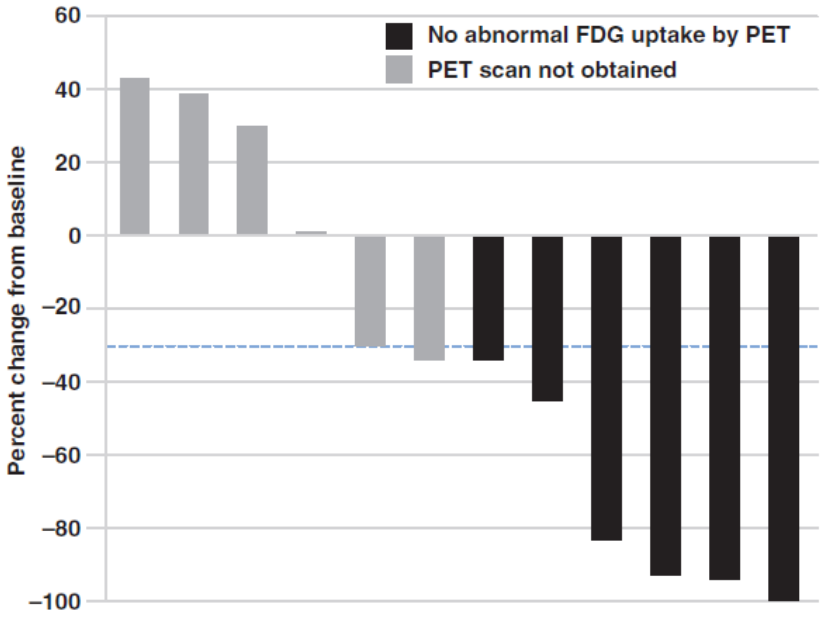

Fig. 1. Waterfall plot of best tumor response by RECIST criteria of all target lesions not treated with SBRT. Each bar represents the response of an individual patient. A dashed line is placed at 30% to indicate the minimum regression of tumor to qualify for a PR by RECIST criteria of target lesions.

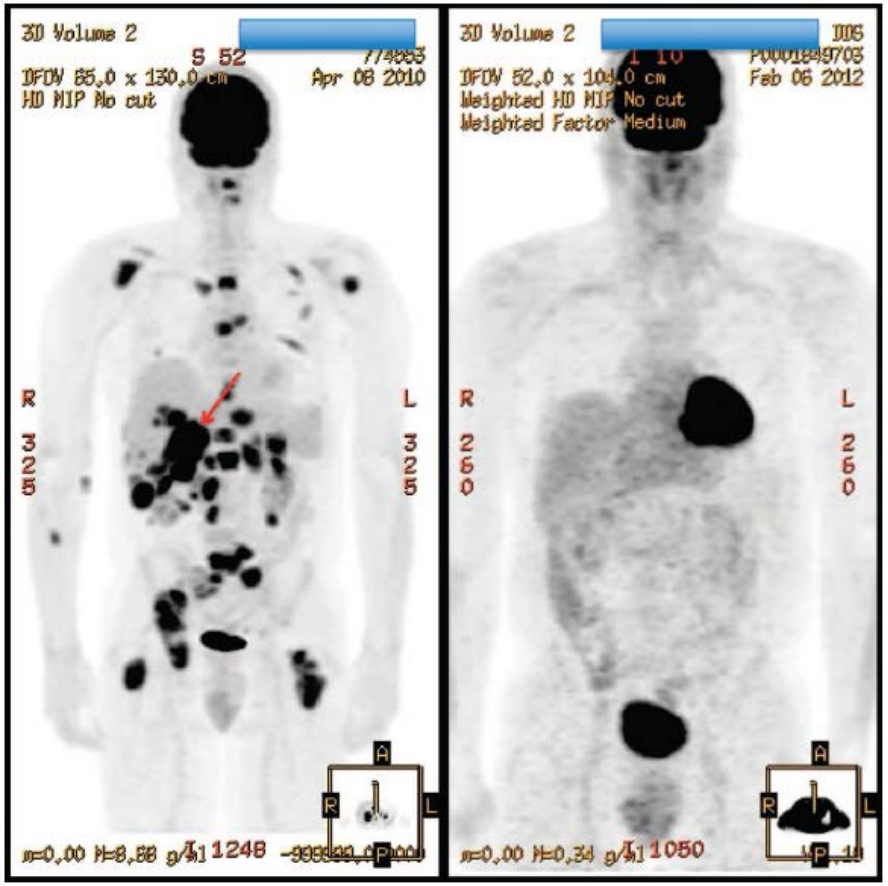

Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

8 (66.3%) patients had an overall response
60% of mRCC patients had a PR

Abscopal Response

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti

12 further patients were enrolled. Abscopal responses occurred in eight (27·6%, 95% CI 12·7–47·2) of the first 29 patients, and 11 (26·8%, 95% CI 14·2–42·9) of 41 accrued patients (specifically in four patients with non-small-cell lung cancer, five with breast cancer, and two with thymic cancer). The most common grade 3–4 adverse events were fatigue (six patients) and haematological (ten patients). Additionally, a serious adverse event of grade 4 pulmonary

www.thelancet.com/oncology Vol 16 July 2015

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

CONCLUSIONS

Progression-free survival was significantly longer with durvalumab than with placebo. The secondary end points also favored durvalumab, and safety was similar between the groups. (Funded by AstraZeneca; PACIFIC ClinicalTrials.gov number, NCT02125461.)

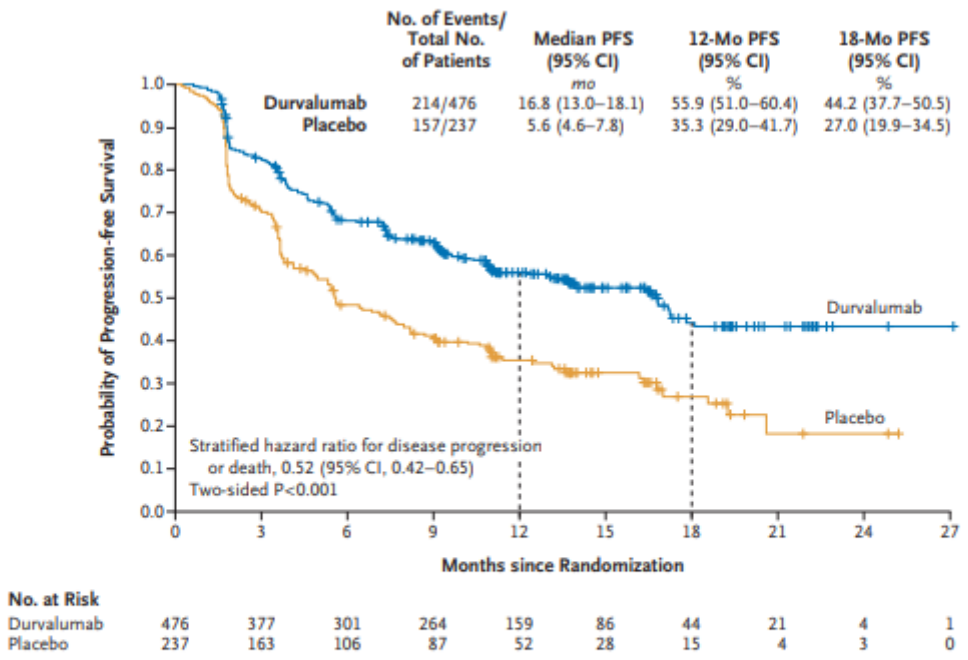

Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Shown are Kaplan–Meier curves for progression-free survival (PFS), defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and assessed by means of blinded independent central review. Tick marks indicate censored observations, and vertical lines indicate the times of landmark PFS analyses. The intention-to-treat population included all patients who underwent randomization.

Outline

- Immunomodulation by radiation therapy (RT)
  - Pre-clinical evidence
  - Limited clinical evidence

- The i-SAbR approach at UTSW
  - Pre-clinical models
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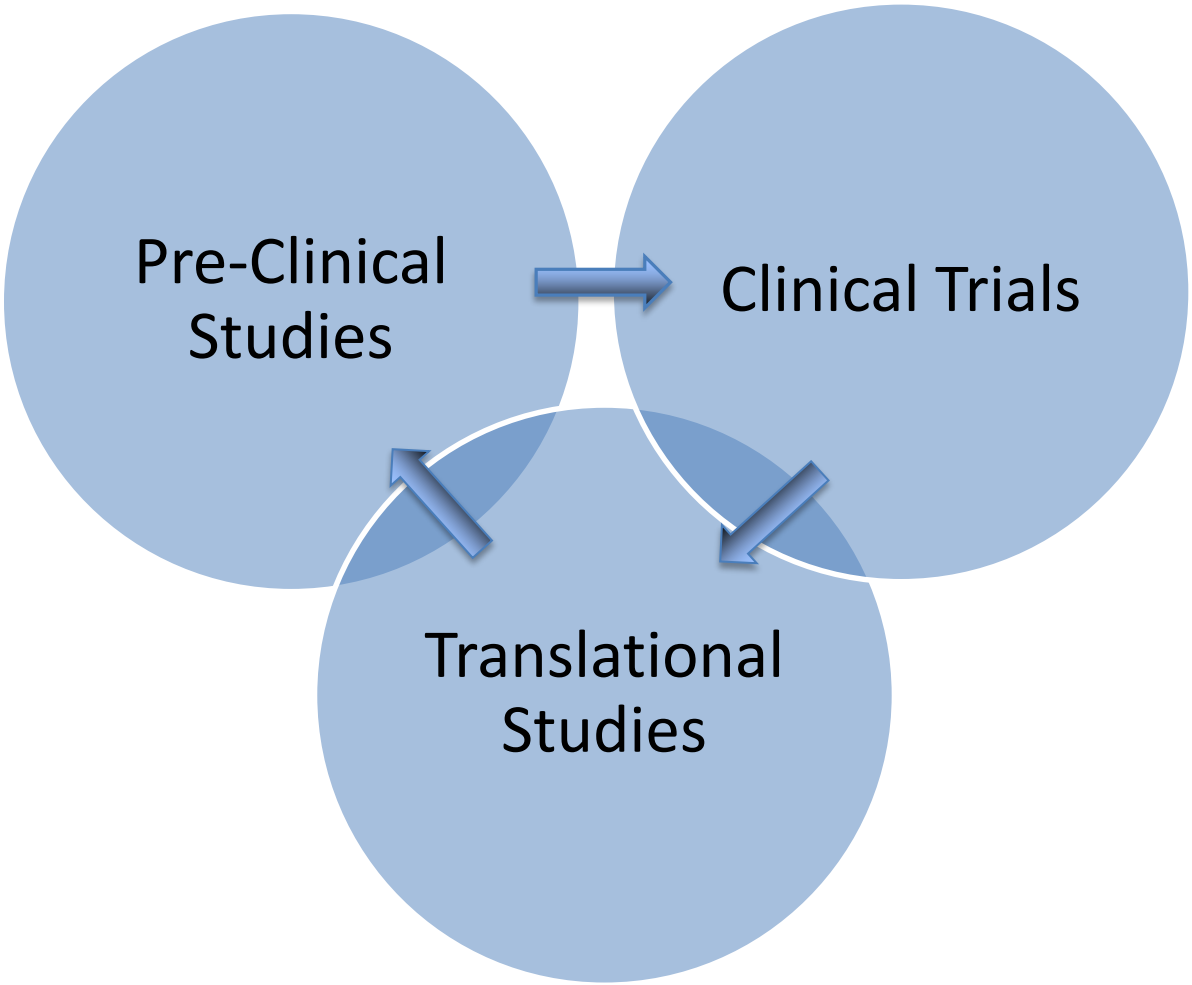
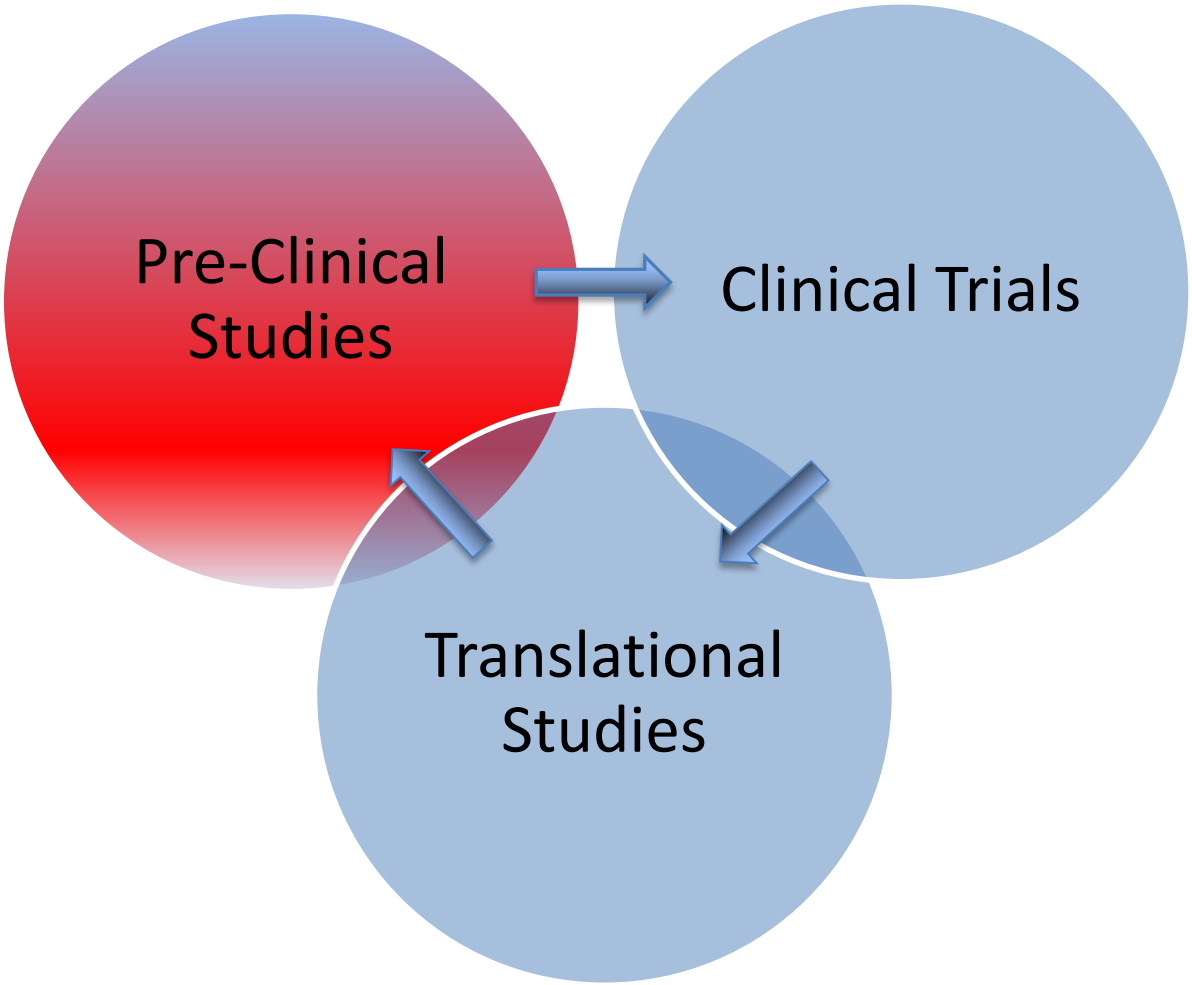
  - Translational studies

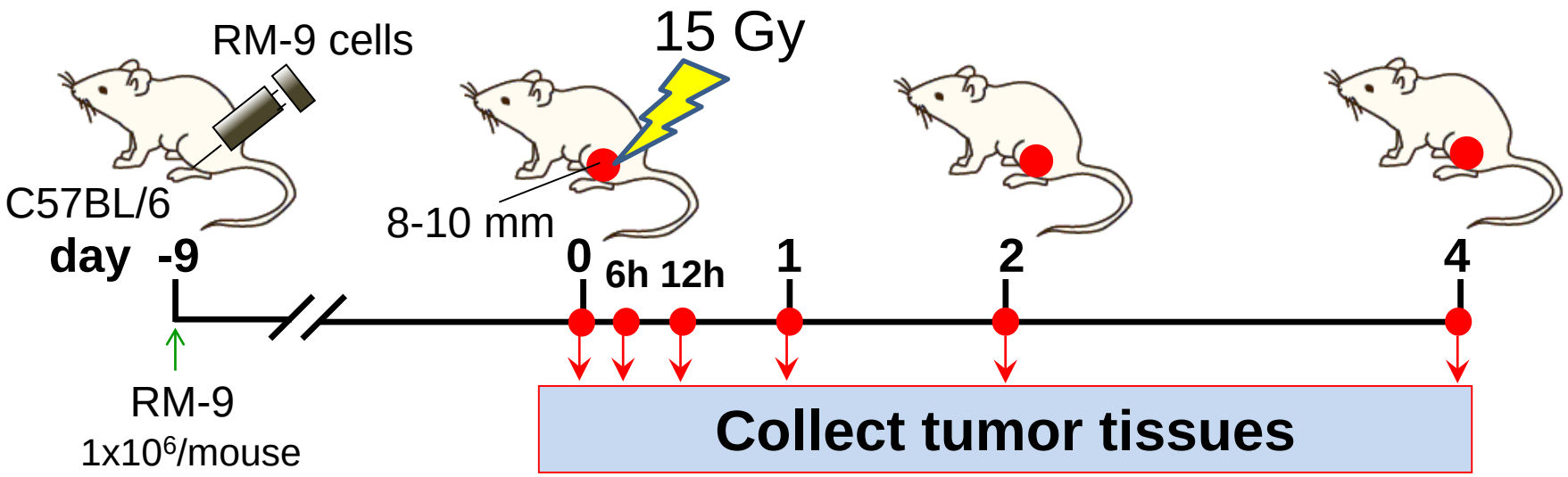
The i-SAbR approach at UTSW

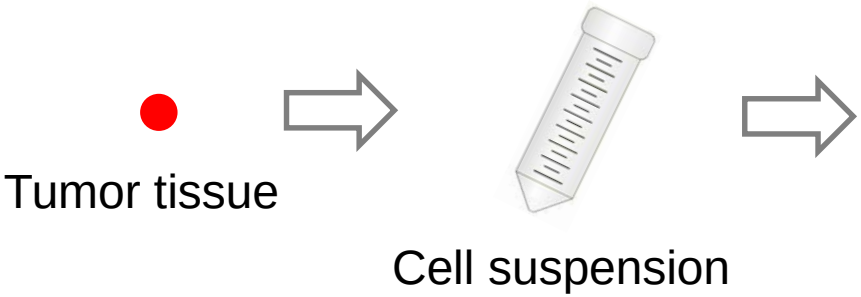


The i-SAbR approach at UTSW

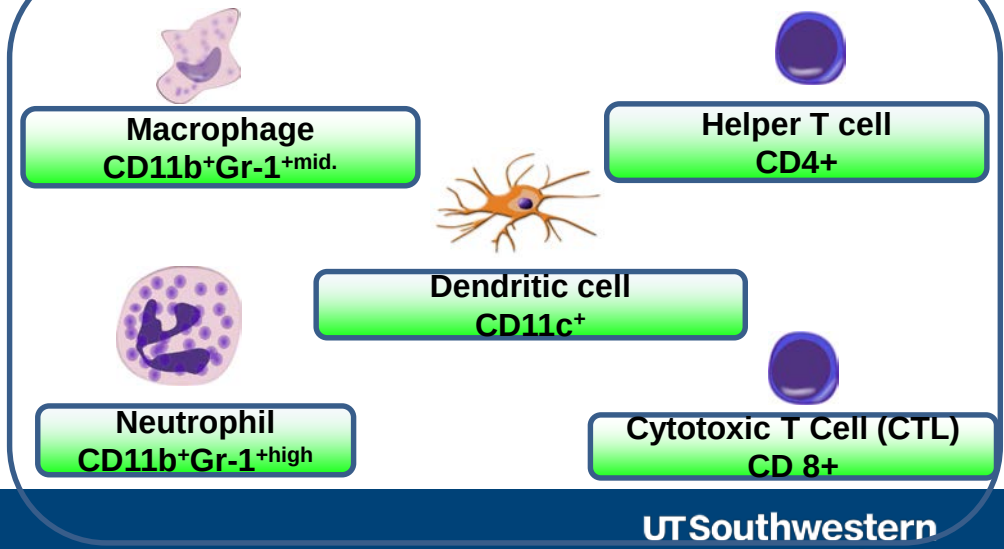


How does RT change the tumor immuno-microenvironment?





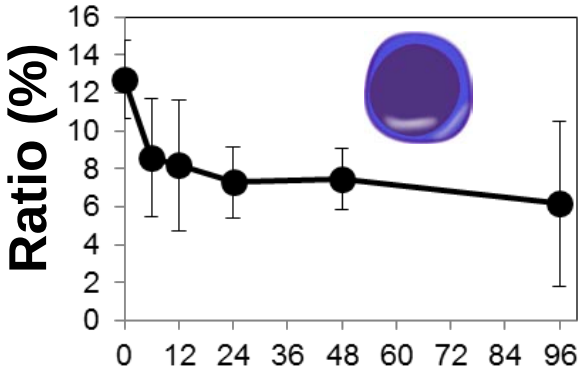
Flow cytometric Analysis



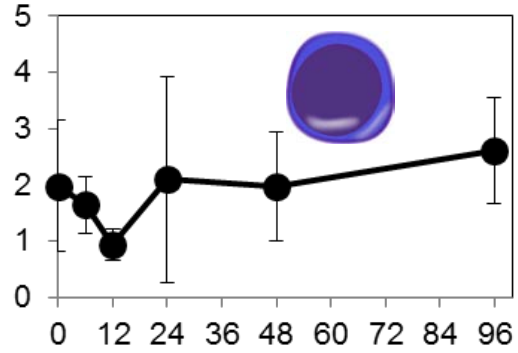
How does RT change the tumor immuno-microenvironment?

RM-9

Helper T ($CD4^+$)

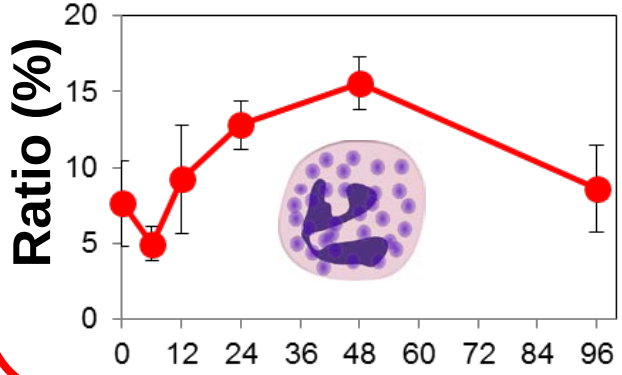


CTL ($CD8^+$)

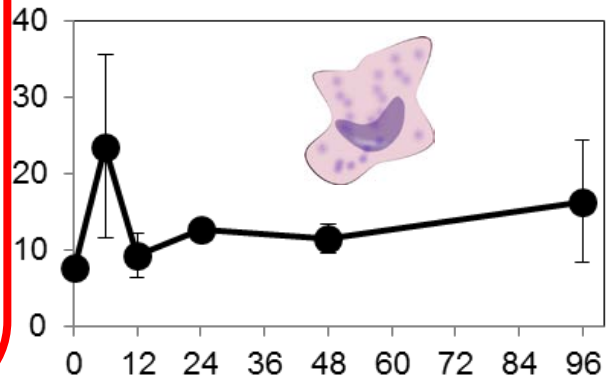


Time after 15 Gy irradiation (h)

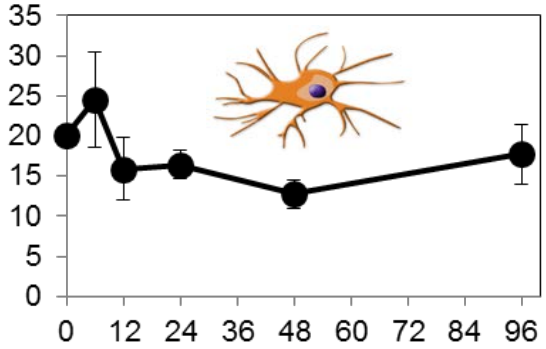
Neut. ($CD11b^+Gr\text{-}1^{+high}$)



Mϕ ($CD11b^+Gr\text{-}1^{+mid}$)



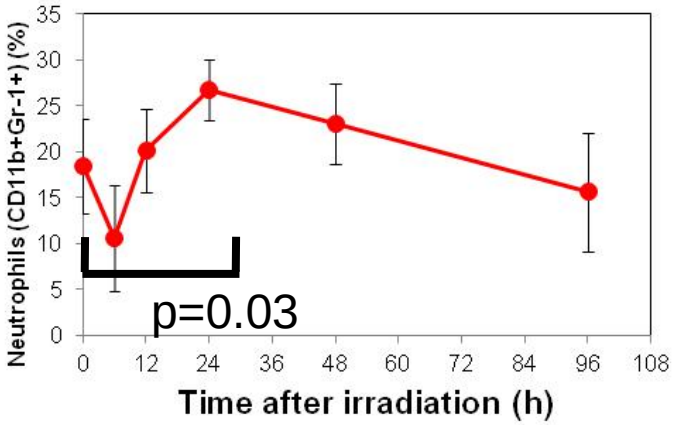
DC ($CD11c^+$)

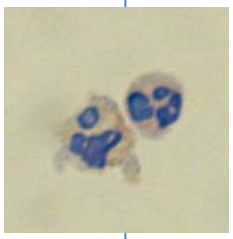


Time after 15 Gy irradiation (h)

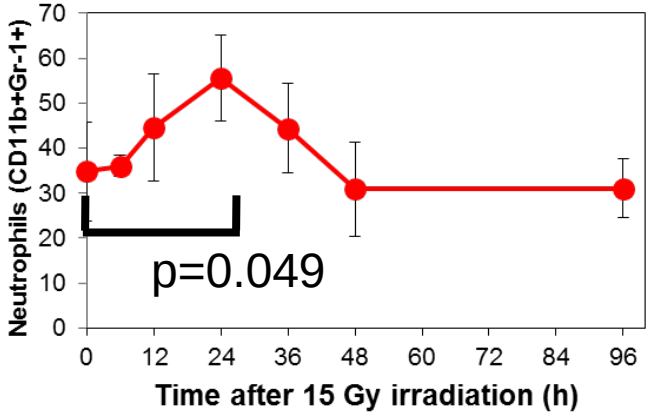
RT Induces Tumor Neutrophilic Infiltration

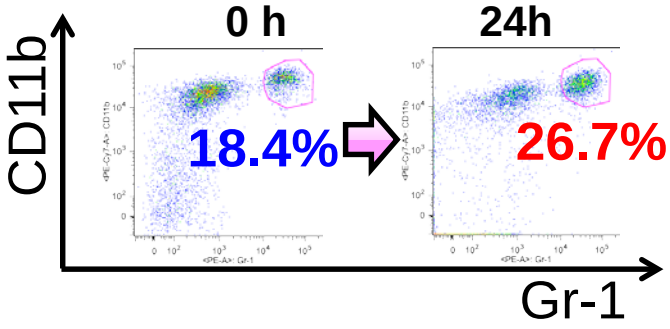
RM-9 in C57BL/6 (N=5)

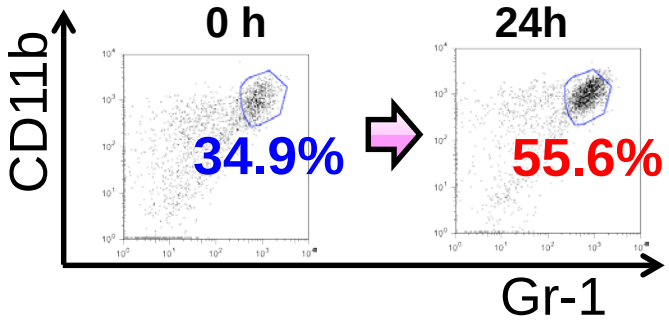




4T1 in BALB/c (N=5)





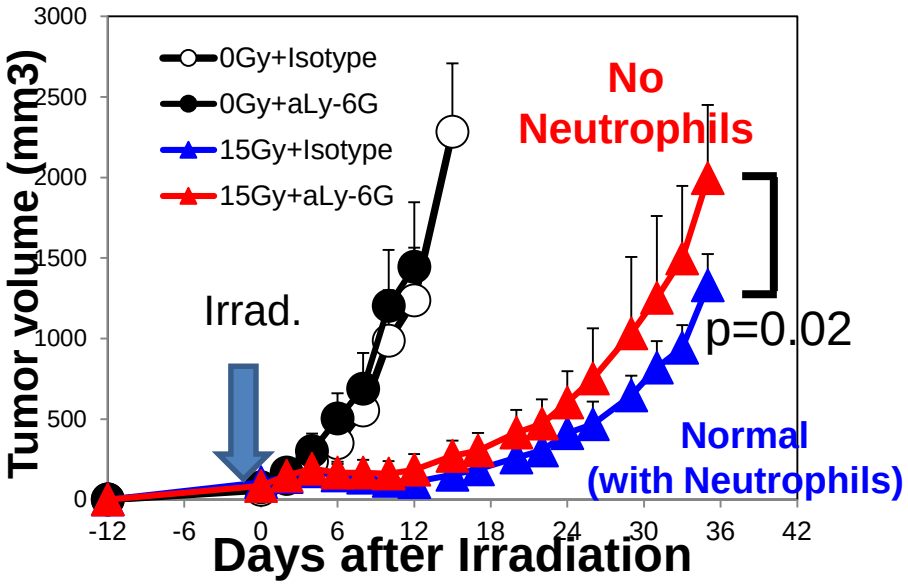


$CD11b^{+}Gr\text{-}1^{+}$ cells peaked at 24 hr after tumor RT

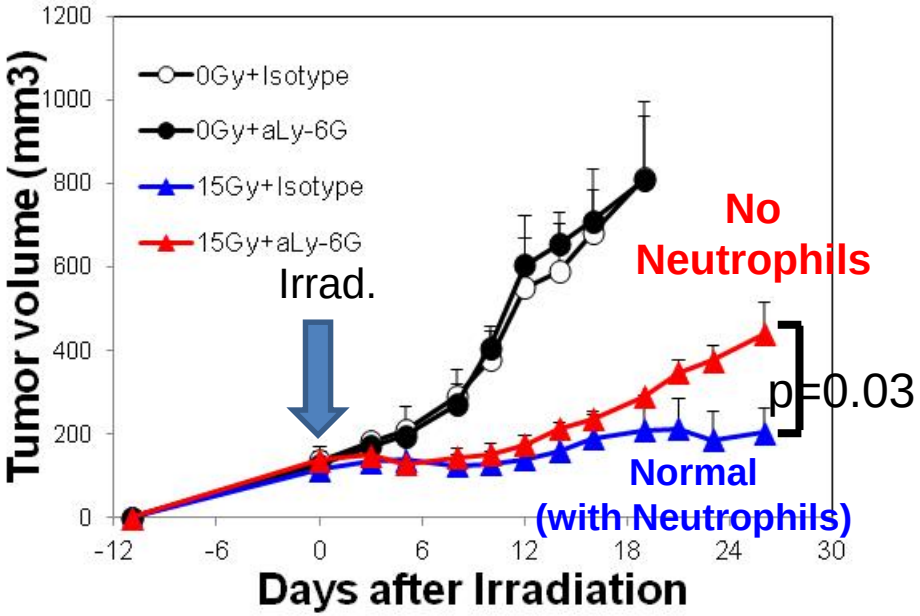
Takeshima and Hannan et. al. unpublished manuscript (under review)

Effect of RT-Neutrophils (RT-Ns) on Tumor Volume

RM-9 (prostate cancer)



4T1 (breast cancer)

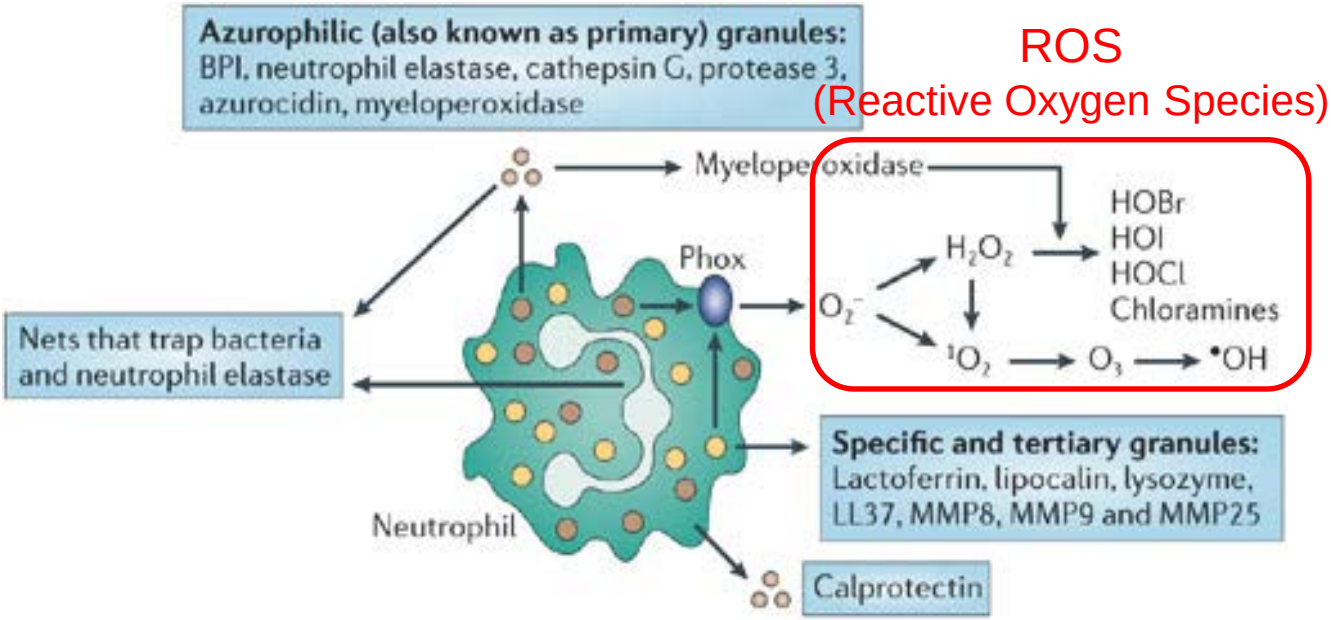


- Radiation-induced neutrophils (RT-N) play a significant role in the anti-tumor effect of RT

RT induced Neutrophils (RT-Ns)

- How does RT-Ns induce tumor growth delay?
- Why does RT-Ns infiltrate tumor after RT?
- Can this be exploited for therapeutic benefit?

Mechanism of RT-N Therapeutic Effect?



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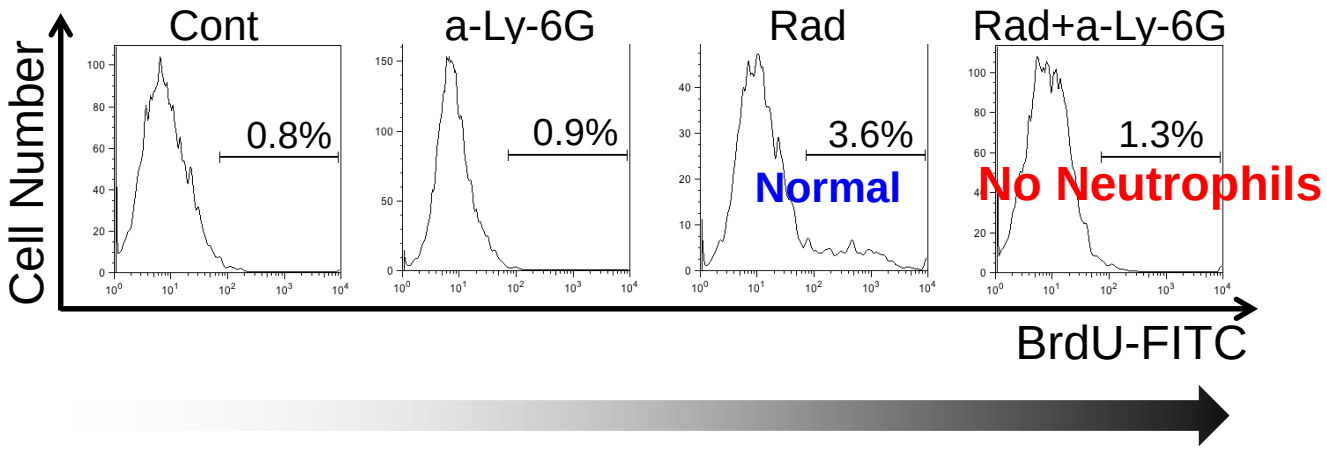
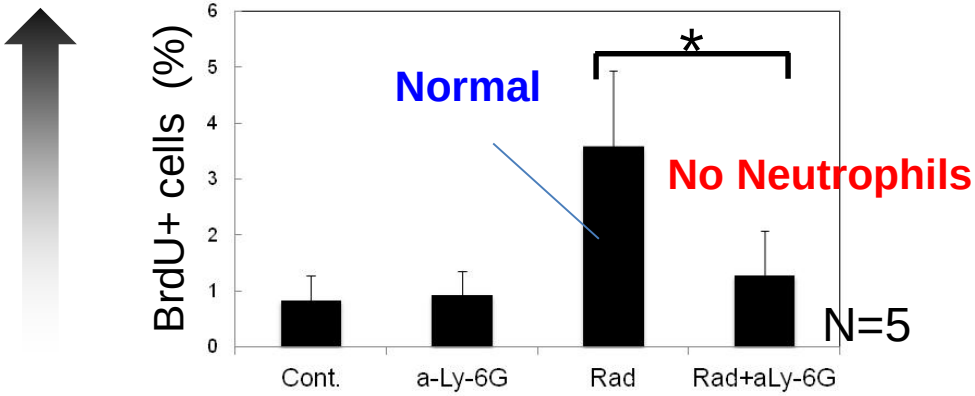
Does RT-Ns Induce Apoptosis in the Tumor?

TUNEL assay by flow cytometry



- RT-Ns induce apoptosis in tumor cells

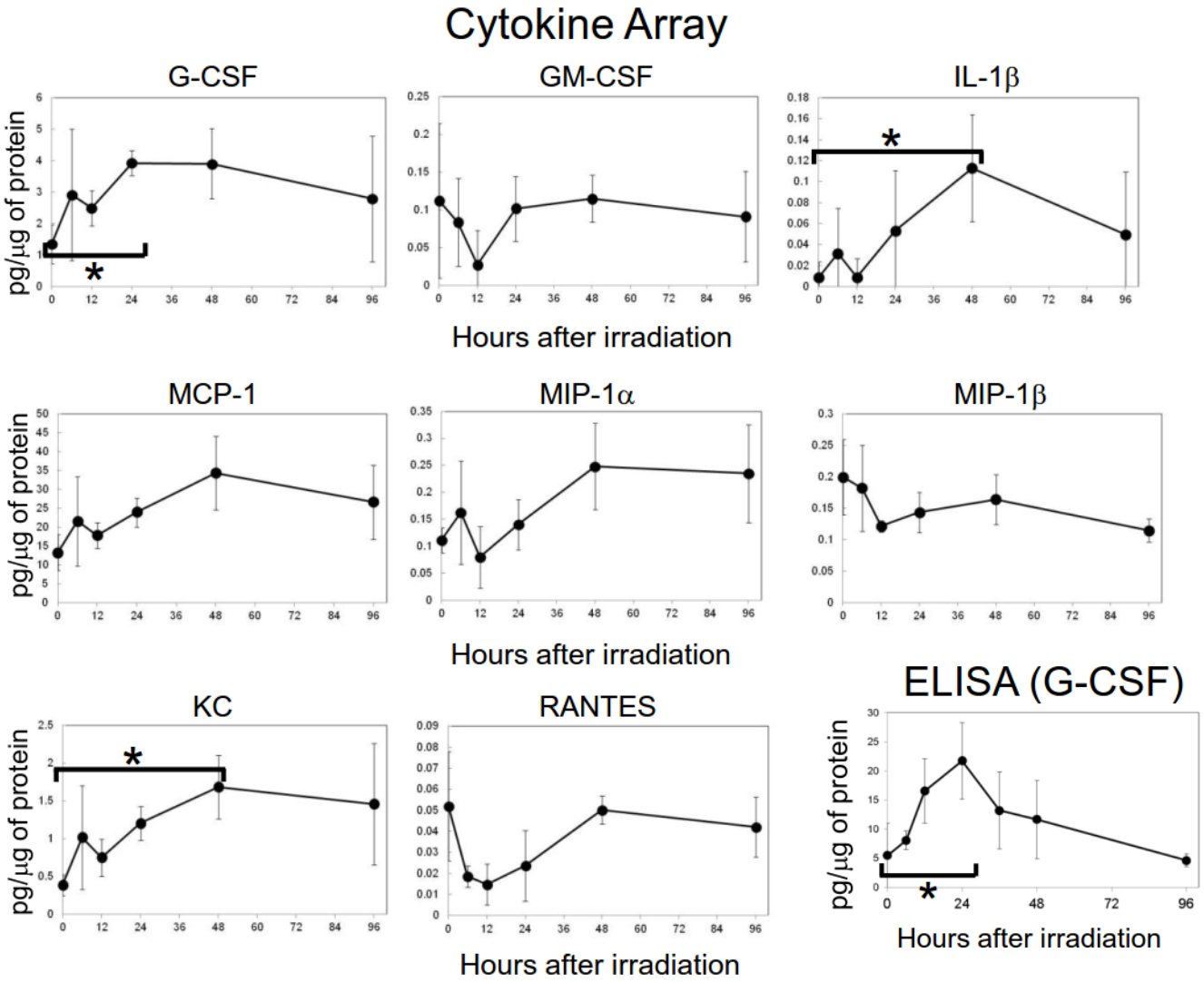
Tumor tissue (Day 4 after RT)



RT induced Neutrophils (RT-Ns)

- How does RT-Ns induce tumor growth delay?
- Why does RT-Ns infiltrate tumor after RT?
- Can this be exploited for therapeutic benefit?

Why does RT-Ns infiltrate tumor after RT?

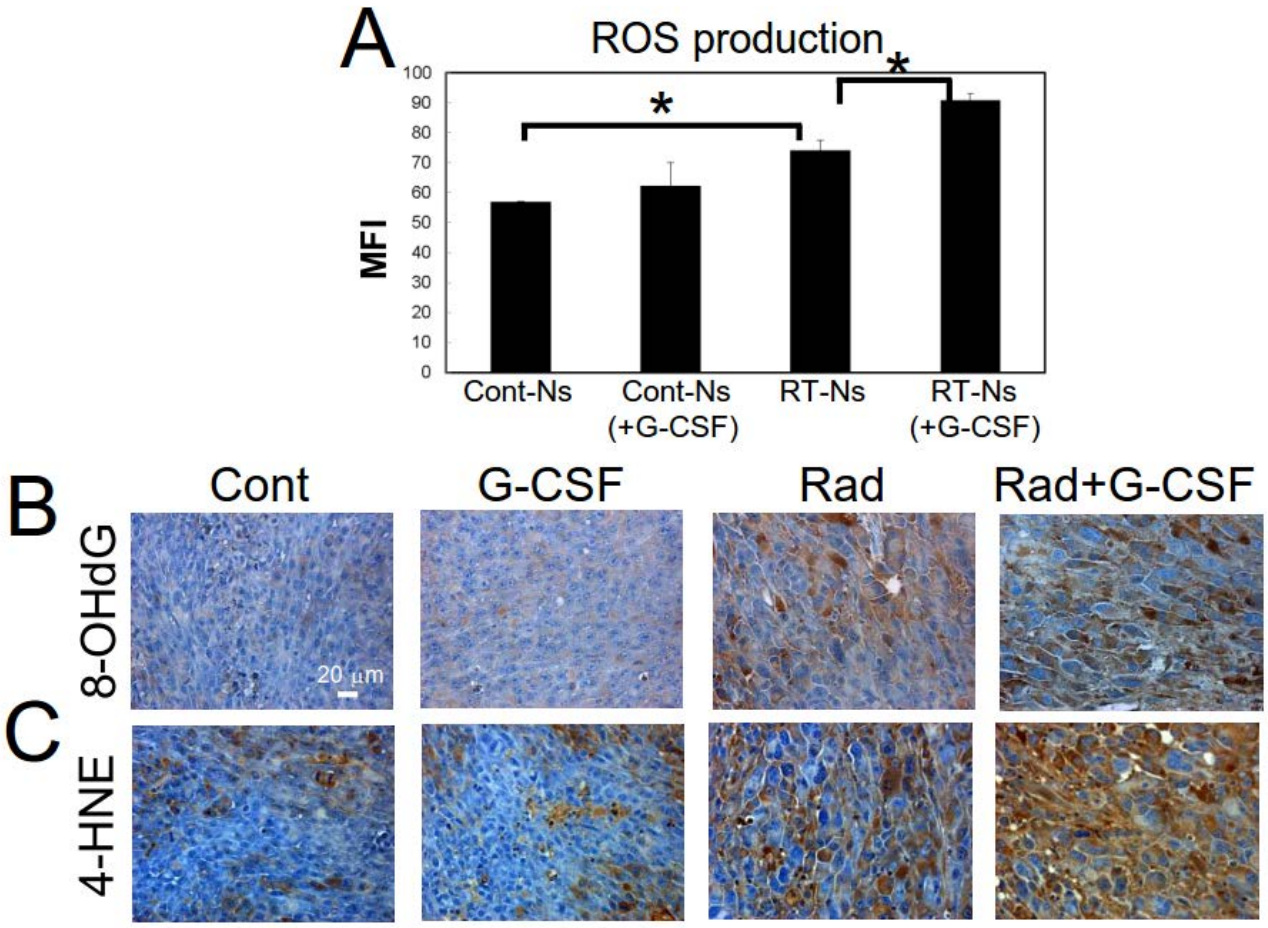


RT induced Neutrophils (RT-Ns)

- How does RT-Ns induce tumor growth delay?
- Why does RT-Ns infiltrate tumor after RT?
- Can this be exploited for therapeutic benefit?

Can G-CSF Increase ROS production by RT-Ns?

FACS of RT-Ns after staining with Dihydrorhodamine 123 (DHR 123)



Takeshima and Hannan et. al. unpublished manuscript (under review)

Does RT-Ns Induce Apoptosis in the Tumor?

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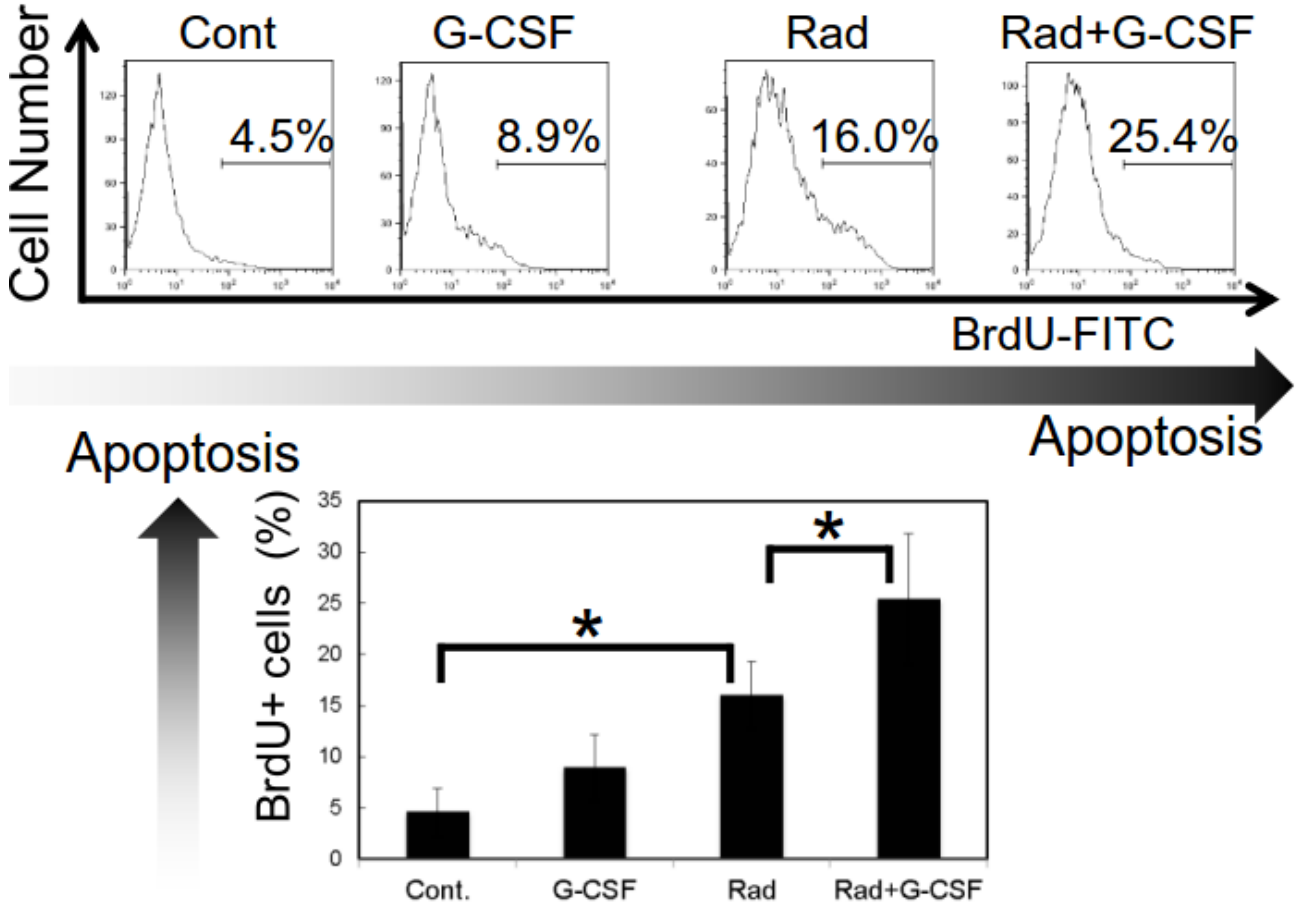
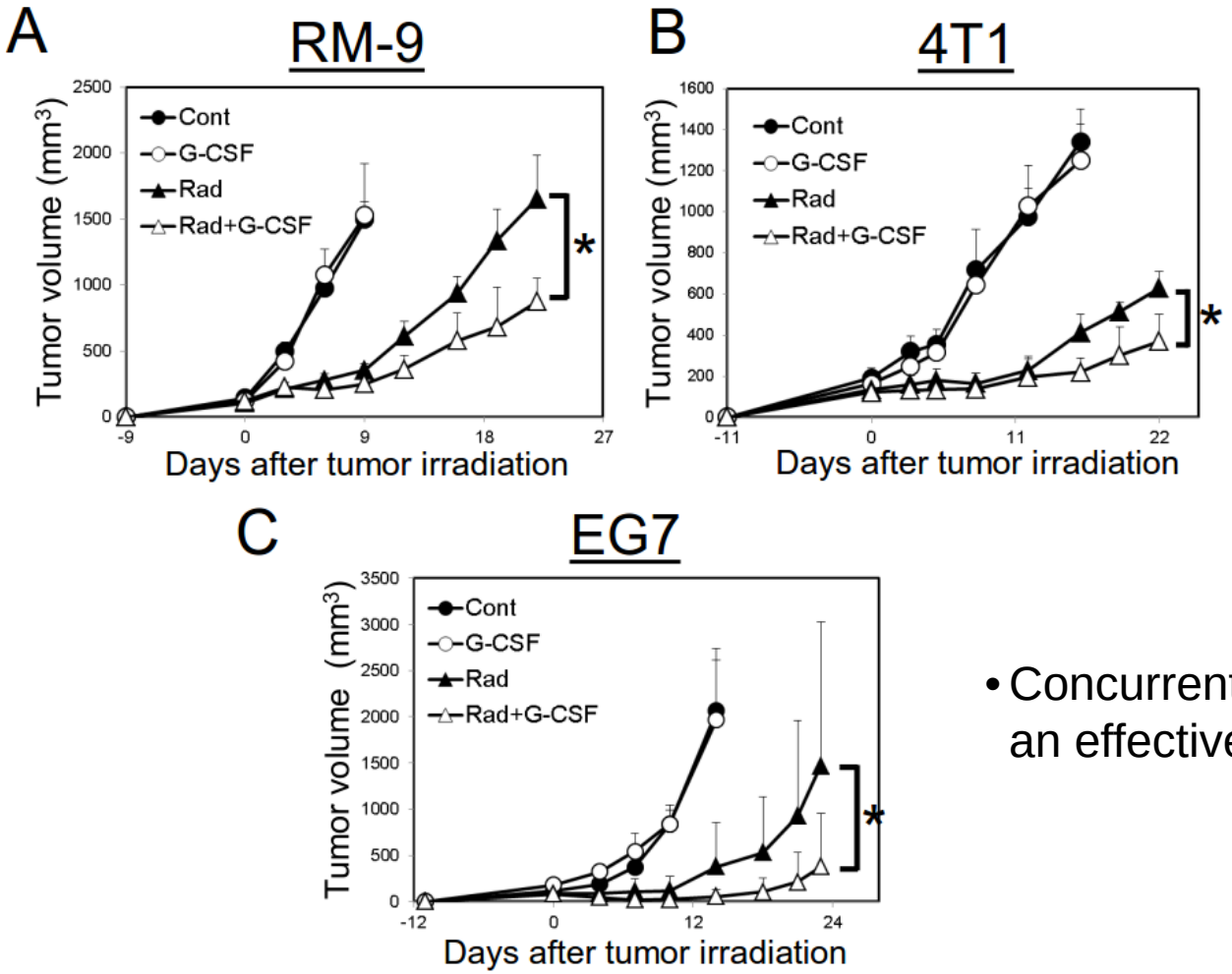


Takeshima and Hannan et. al. unpublished manuscript (under review)

G-CSF Increases RT-N Induced Tumor Growth Delay



- Concurrent G-CSF + RT can be an effective therapeutic regimen

Takeshima and Hannan et. al. unpublished manuscript (under review)

Conclusion

- RT induces the infiltration of neutrophils (RT-Ns) in the tumor
  - Early event that happens within 24-48 hours
- RT-Ns play a role in increasing the therapeutic effect of RT
- This increase is likely mediated by ROS induced apoptosis

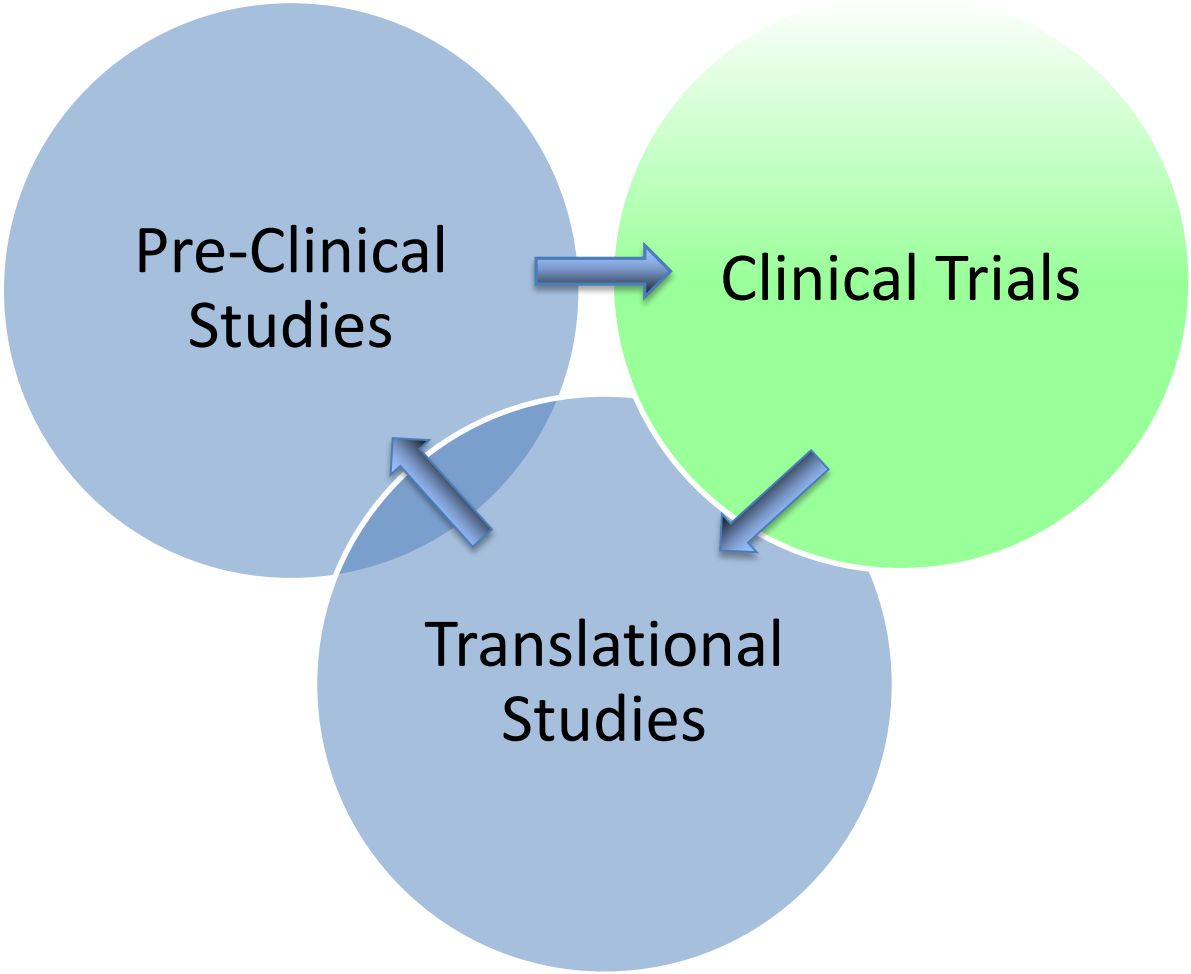
- G-CSF likely plays a role in the recruitment of RT-Ns
- G-CSF can further increase the potency of RT-Ns via ROS
- G-CSF + RT increases tumor-specific CTLs

- G-CSF + RT may be a promising therapeutic strategy to increase RT efficacy and the immunomodulatory effect of RT

Outline

- Immunomodulation by radiation therapy (RT)
  - –Pre-clinical evidence
  - –Limited clinical evidence
- The i-SAbR approach at UTSW
  - –Pre-clinical models
  - –Clinical Trial Design
  - –Translational studies

The i-SAbR approach at UTSW

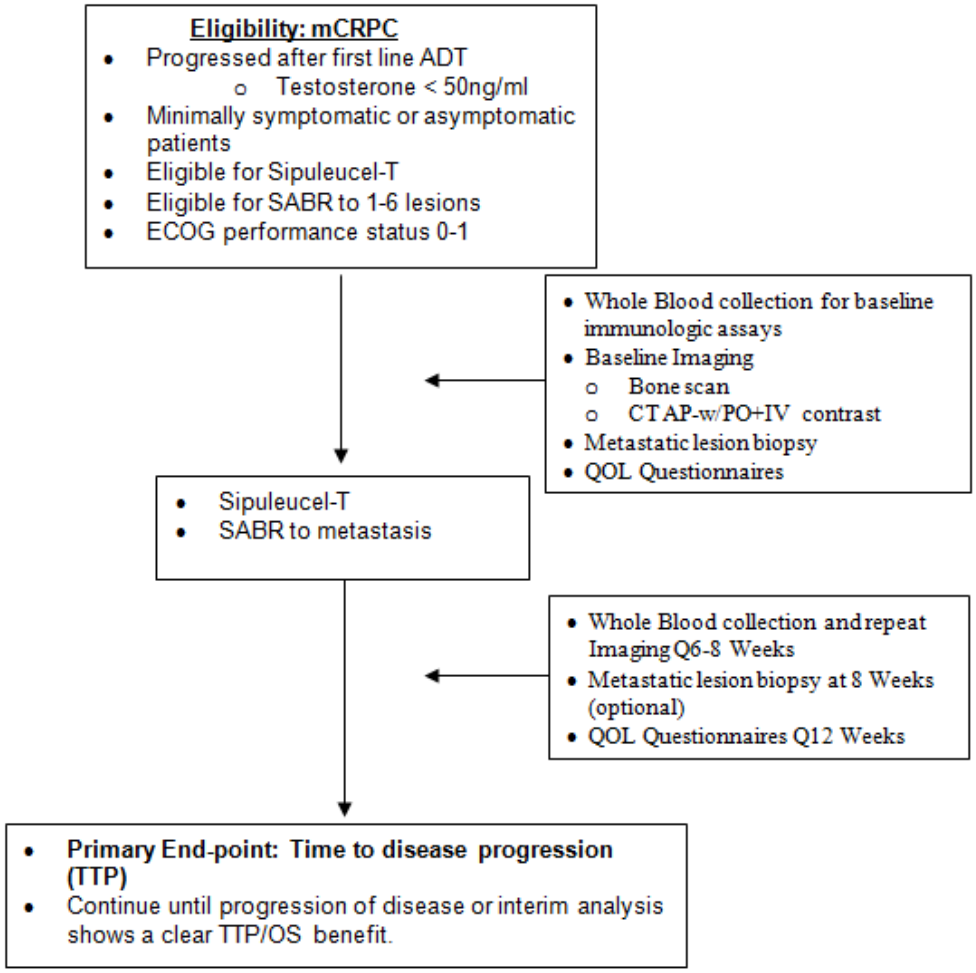


Immunotherapy + SAbR = i-SAbR

i-SAbR Clinical Trials

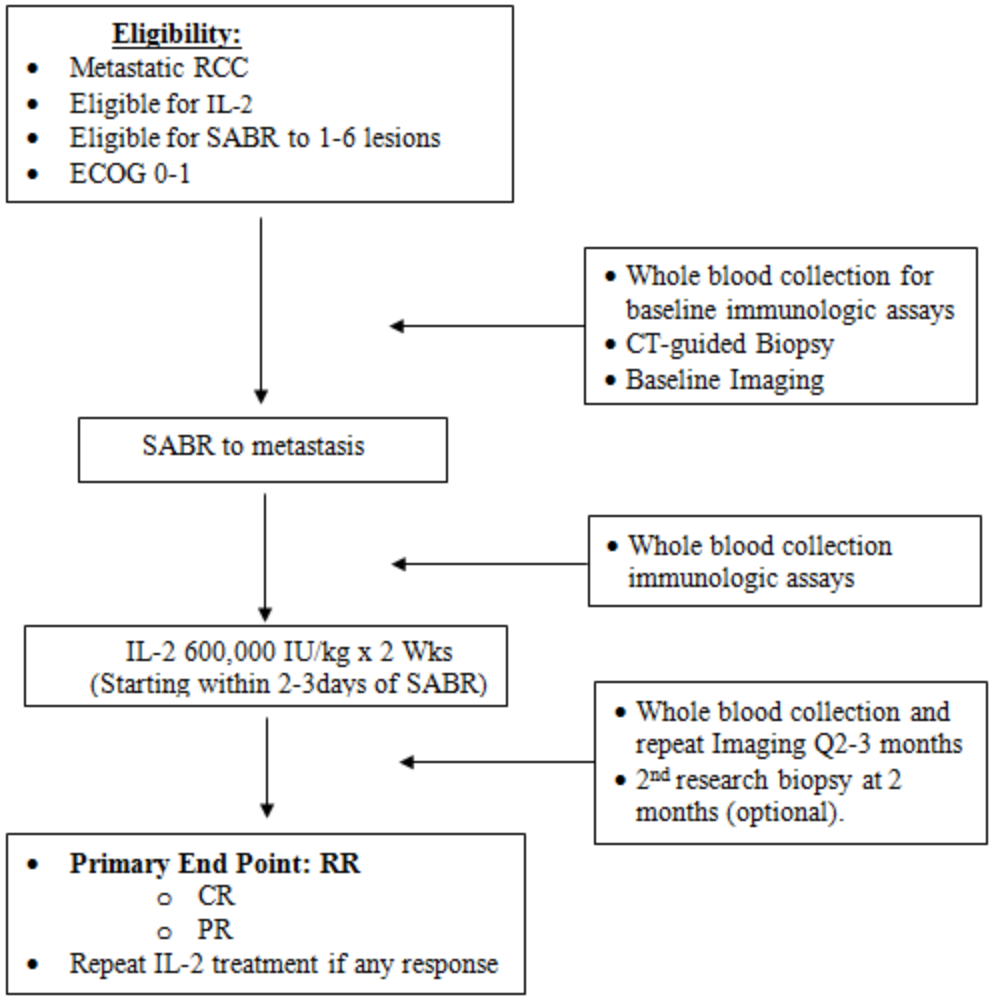
- i-SAbR Sipuleucel-T Trial
- i-SAbR IL-2 Trial
- i-SAbR Nivolumab Trial

i-SAbR Sipuleucel-T Trial



- Combines SAbR with Sipuleucel-T for mCRPCa pts.
- Phase II single arm trial with the historic control being IMPACT
  - Kantoff et. al, NEJM 2010
- SAbR of 1 (21-27Gy) or 3 (26.5-33Gy) fraction to 1-6 sites of disease
- Primary end-point TTP
  - Immune RECIST
- Accrual goal 41

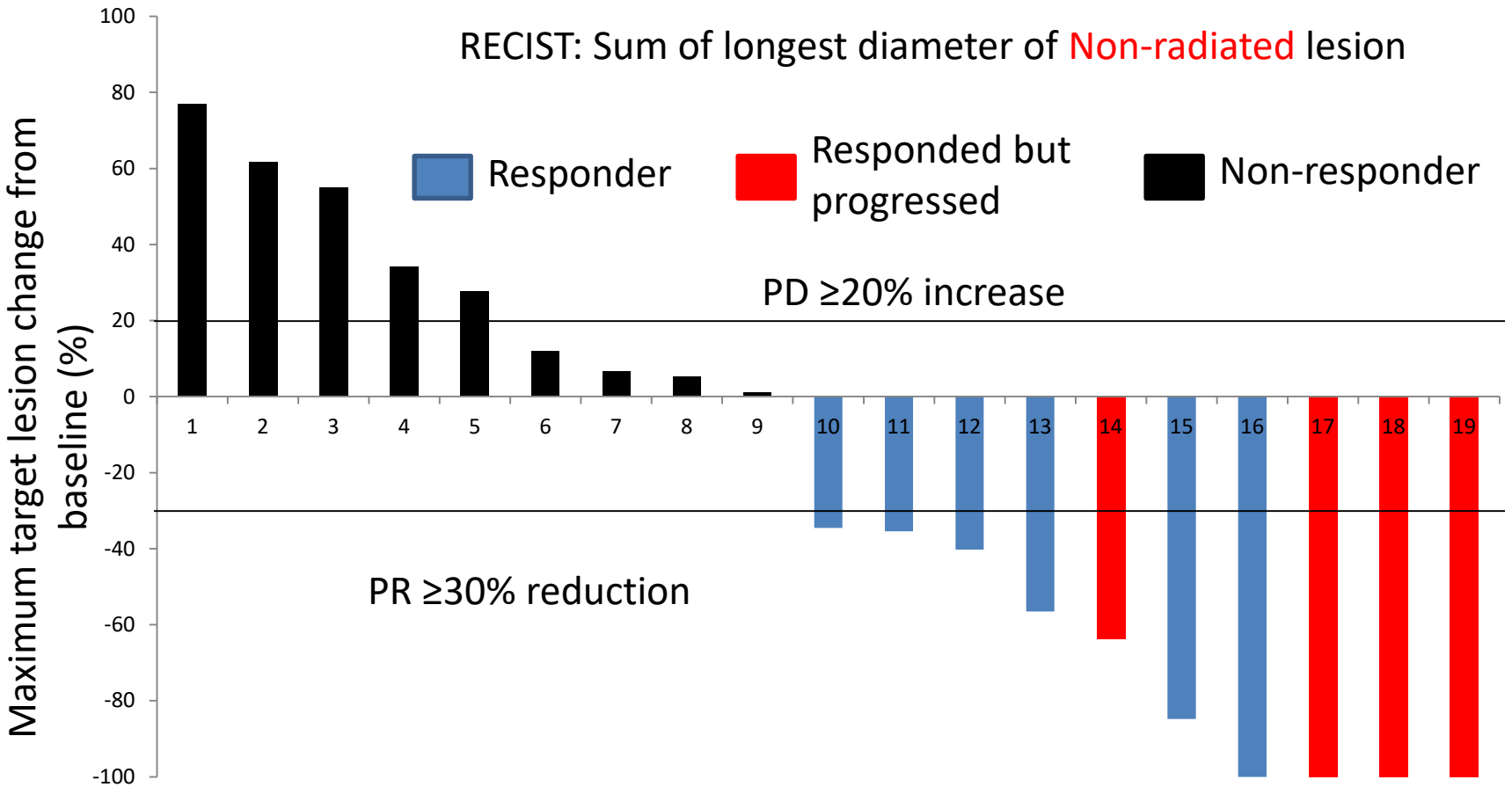
i-SAbR IL-2 Trial



- Single Arm Phase II trial:
  - Well documented historic data available for comparison:
    - McDermott et. al. JCO 2005
    - RR 20-23%; CR 7-9%;
- Primary Endpoint is RR
  - Immune RECIST
- Simon's 2-phase design
  - >60% improvement in RR
    - 23%→36.8%
  - Accrual goal 31
  - If >9 response → phase III trial
- Secondary endpoint of Toxicity, PFS, TTP & OS

i-SAbR IL-2 Trial:

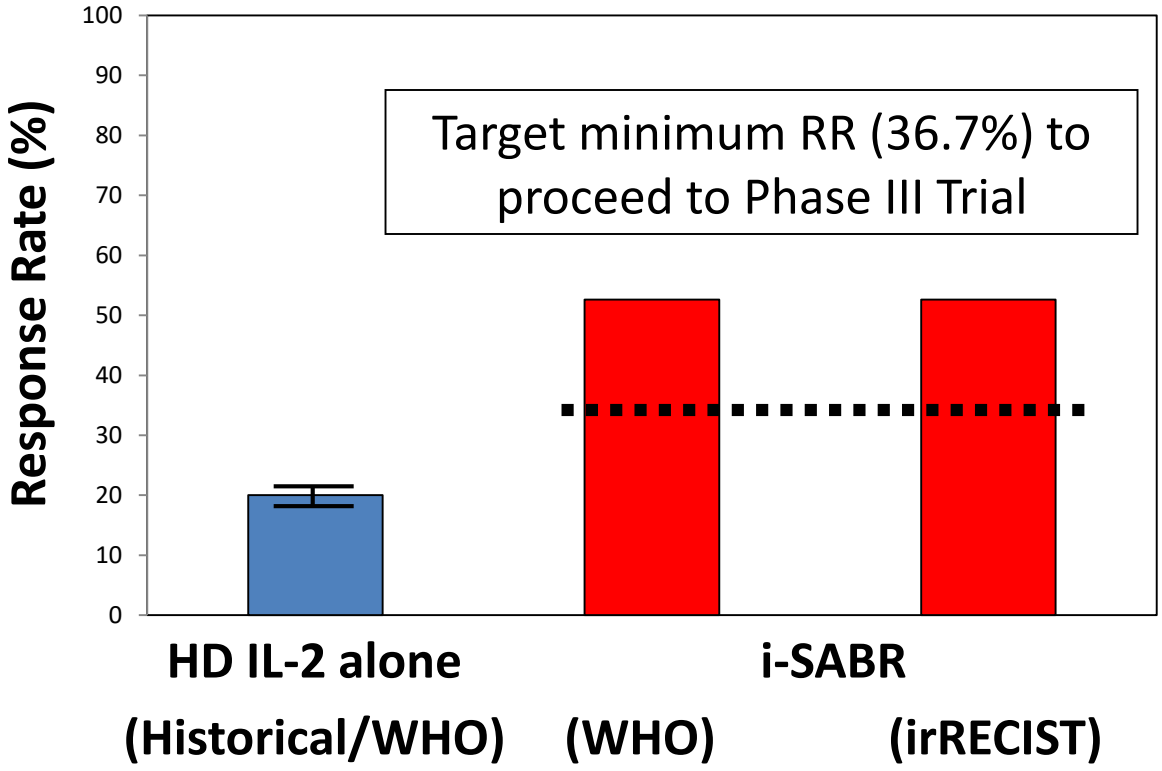
Target lesion abscopal response per patient by irRECIST



- Overall Response: 10 /19 patients responded = 52.6%
- Complete Response: 2/19 = 10.5%

i-SAbR IL-2 Trial:

Target lesion abscopal response per patient by irRECIST



i-SAbR Nivolumab Trial Rationale

Clinical Rationale:

- SAbR is non-invasive metastasectomy
  - Tumor debulking → decreases overall burden of disease
- Bulky metastases are more resistant to systemic therapy
- Larger mets are likely sources of
  - Additional metastases
  - Produces immunosuppresive factors

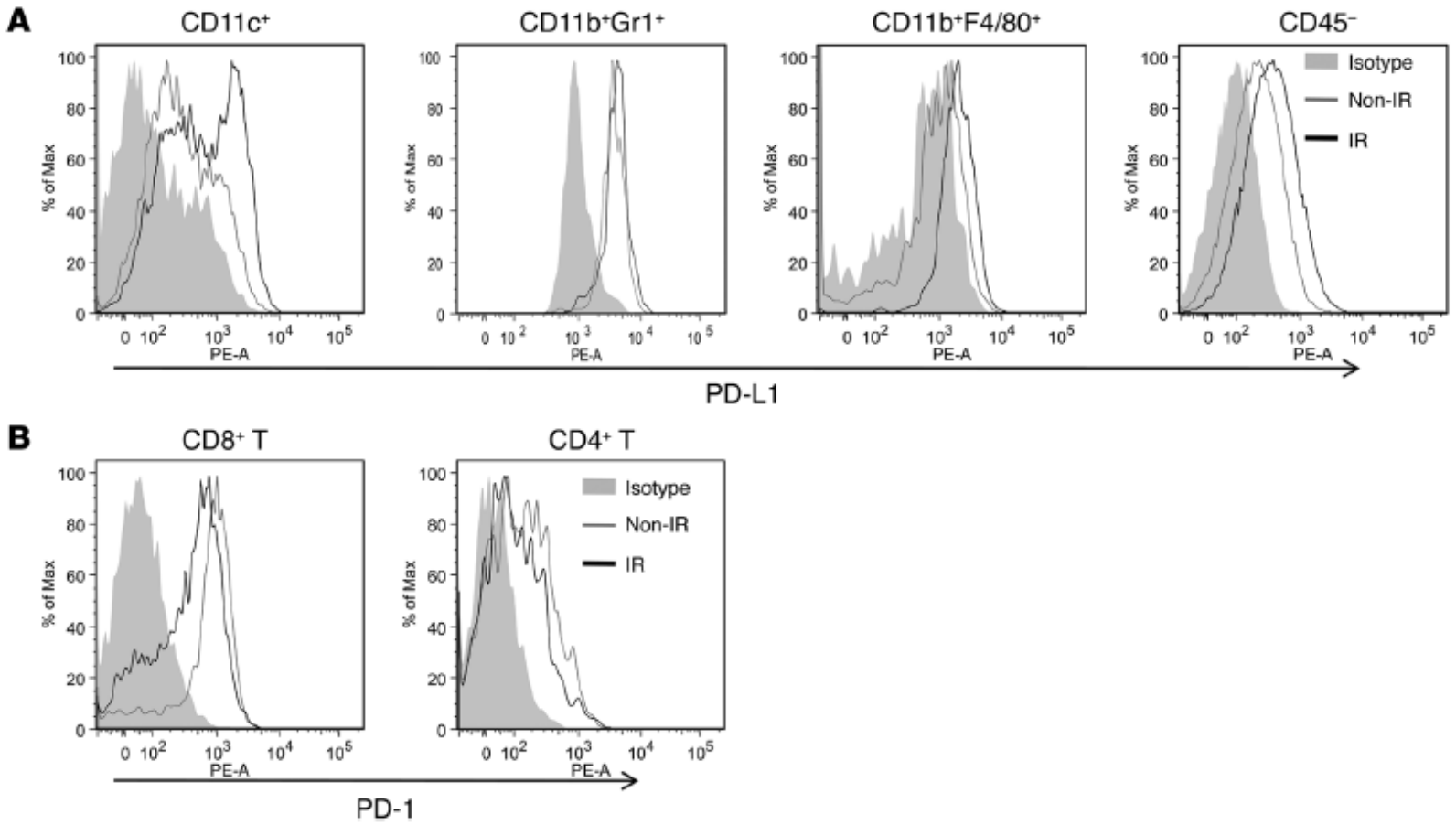
Immunologic Rationale:

- SAbR induces tumor-specific CTLs
  - Lugade et. al. *J Immunol* 2005; Tekeshima et. al *Can Res* 2011; Hannan et. al. *CII* 2012
- SAbR induces PD-L1 expression
  - Deng and Fu et. al. JCI 2014
- SAbR induced CTL has increased PD-1
  - Filatenkov et. al. *CCR*, 2015

Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice

The Journal of Clinical Investigation http://www.jci.org Volume 124 Number 2 February 2014

Liufu Deng,[1] Hua Liang,[1] Byron Burnette,[1] Michael Beckett,[1]
Thomas Darga,[1] Ralph R. Weichselbaum,[1] and Yang-Xin Fu[2]



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Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade

Cancer Res; 74(19) October 1, 2014

Simon J. Dovedi[1], Amy L. Adlard[2], Grazyna Lipowska-Bhalla[1], Conor McKenna[1], Sherrie Jones[1], Eleanor J. Cheadle[1], Ian J. Stratford[2], Edmund Poon[3], Michelle Morrow[3], Ross Stewart[3], Hazel Jones[3], Robert W. Wilkinson[3], Jamie Honeychurch[1], and Tim M. Illidge[1]

PD-1 Restrains Radiotherapy-Induced Abscopal Effect

Cancer Immunol Res; 3(6) June 2015

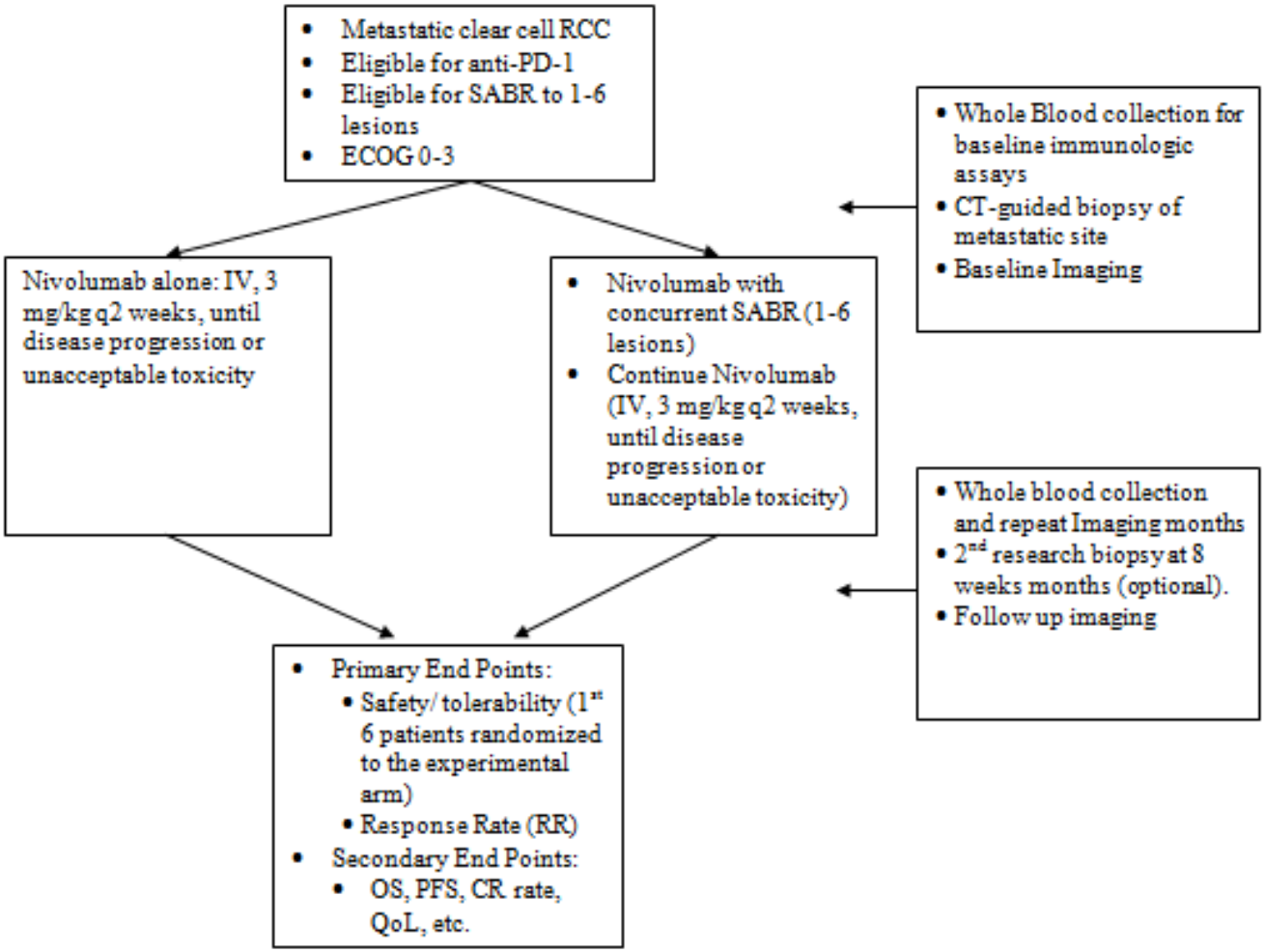
Sean S. Park[1], Haidong Dong[2,3], Xin Liu[3], Susan M. Harrington[3], Christopher J. Krco Michael P. Grams[1], Aaron S. Mansfield[4], Keith M. Furutani[1], Kenneth R. Olivier[1], and Eugene D. Kwon[2,3]

Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Christina Twyman-Saint Victor[1,2*], Andrew J. Rech[2*], Amit Maity[3,4], Ramesh Rengan[3,4†], Kristen E. Pauken[5,6], Erietta Stelekati[5,6], Joseph L. Benci[2,3], Bihui Xu[2,3], Hannah Dada[2,3], Pamela M. Odorizzi[5,6], Ramin S. Herati[1,6], Kathleen D. Mansfield[5,6], Dana Patsch[3], Ravi K. Amaravadi[1,4], Lynn M. Schuchter[1,4], Hemant Ishwaran[7], Rosemarie Mick[4,8], Daniel A. Pryma[4,9], Xiaowei Xu[4,10], Michael D. Feldman[4,10], Tara C. Gangadhar[1,4], Stephen M. Hahn[3,4†], E. John Wherry[4,5,6§], Robert H. Vonderheide[1,2,4,6§] & Andy J. Minn[2,3,4,6§]

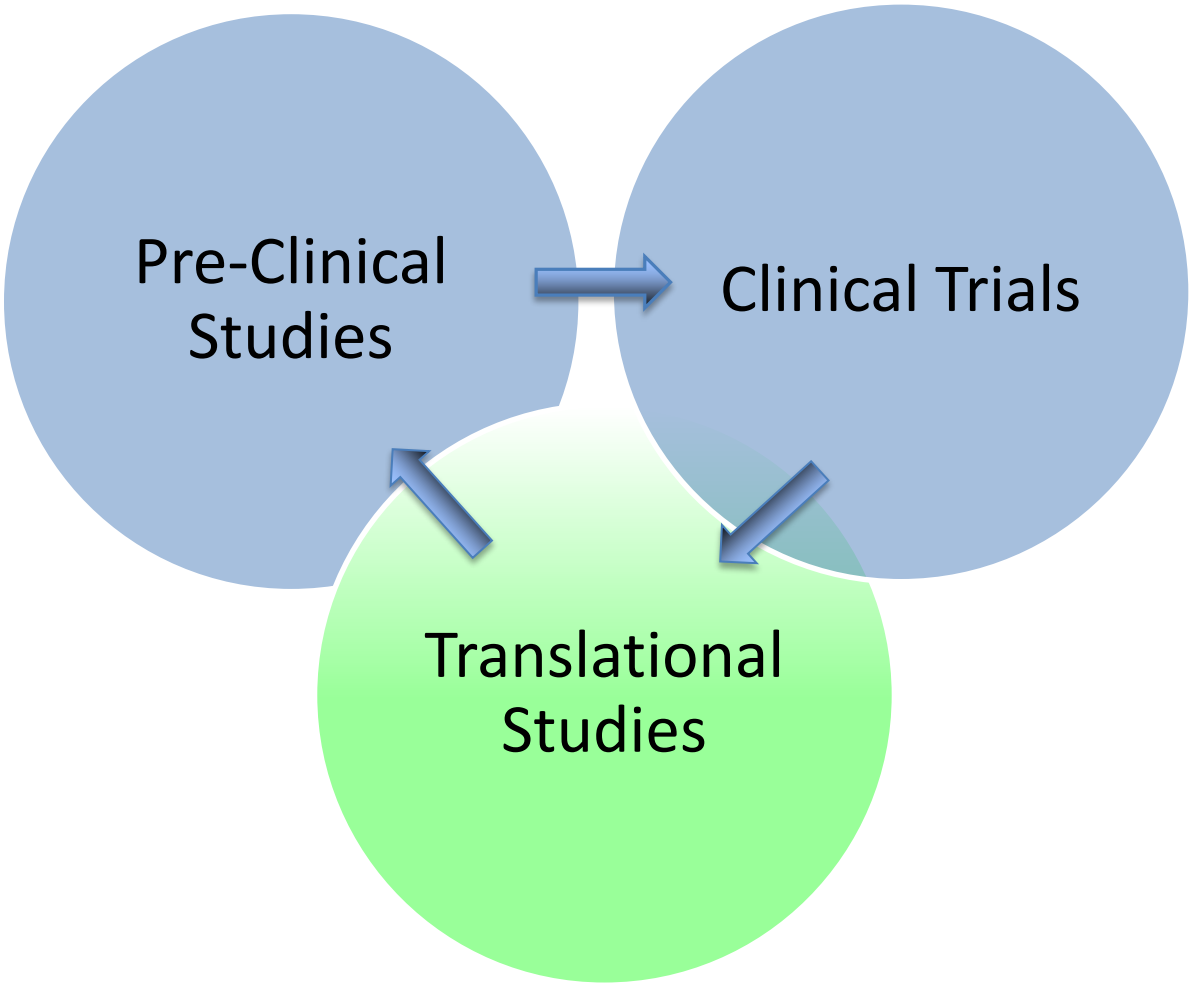
Phase II Randomized Trial of Nivolumab and SAbR versus Nivolumab Alone for mRCC

STUDY SCHEMA



1:2 Randomization: 58 and 29 patients required in the arms respectively

The i-SAbR approach at UTSW



NRG-LU002

Maintenance Systemic Therapy Versus Consolidative Stereotactic Body Radiation Therapy (SBRT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial

Puneeth Iyengar MD, PhD, *UT Southwestern*	PI
Daniel Gomez MD, *MDAnderson Cancer Center (MDACC)*	Co-PI
Robert Timmerman MD *UT Southwestern* **Hak Choy MD, *UT Southwestern*** **Clifford Robinson MD, *Washington University of St. Louis*** **Charles Simone MD, *Maryland Proton Center***	Co-Chairs
David Gerber MD, *UT Southwestern* **Saiama Waqar MD, *Washington University of St. Louis***	Med Oncology
Michael Weldon MSc, DABR, *Ohio State University* **Jackie Wu PhD, *Duke***	Physics
Ben Movsas MD, *Henry Ford Hospital*	Quality of Life
Kirk Jones MD, *University of California at San Francisco*	Pathology
Adam Dicker MD, PhD, *Jefferson* **Max Diehn MD, PhD, *Stanford*** **John Heymach, MD, MDACC**	Translational
Chen Hu, PhD, *Johns Hopkins University/NRG Oncology*	Statistics

Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy **Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery**	**STRATIFY**	**Histology:** **Squamous vs. Non-squamous** **Systemic Therapy:** **Immunotherapy vs Cytotoxic Chemotherapy**	**RANDOMIZE**	**Arm 1:** **Maintenance systemic therapy alone** **Arm 2:** **SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation.**

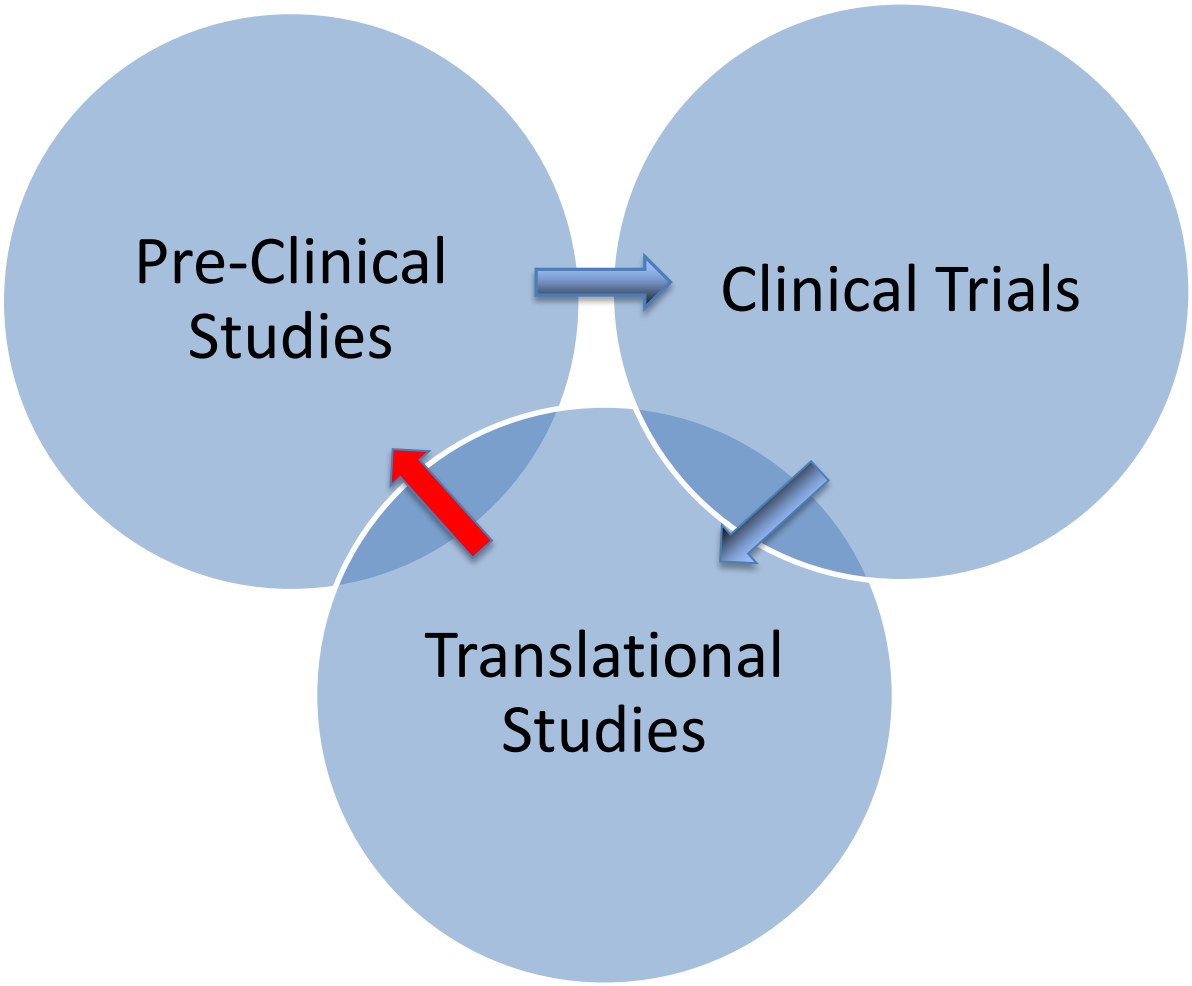
i-SAbR Trial Translational Correlates

- Patient tissue, sera and PBMC collected before (and occasionally after) treatment.
  - PBMCs are frozen with Serum/DMSO for functional assay

Goals of Translational Correlatives

- Identify mechanisms of synergy
  - Can we improve on the current regimen?
- Identify mechanisms of resistance
  - About 50% of patients are still expected to fail!
- Predictive Biomarker?
  - Can we better select patients who will respond?

The i-SAbR approach at UTSW



Thank You
Questions/suggestions?