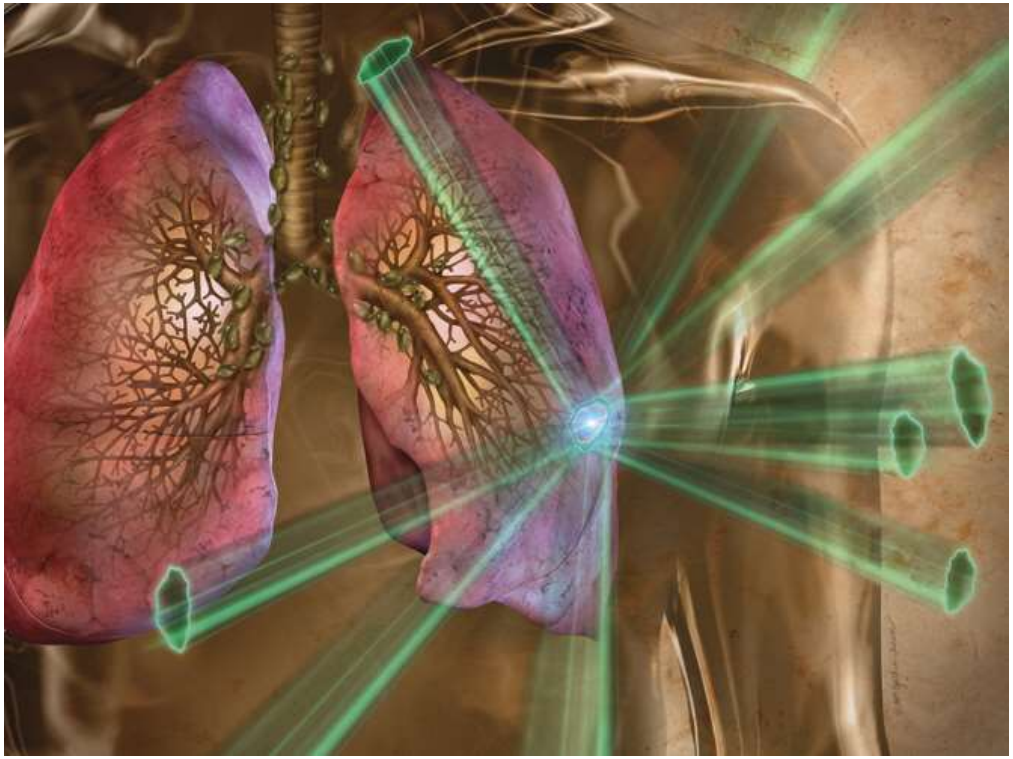
Exploiting Radiation – IO Combinations for Solid Tumors



Puneeth Iyengar, MD, PhD

Assistant Professor

Thoracic Radiation Oncology Chief

Associate Vice Chair of Clinical Research

Department of Radiation Oncology

Harold Simmons Comprehensive Cancer Center

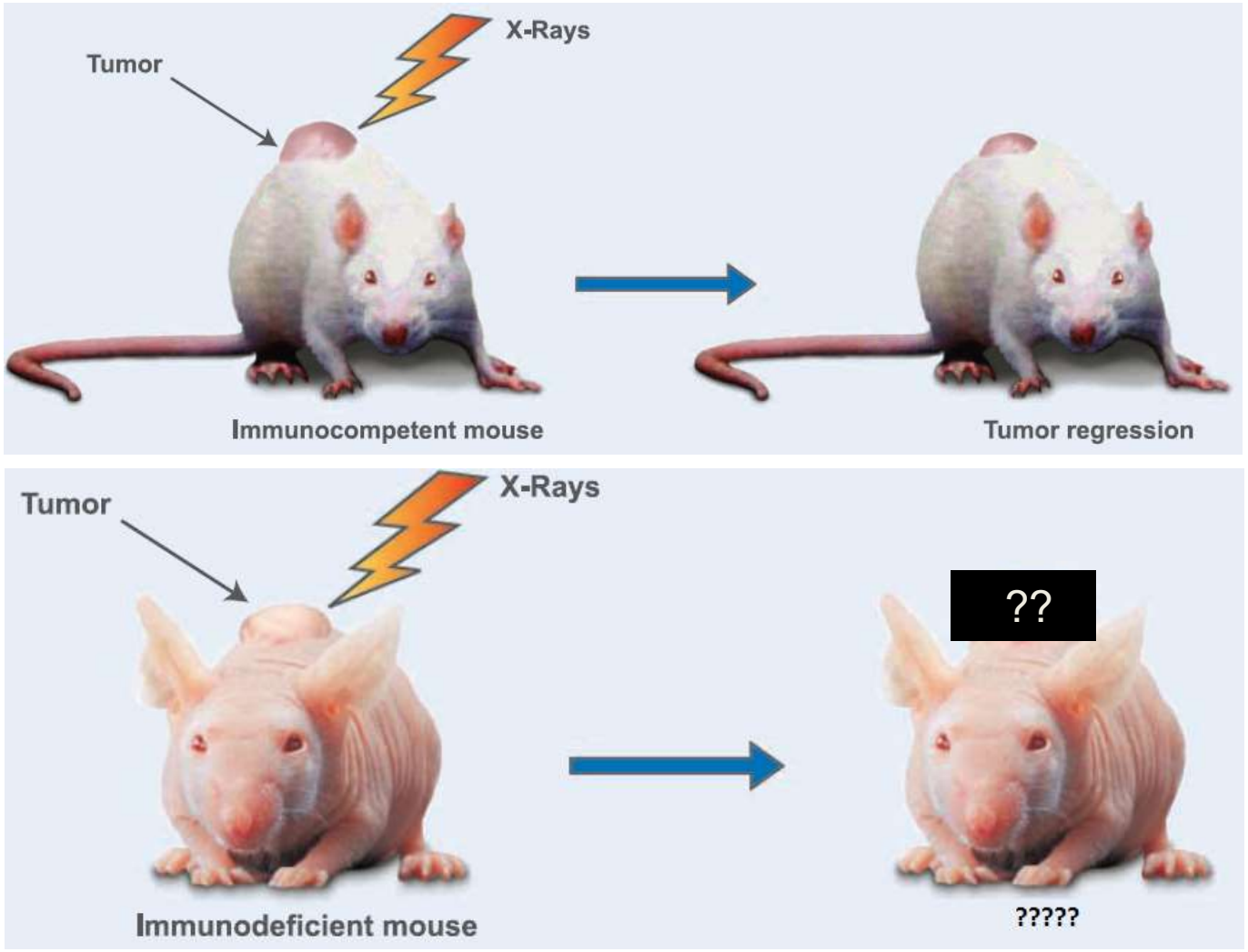
Center for Human Nutrition

UT Southwestern Medical Center

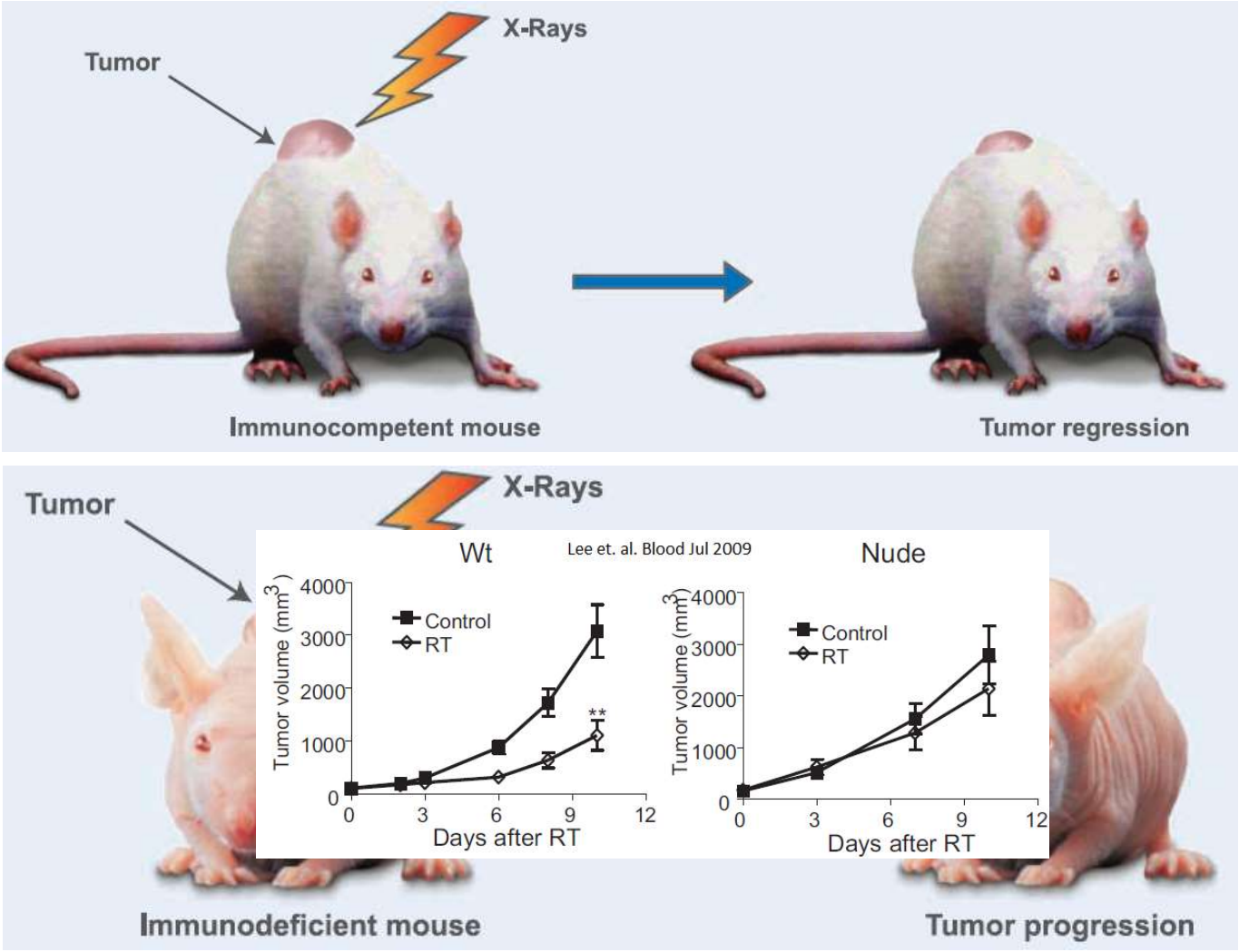
UT SOUTHWESTERN

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

Immunomodulation by Radiation Therapy



Immunomodulation by Radiation Therapy



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

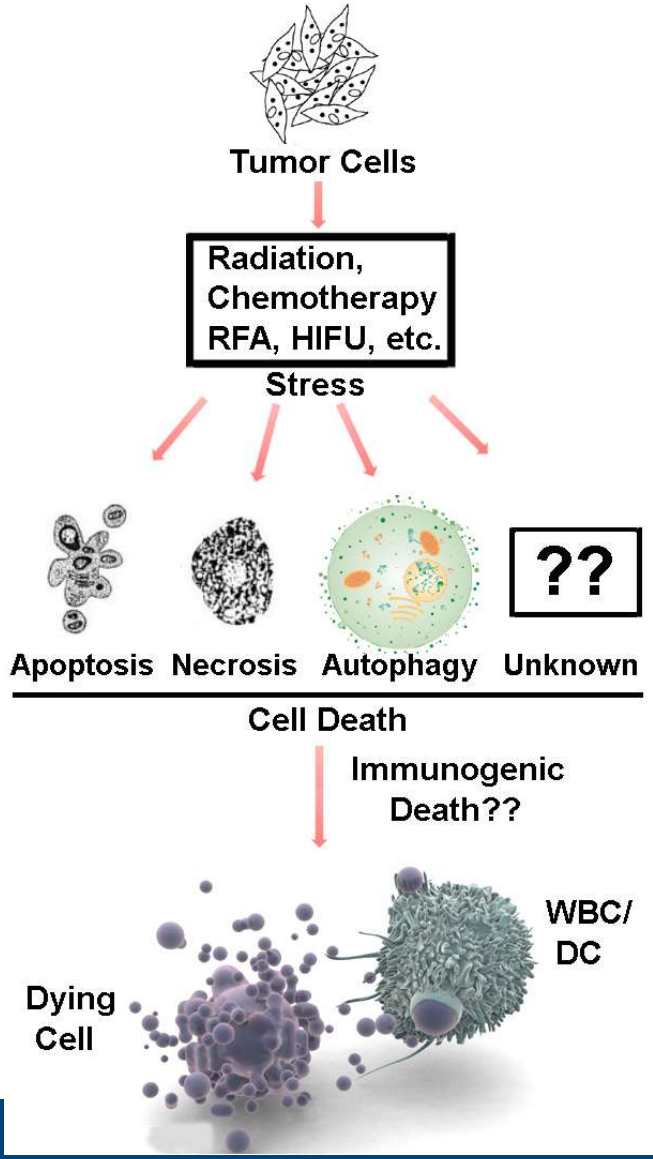
Outline

- Immunomodulation of tumor development by radiation therapy (RT)
  - **Pre-clinical evidence**
  - Limited clinical evidence
- Combining IO and RT
  - Pre-clinical models
  - Clinical trials and 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
    - –Radiation also spares the regional draining lymph nodes
  - –Keeps the antigen depot within the host and induces an immunogenic cell death

Immunomodulation by RT

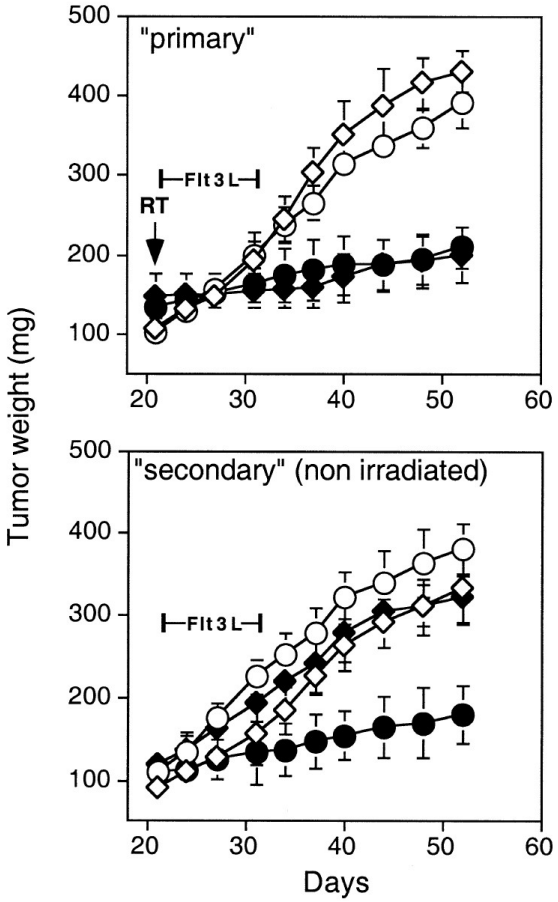


- RT leads to the translocation and release of Danger (or Damage)-Associated Molecular Patterns (DAMPS)
  - HMGB1, HSP70, Calreticulin, ATP
  - DAMPS recruit Dendretic Cells into the tumor-microenvironment
- RT increases pro-inflammatory cytokine release
- RT increases the permeability of the tumor -microenvironment

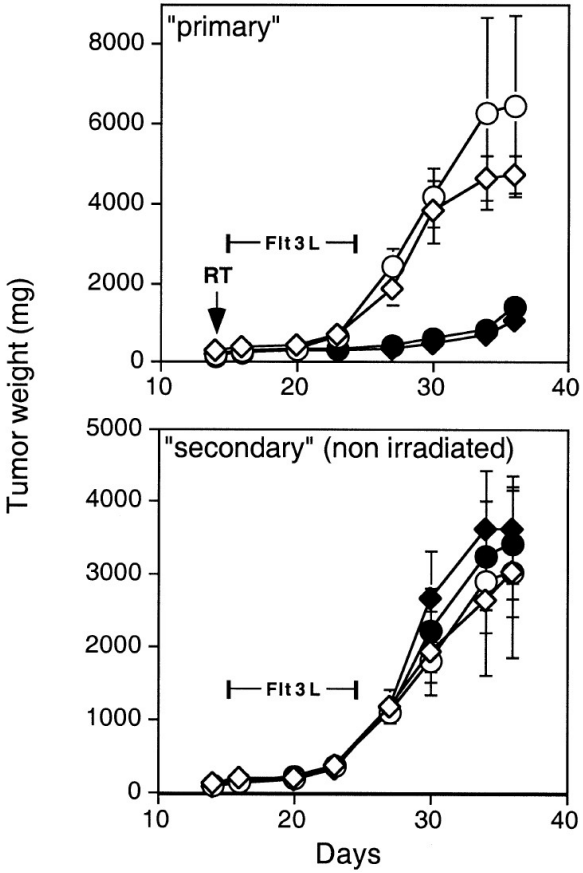
IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

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

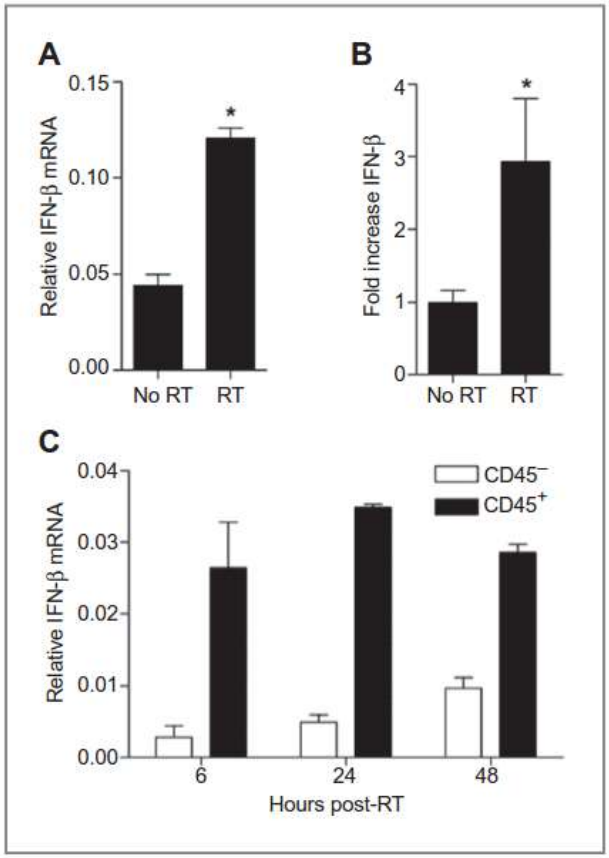
Filled Diamonds=RT

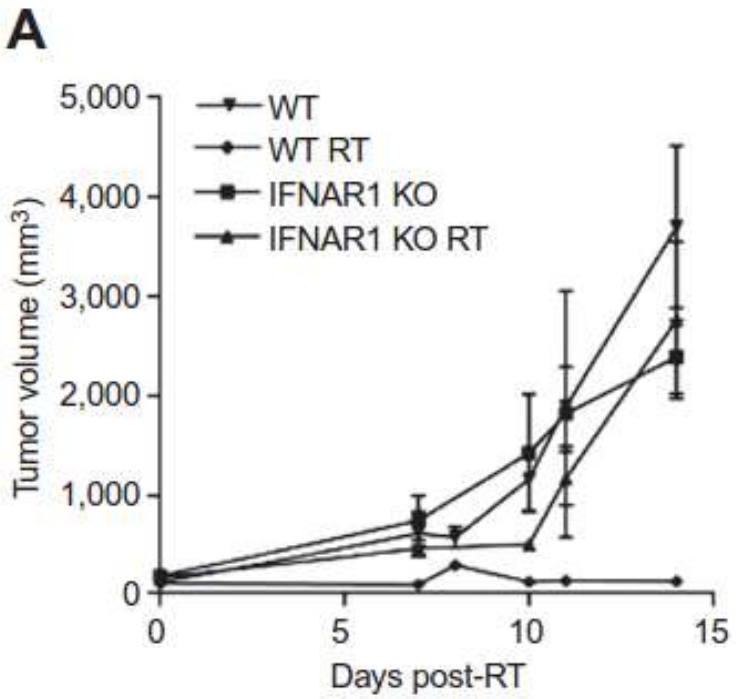
Filled Circles= Flt3-L+RT

Microenvironment and Immunology 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]

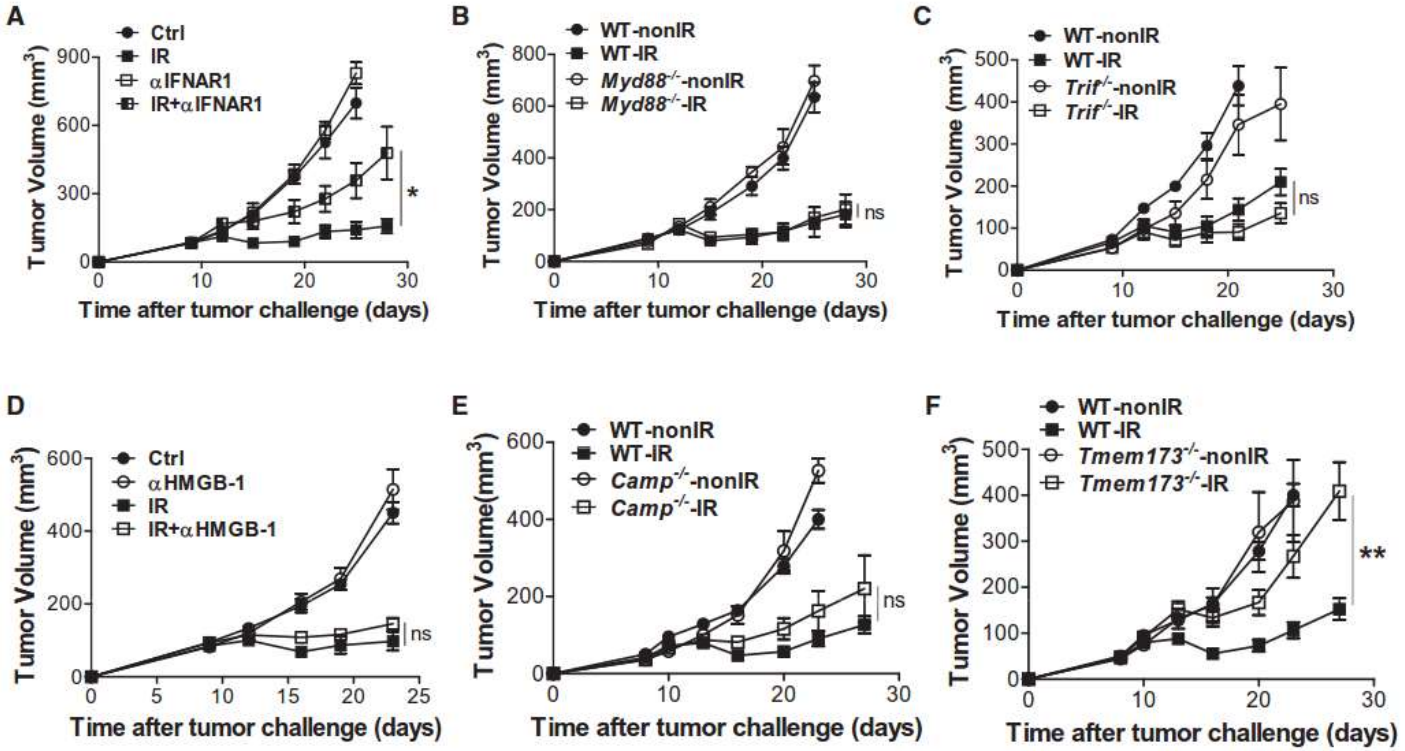




Immunity
Article
Immunity *41*, 843–852, November 20, 2014 ©2014 Elsevier Inc.
CellPress

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,*]

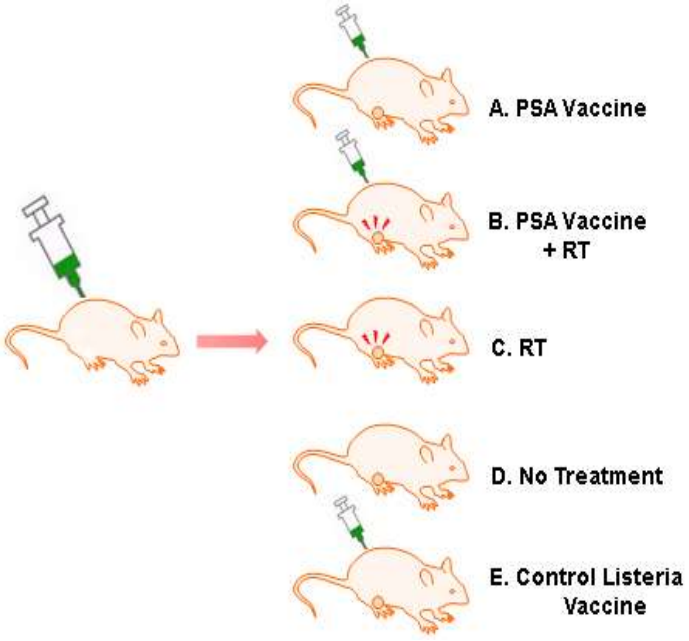


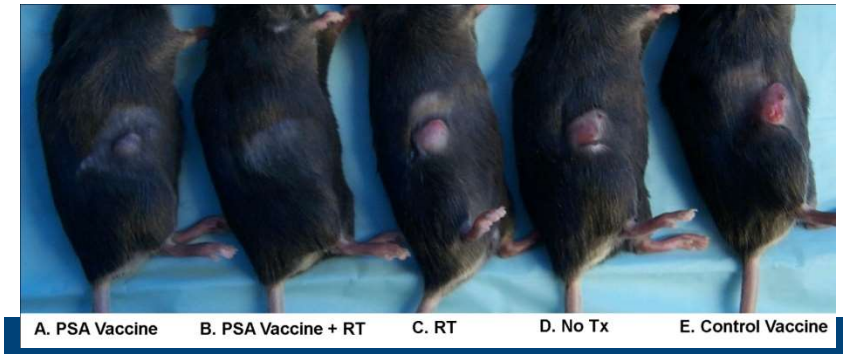
Immunomodulation by RT

Can RT immunomodulation be exploited for therapeutic benefit?

Pre-Clinical Data

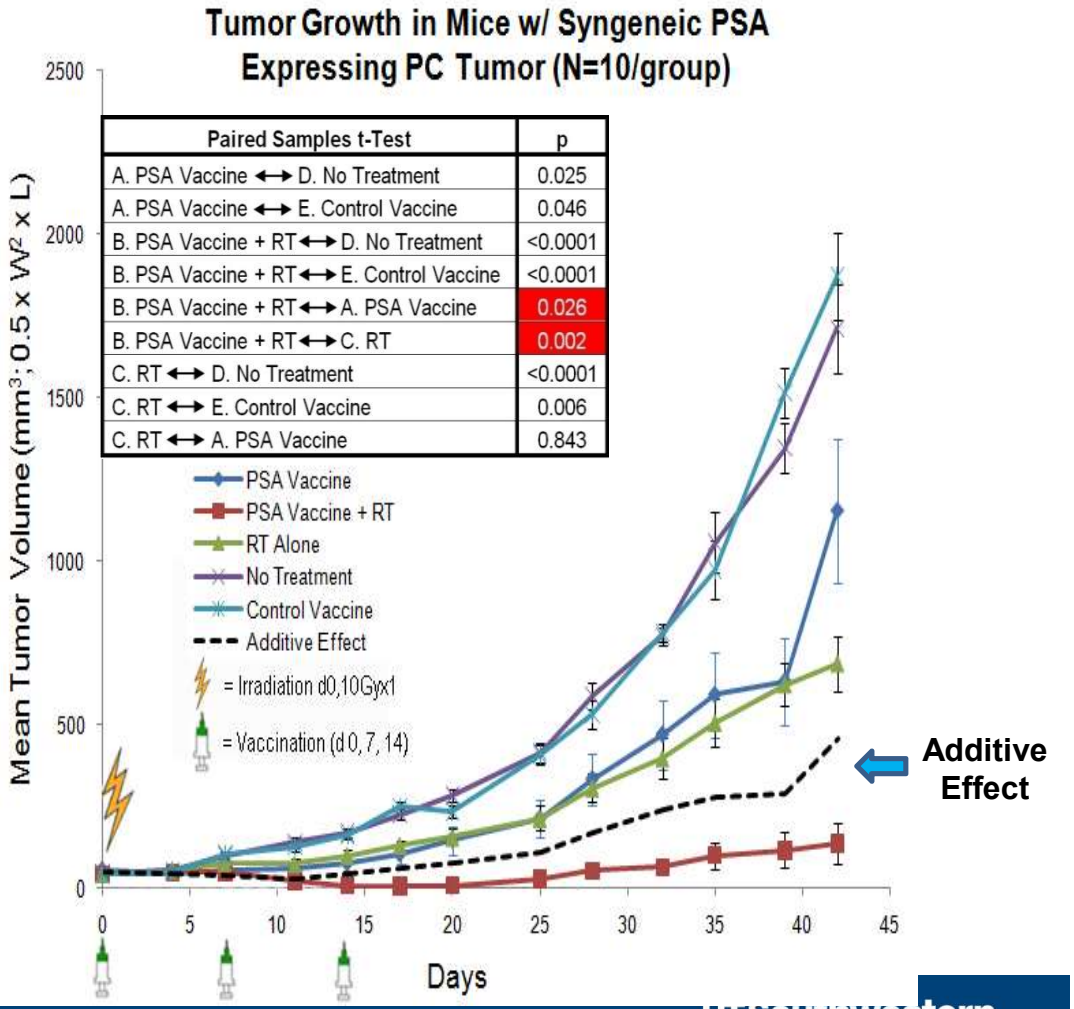
Synergy between RT and IT:





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



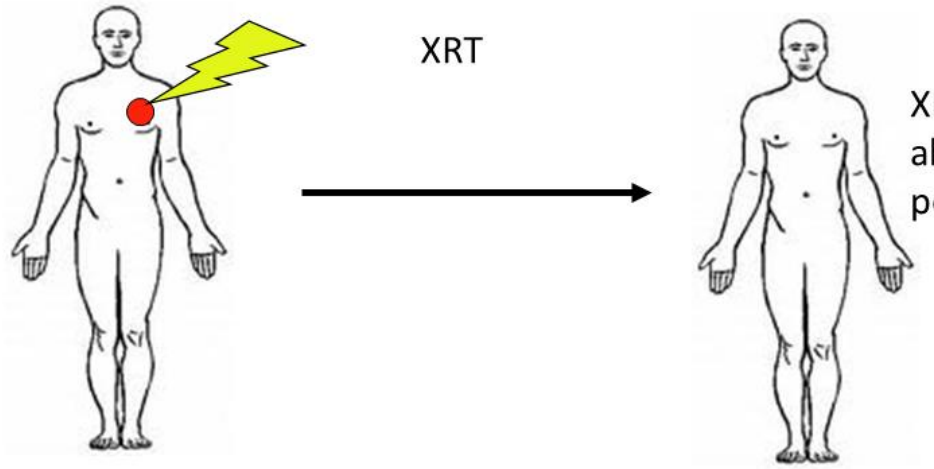
Hannan et. al. , Cancer Immunol Immunother, May 2012

UTSouthwestern Medical Center

Outline

- Immunomodulation of tumor development by radiation therapy (RT)
  - –Pre-clinical evidence
  - –**Limited clinical evidence**
- Combining IO and RT
  - –Pre-clinical models
  - –Clinical trials and translational studies

Abscopal Response

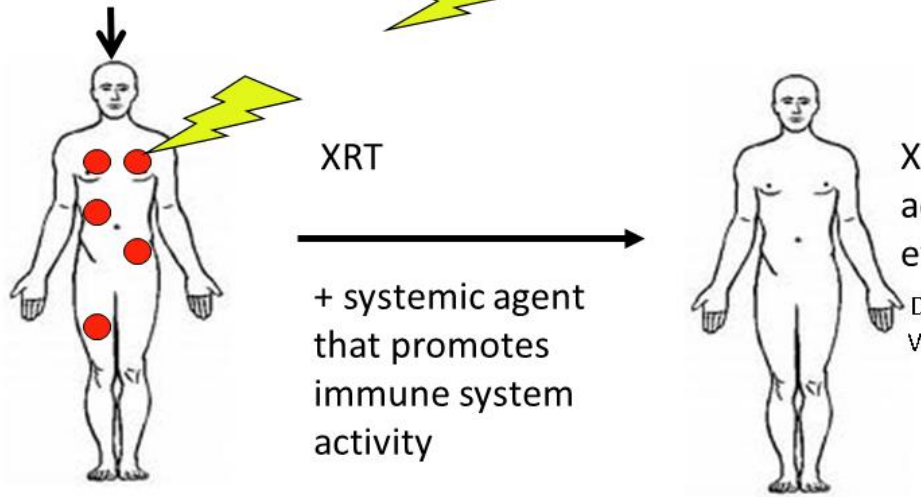


XRT has direct cell kill function; ablative effect during high dose per fraction radiation.

= Tumor site

Immunotherapy

XRT = external beam radiation



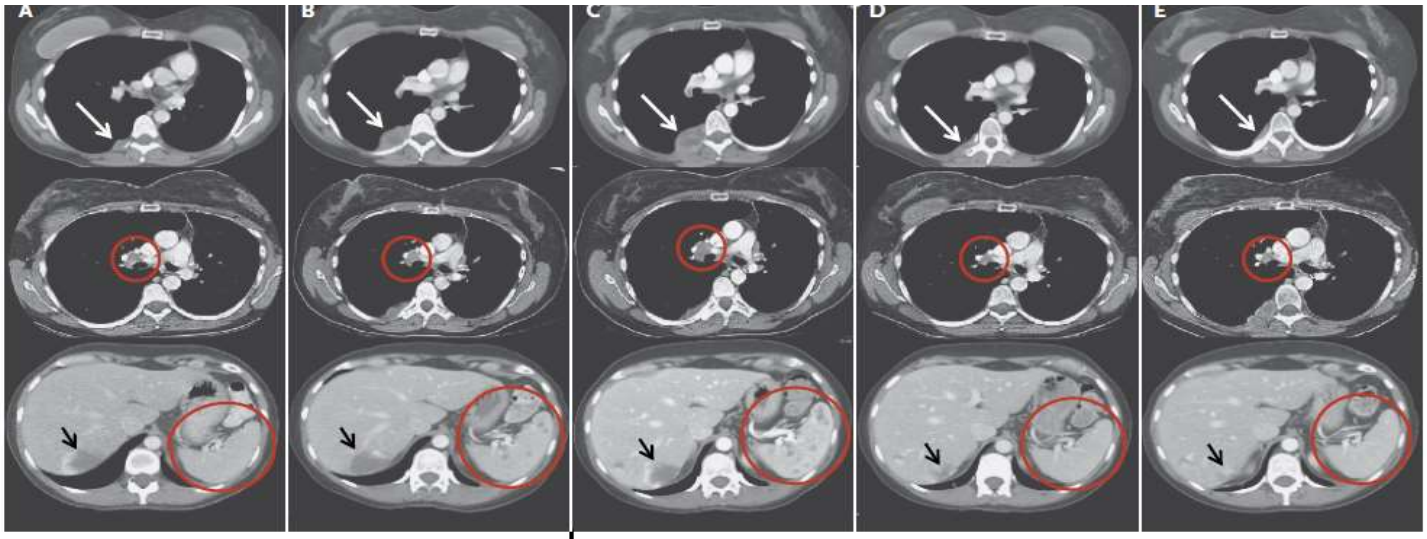
XRT stimulates immune action against all tumor sites, even those not irradiated.

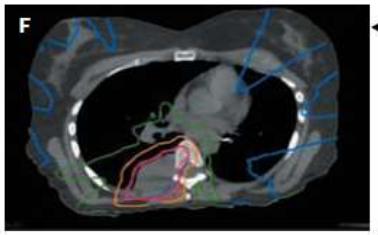
Dendritic cell recruitment, T cell activation, Vascular permeability, Increased antigen presentation

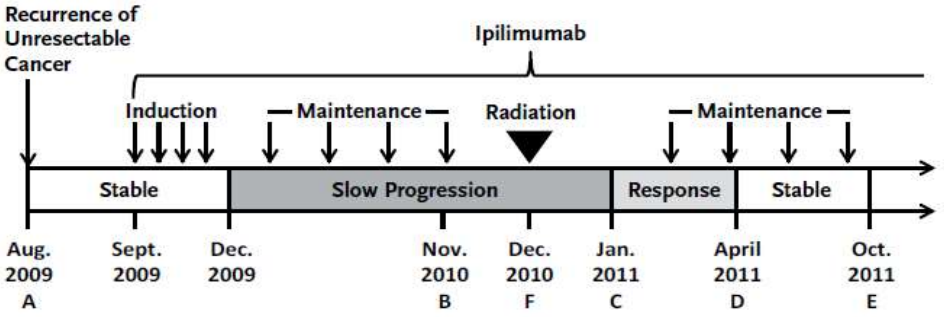
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma







Postow et. al. NEJM March 8th, 2012

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BRIEF REPORT

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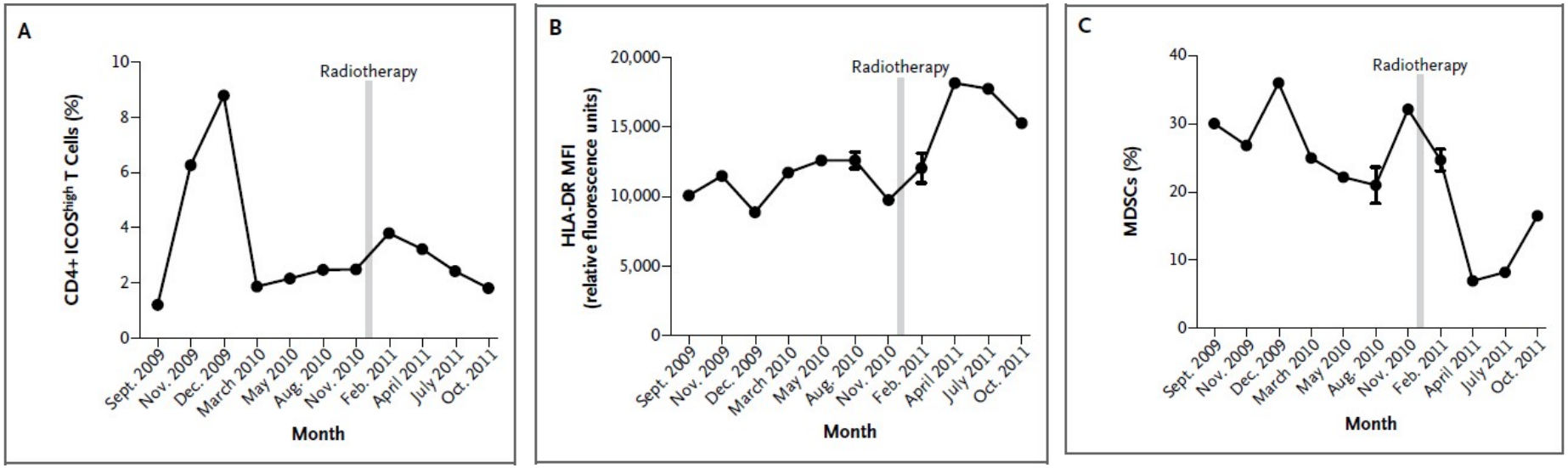

Postow et. al. NEJM March 8th, 2012

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

Steven K. Seung *et al.*

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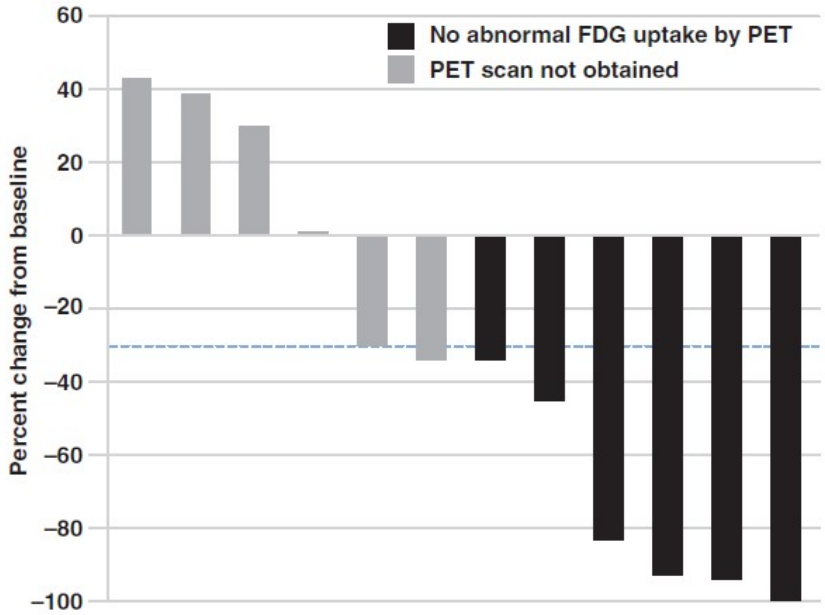


Fig. 1. Waterfall plot of best tumor response by RECIST criteria of all target lesions not treated with SBRT. Each bar represents the response of an individual patient. A dashed line is placed at 30% to indicate the minimum regression of tumor to qualify for a PR by RECIST criteria of target lesions.

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

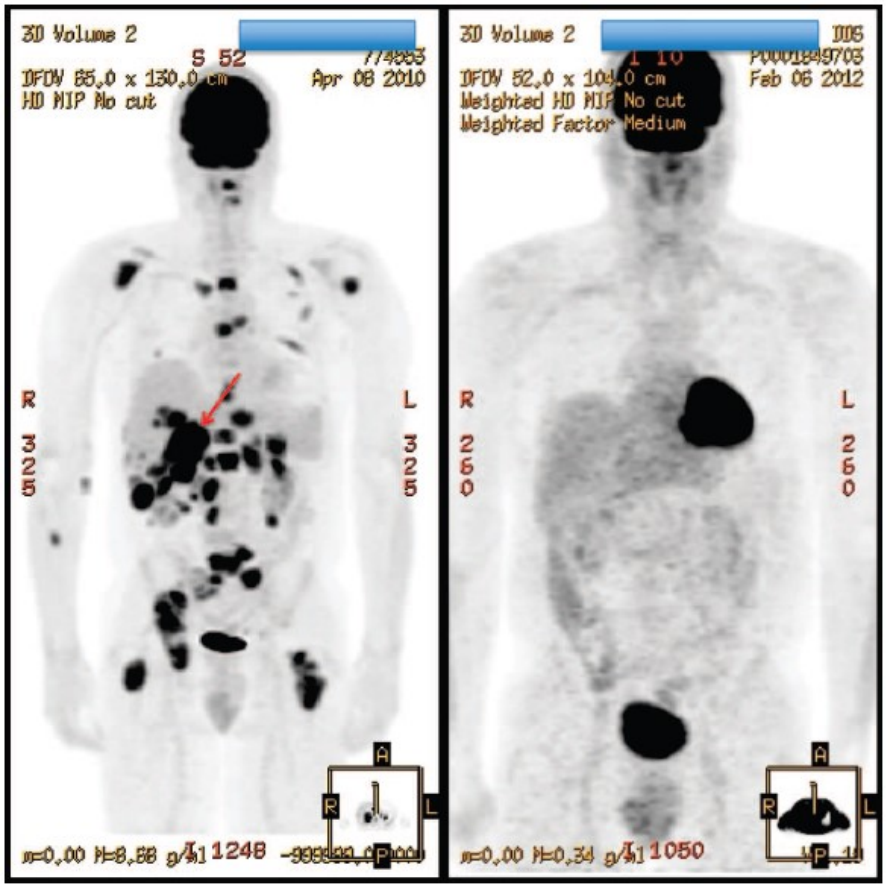


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

Outline

- Immunomodulation of tumor development by radiation therapy (RT)
  - –Pre-clinical evidence
  - –Limited clinical evidence
- Combining IO and RT
  - **–Pre-clinical models**
  - –Clinical trials and translational studies

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.)

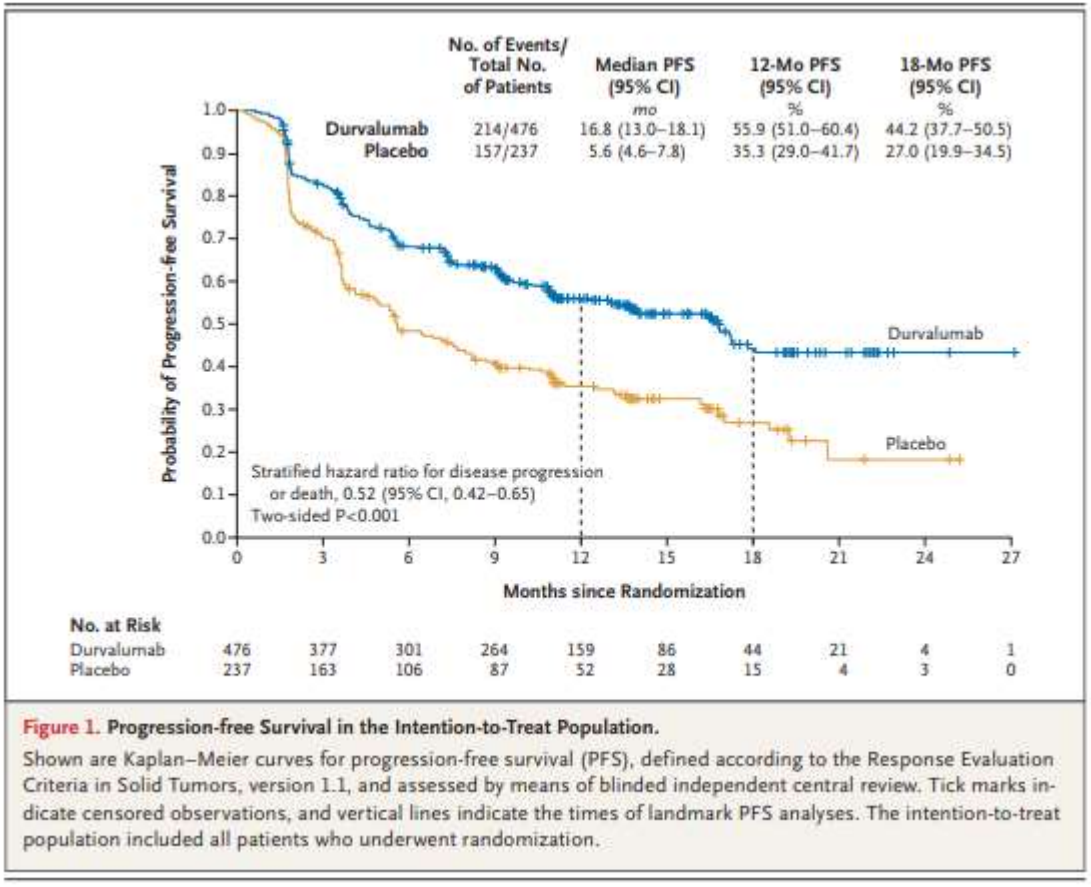
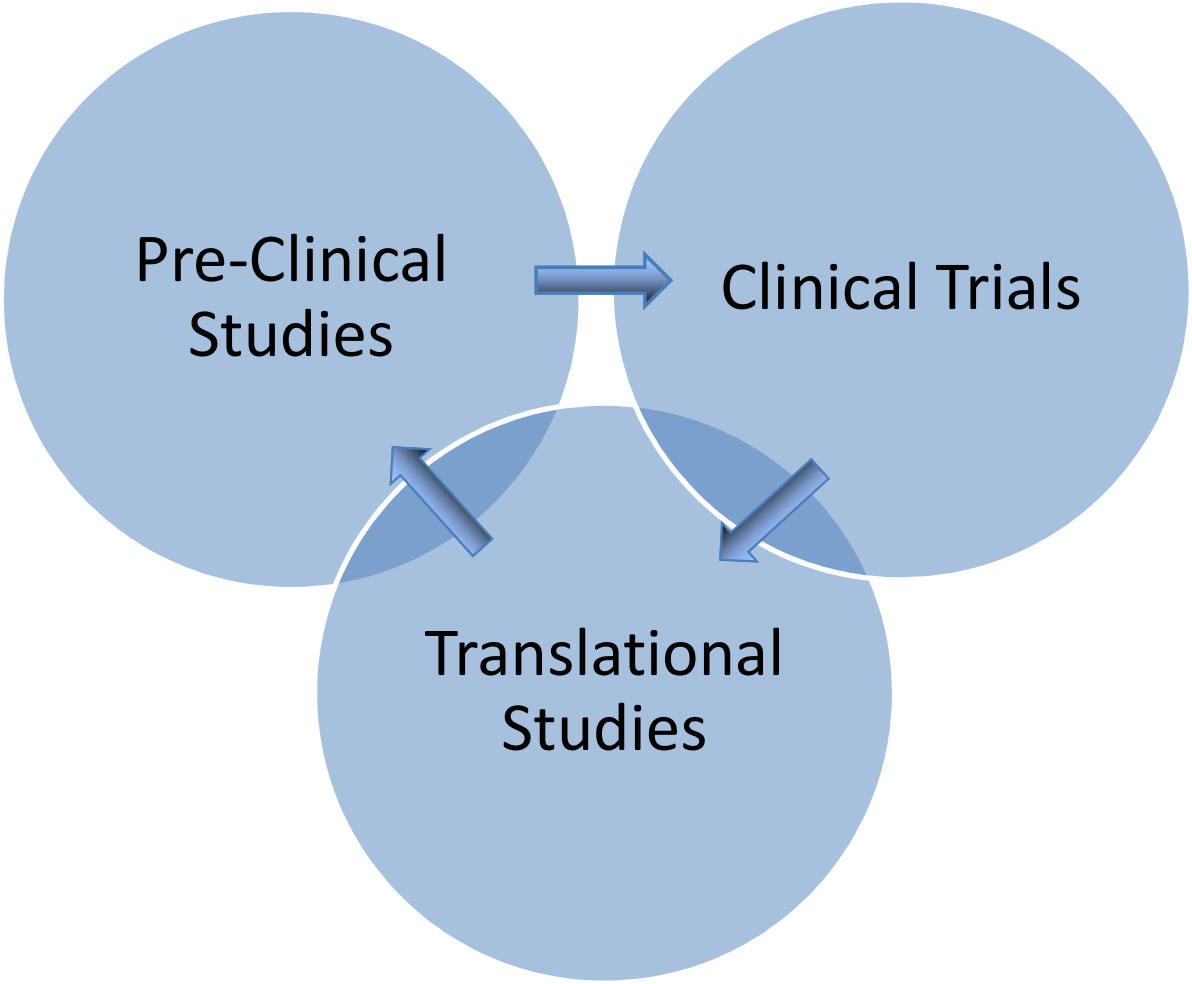


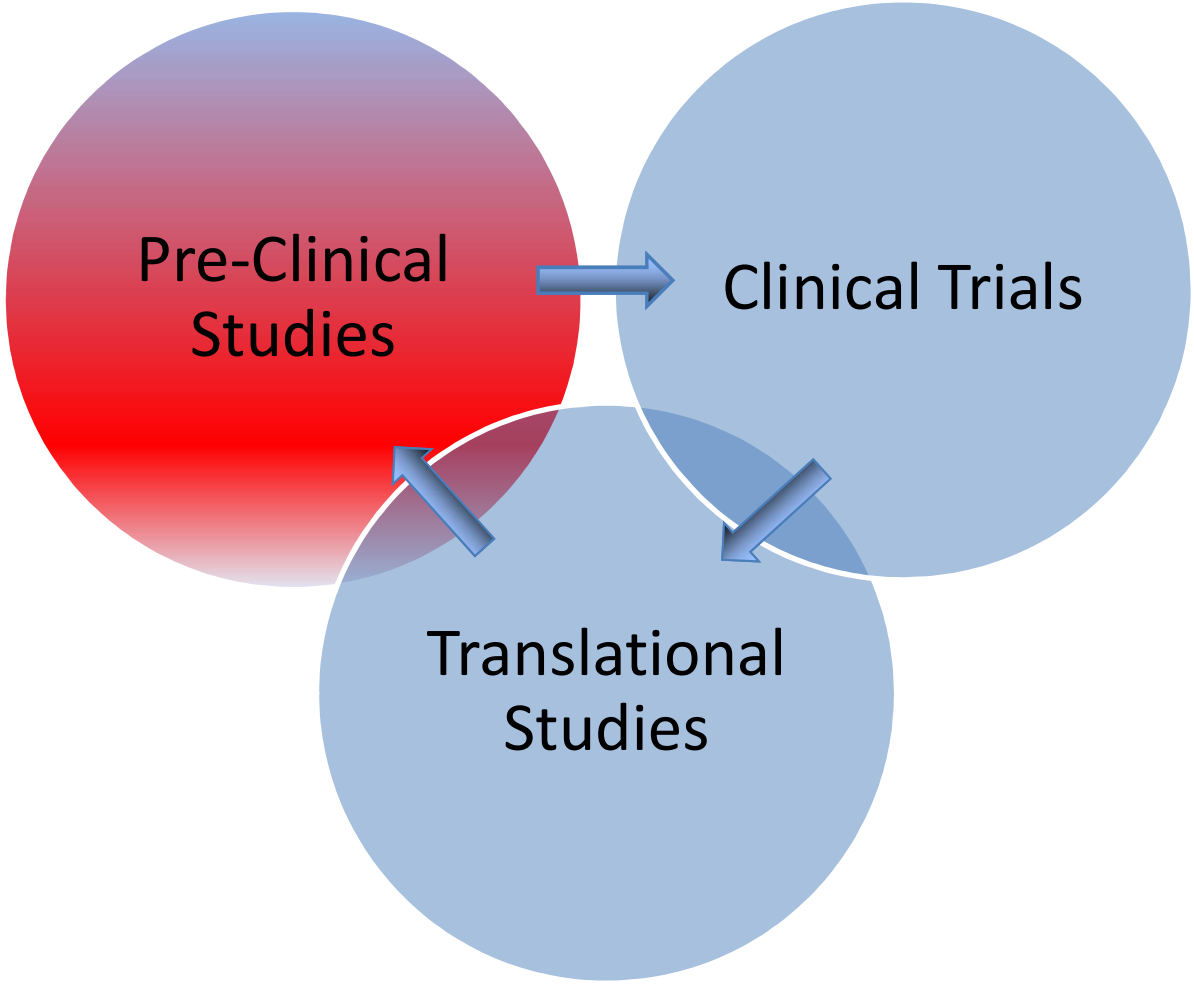
Figure 1. Progression-free Survival in the Intention-to-Treat Population.

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.

Radiation IO Combination Therapies

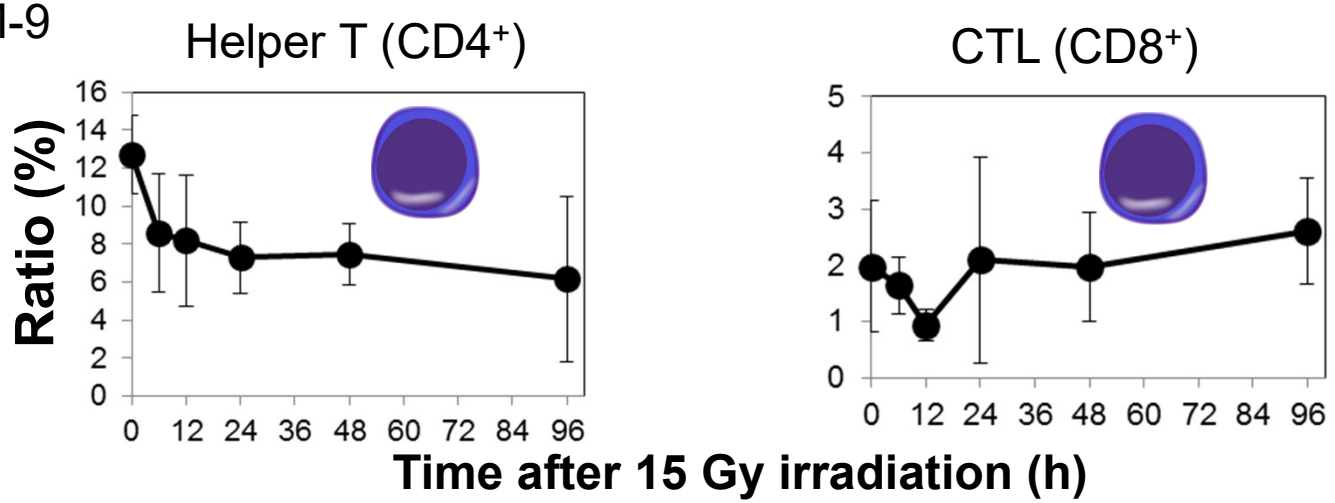


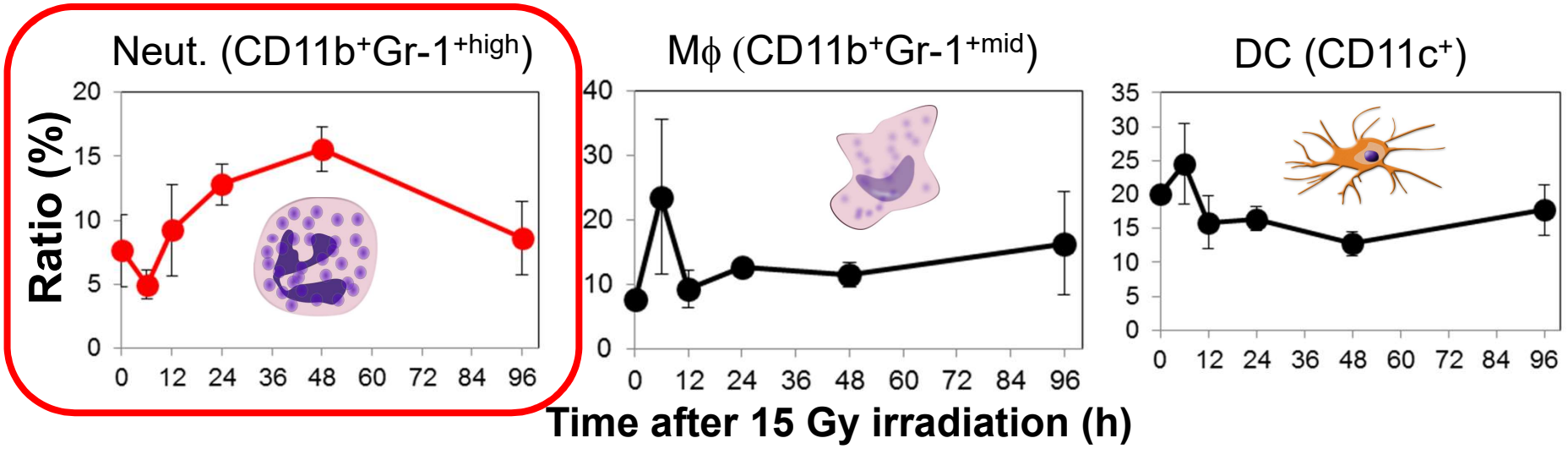
Radiation IO Combination Therapies



How does RT change the tumor immuno-microenvironment?

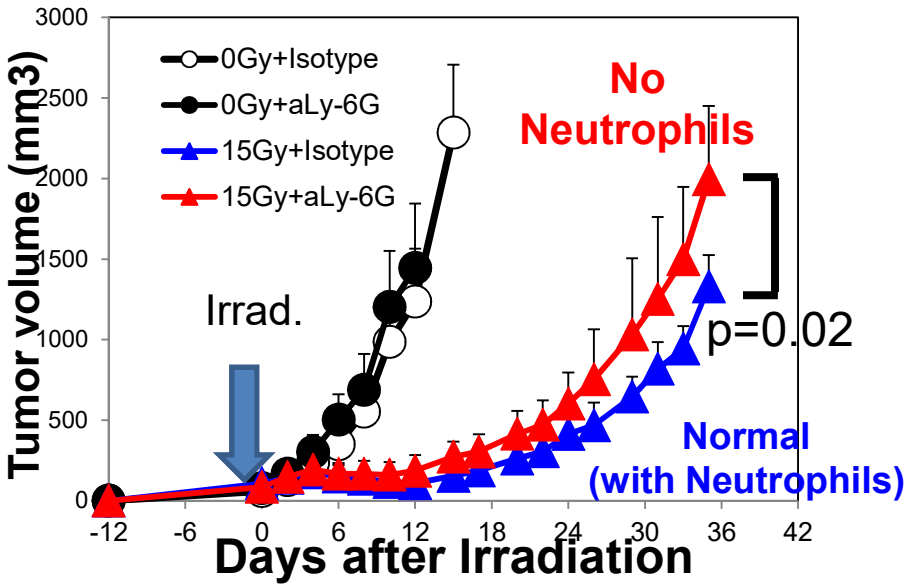
RM-9



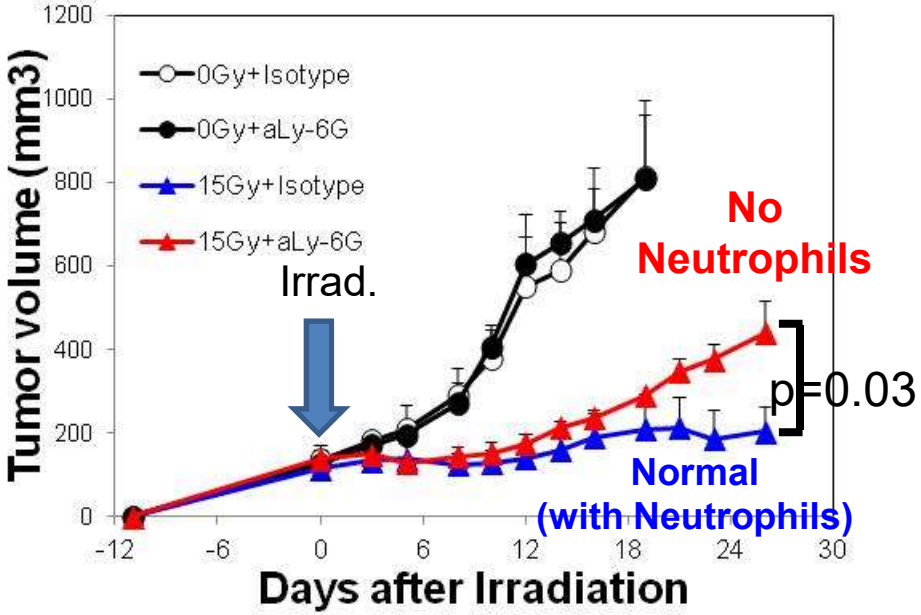


Effect of RT-Neutrophils (RT-Ns) on Tumor Volume

RM-9 (prostate cancer)



4T1 (breast cancer)

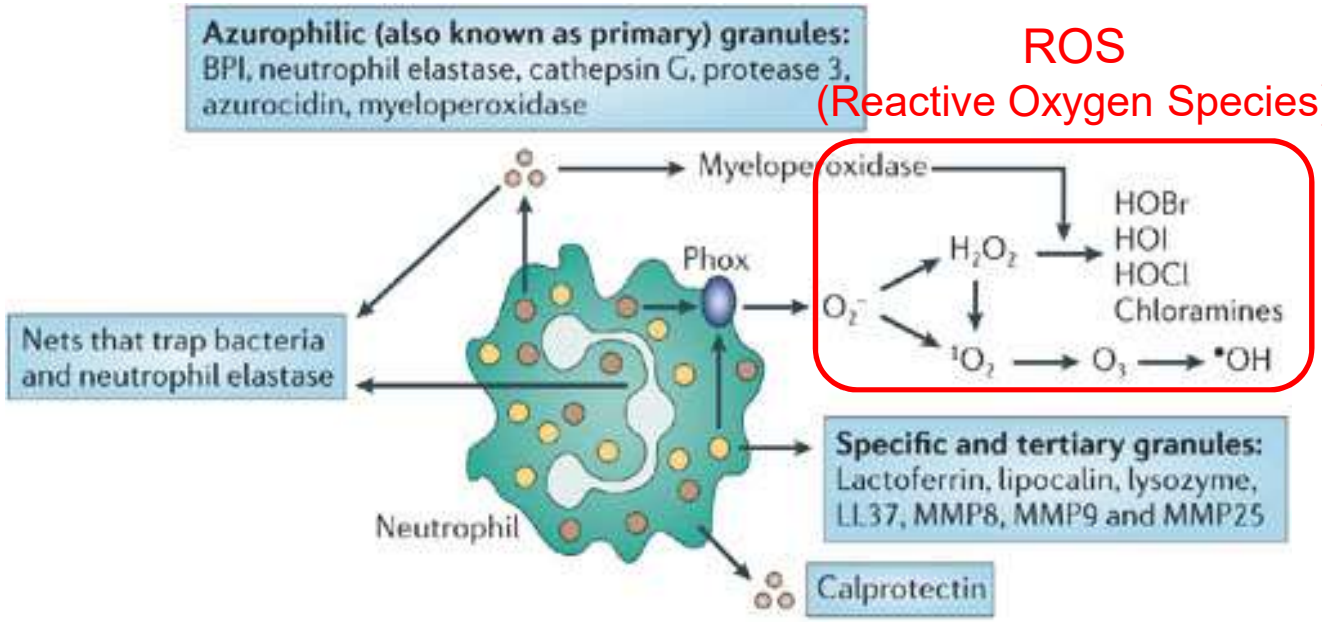


- Radiation-induced neutrophils (RT-N) play a significant role in the anti-tumor effect of RT

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?

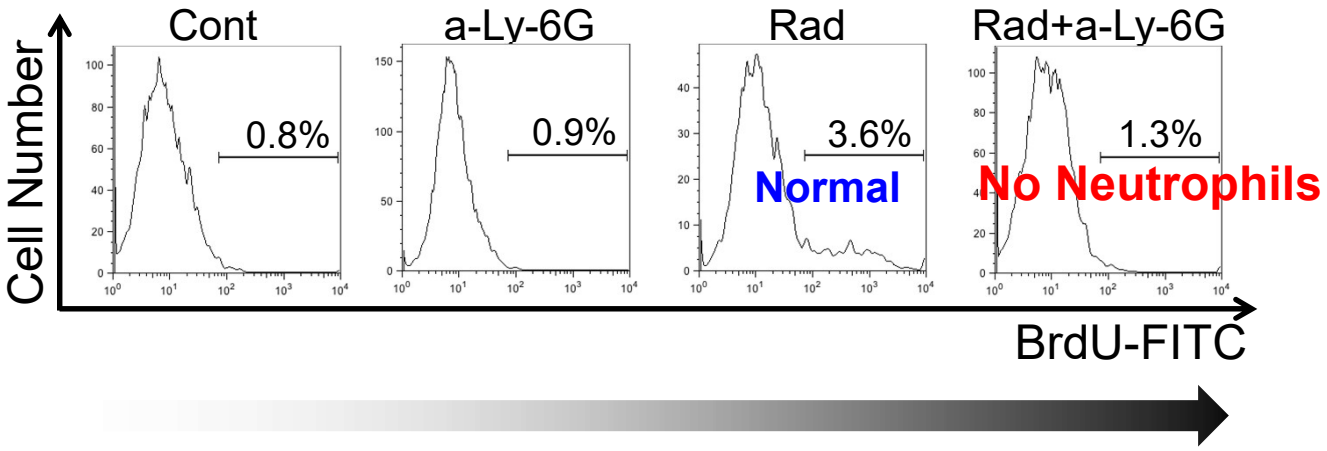
Mechanism of RT-N Therapeutic Effect?



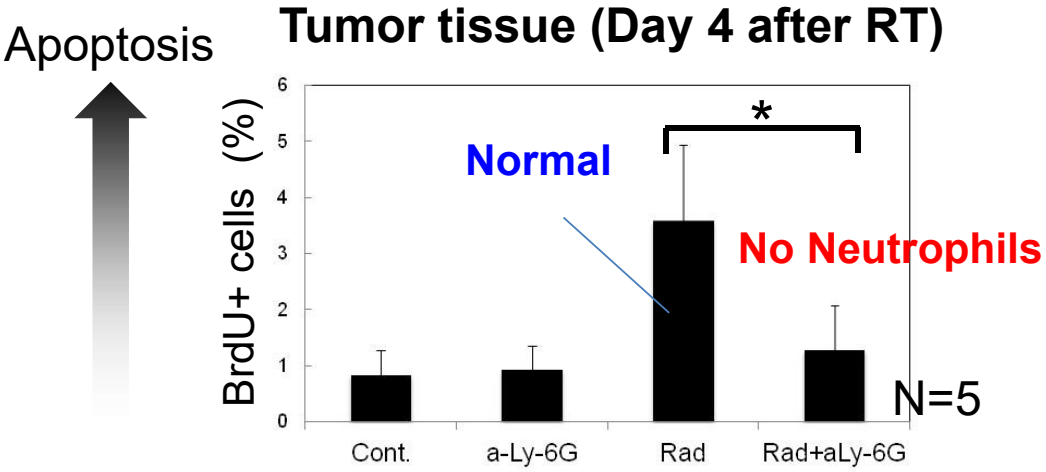
NATURE REVIEWS | IMMUNOLOGY VOLUME 6 | MARCH 2006 | 173

Does RT-Ns Induce Apoptosis in the Tumor?

TUNEL assay by flow cytometry



- RT-Ns induce apoptosis in tumor cells



RT induced Neutrophils (RT-Ns)

- How does RT-Ns induce tumor growth delay?
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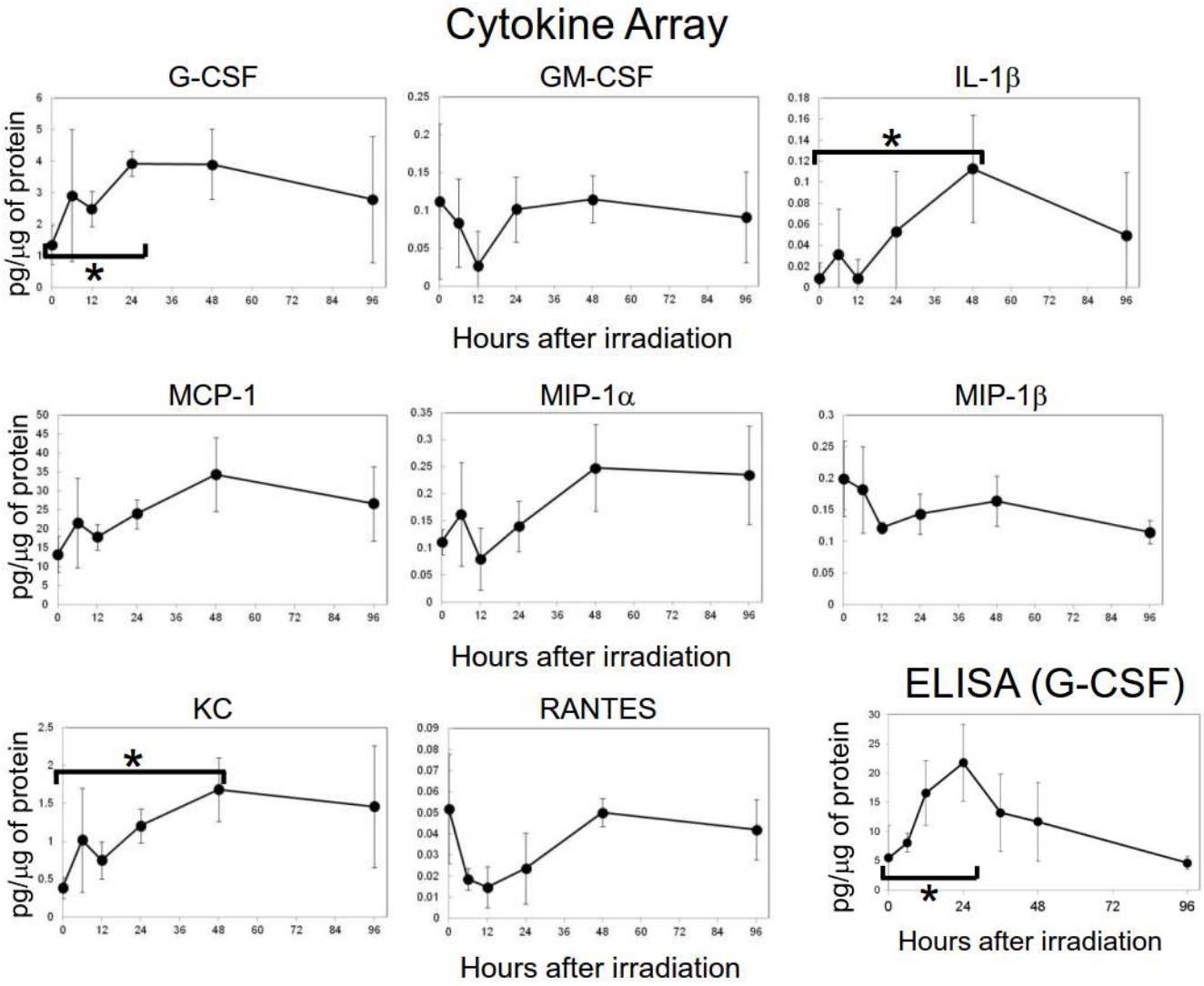
Why does RT-Ns infiltrate tumor after RT?

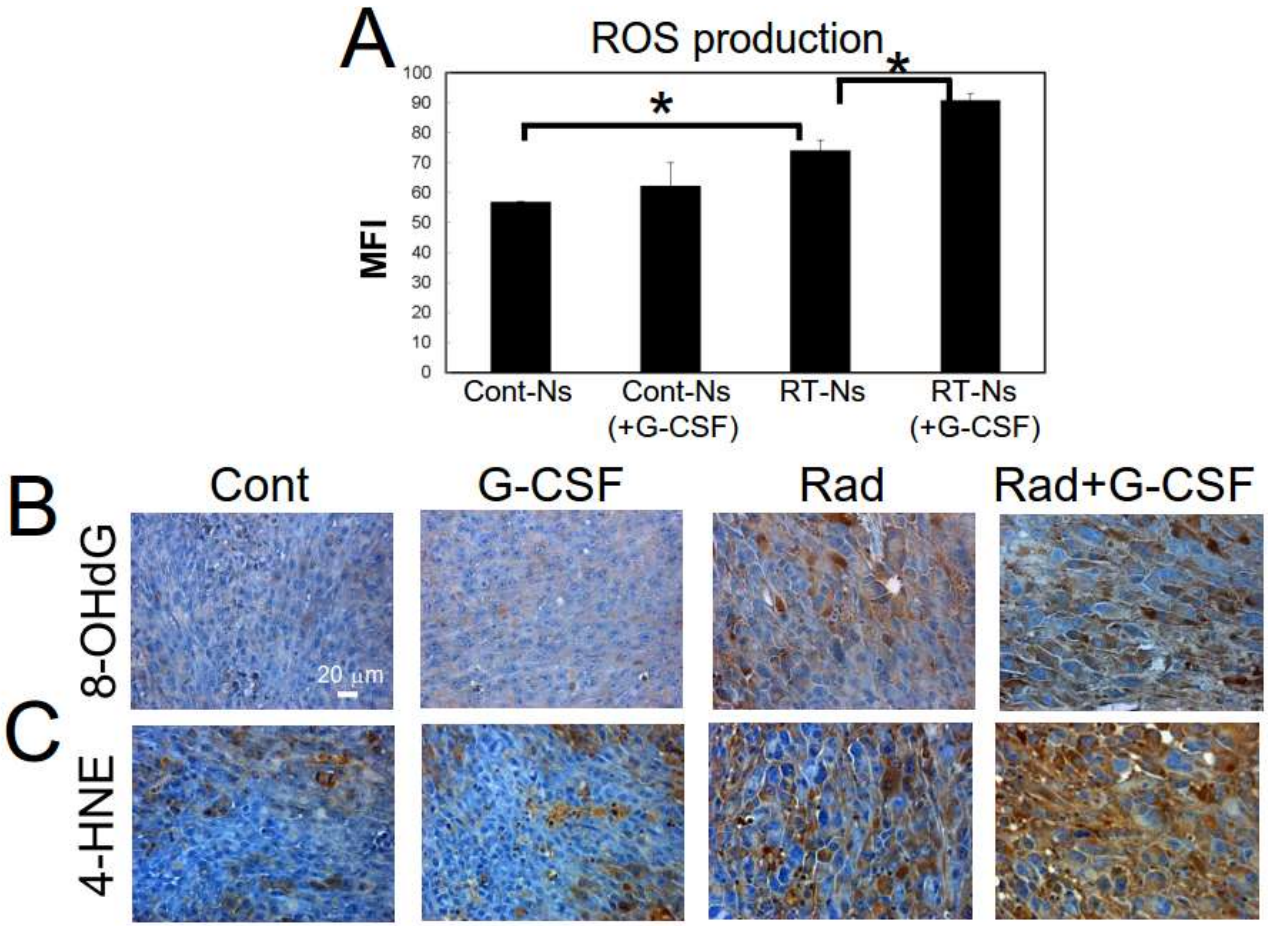


RT induced Neutrophils (RT-Ns)

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

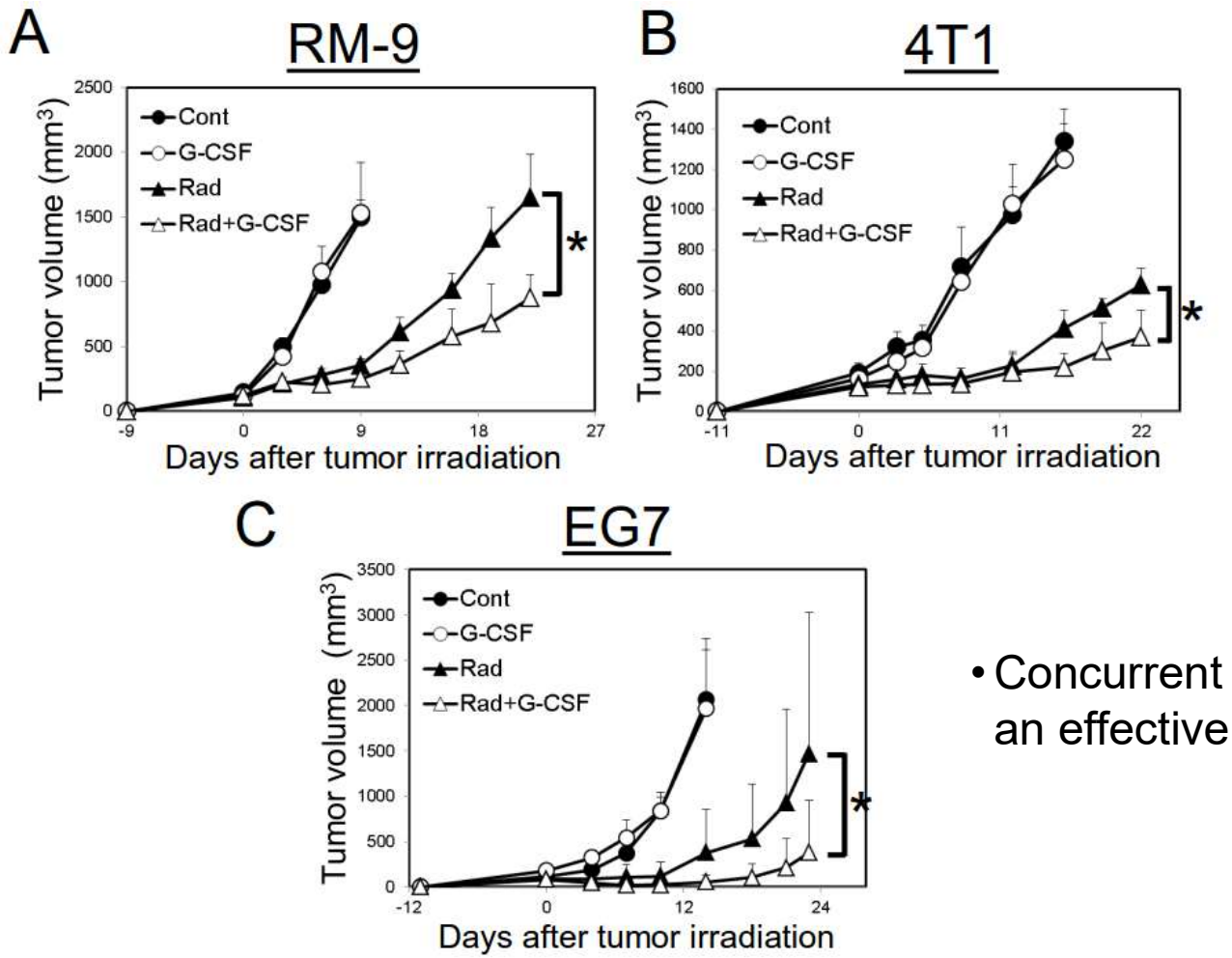
Can G-CSF Increase ROS production by RT-Ns?

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



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

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

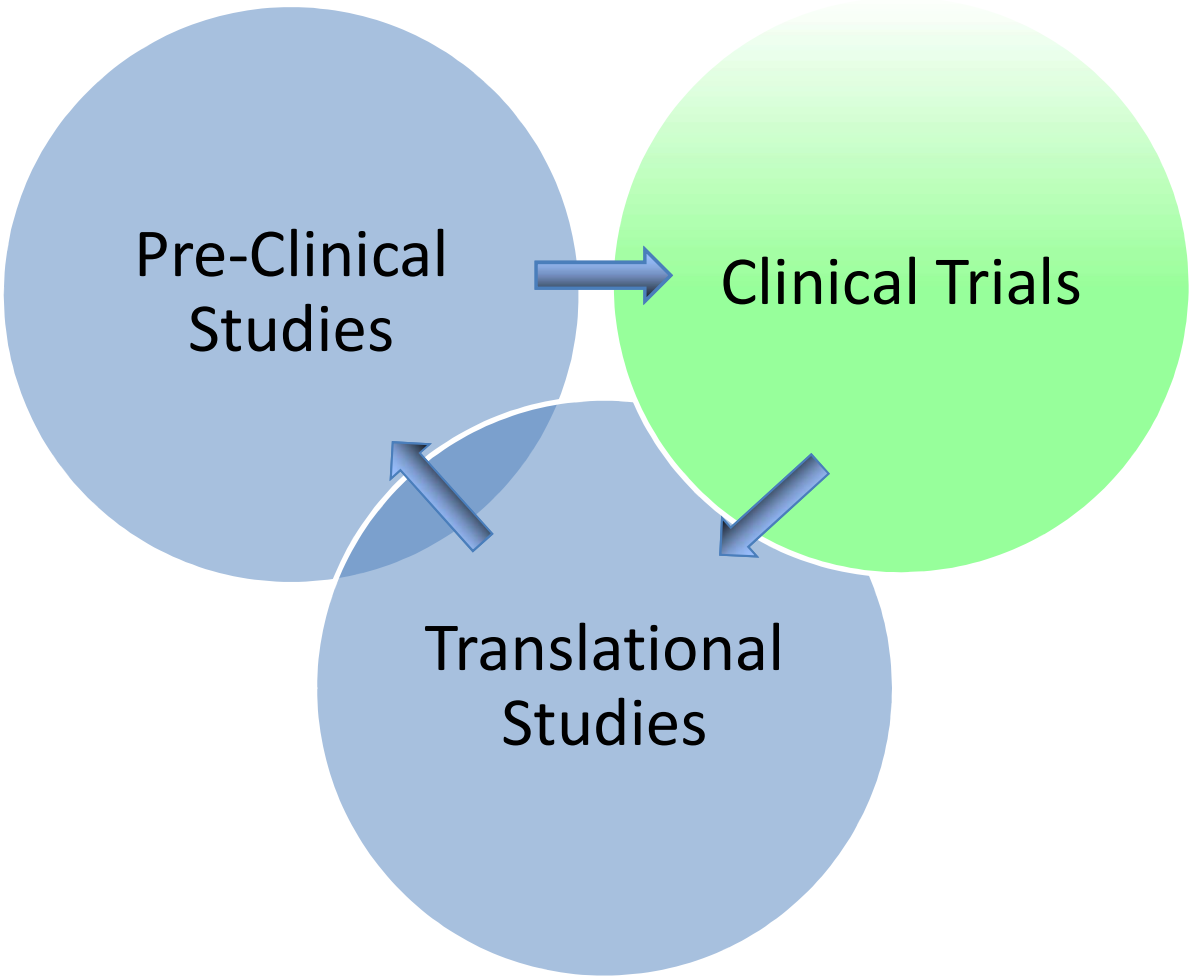
- G-CSF likely plays a role in the recruitment of RT-Ns
- G-CSF can further increase the potency of RT-Ns via ROS
- G-CSF + RT increases tumor-specific CTLs

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

Outline

- Immunomodulation of tumor development by radiation therapy (RT)
  - –Pre-clinical evidence
  - –Limited clinical evidence
- Combining IO and RT
  - –Pre-clinical models
  - **–Clinical trials and translational studies**

Radiation IO Combination Therapies



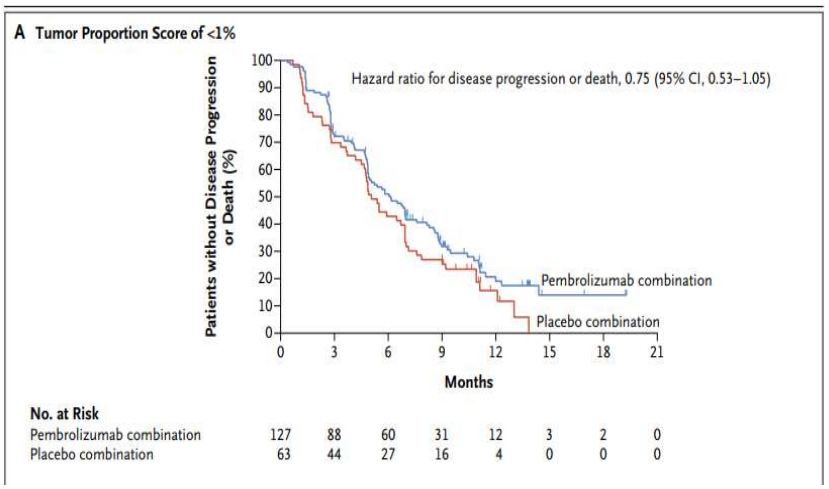
Immunotherapy

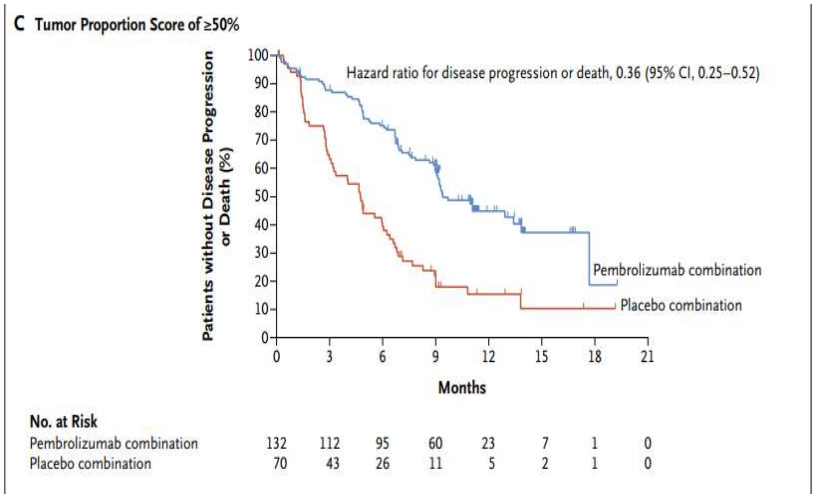
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*





Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC):

NRG-LU 002 A Randomized Phase II/III Trial

Puneeth Iyengar MD, PhD, *UT Southwestern*	PI
Daniel Gomez MD, *Memorial Sloan Kettering Cancer Center (MSKCC)*	Co-PI
Robert Timmerman MD *UT Southwestern* Hak Choy MD, *UT Southwestern* Clifford Robinson MD, *Washington University of St. Louis* Charles Simone MD, *Memorial Sloan Kettering Cancer Center (MSKCC)*	Co-Chairs
David Gerber MD, *UT Southwestern* Saiama Waqar MD, *Washington University of St. Louis*	Med Oncology
Jessica Donington MD, *University of Chicago* Stephen Swisher MD, *MD Anderson Cancer Center (MDACC)*	Surg 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, *MD Anderson Cancer Center (MDACC)*	Translational
Chen Hu, PhD, *Johns Hopkins University/NRG Oncology*	Statistics

SWOG Champion – Daniel Gomez MD, ECOG Champion – Sukhmani Padda MD,
ALLIANCE Champion – Pranshu Mohindra, MD

NRG – Wally Curran, Jeffrey Bradley, Jennifer Presley, Jeffery Serianni, Fran Bradley, Amy Krystkiewicz

NRG-LU 002

156/378 - 80%+ IO -/+ XRT

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.

NRG-LU002

OBJECTIVES

- Ph II: Evaluate impact on PFS of adding SBRT to maintenance systemic therapy versus maintenance systemic therapy alone for patients with metastatic NSCLC → no evidence of progression/limited metastatic sites after first-line systemic therapy
- Ph III: Evaluate impact on OS of adding SBRT to maintenance systemic therapy versus maintenance systemic therapy alone for patients with metastatic NSCLC → no evidence of progression/limited metastatic sites after first-line systemic therapy

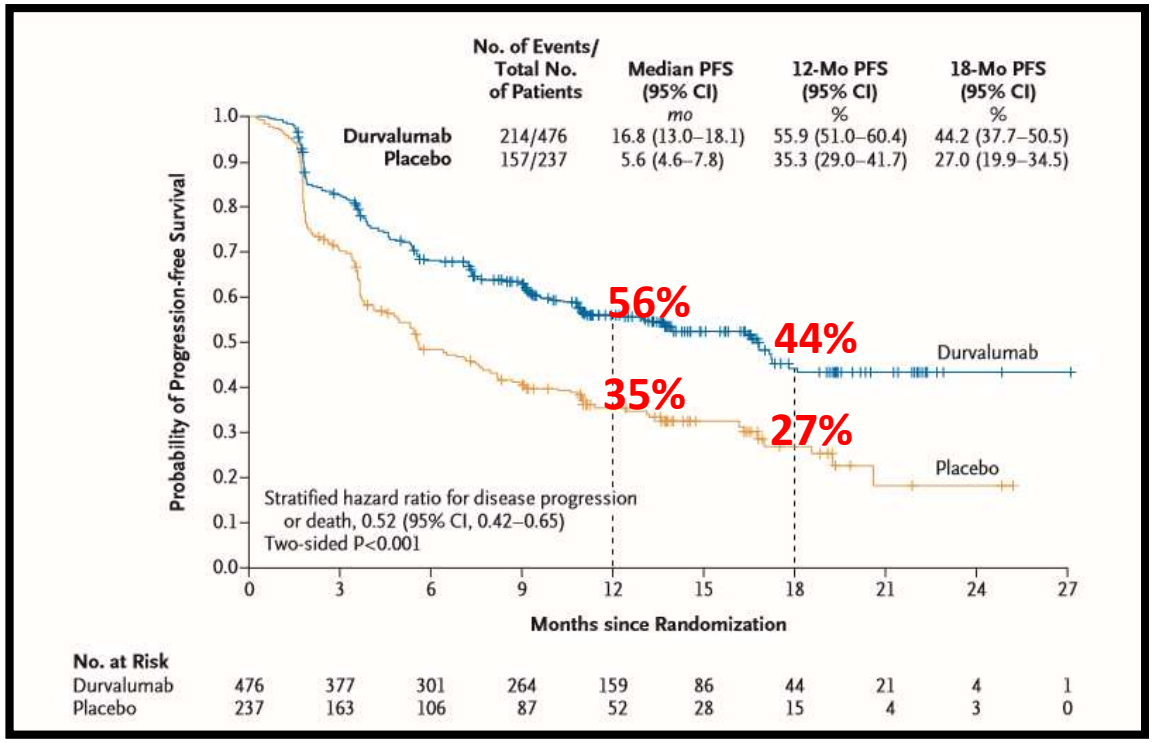
SECONDARY OBJECTIVES

- Evaluate effect on Quality of Life of adding SBRT to systemic therapy in limited stage IV NSCLC
- Collect biospecimens → evaluate correlation between clinical outcomes and circulating tumor DNA (ctDNA)

PACIFIC: ChemoRad -/+ IO for Stage III NSCLC

- Randomized, double blind, international, phase 3
- 709 patients from 2014-2016 with stage III, unresectable NSCLC who received 2 or more cycles of platinum based chemotherapy concurrently with definitive RT (54-66Gy, V20 LUNG<35%), WHO Performance status of 0 or 1.
- Design: Within 42 days after chemoradiotherapy in a 2:1 randomization ratio to receive durvalumab (anti-PDL1 antibody,10mg/kg IV q2 weeks for 12 months) vs. placebo
- Patients stratified to age, sex, smoking history (current, former, and never).
- Primary end points: PFS, OS

Pacific: PFS



Significant increase in PFS with manageable side effects after chemoradiotherapy.

Immunotherapy trials in LA-NSCLC 2016 – Since then, # trials would fit 10 slides

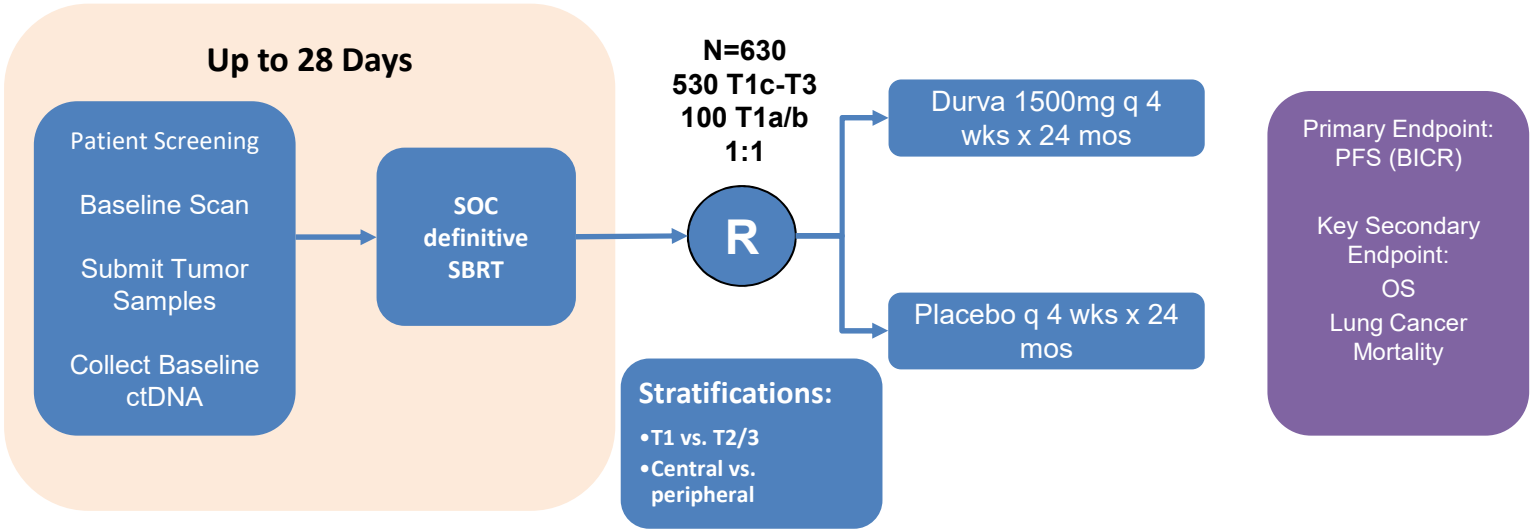
Recently completed and currently accruing studies examining the role of immunotherapy in LA-NSCLC

Immunotherapy target	Trial name	NCT trial number	Drug name	Outcome	Phase	n	Duration of immunotherapy	Trial status
Programmed cell death 1	NICOLAS	02434081	Nivolumab	Safety (pneumonitis)	II	43	1 year	Not yet recruiting
Programmed cell death ligand-1	PACIFIC	02125461	MED14736	OS	III	702	1 year	Recruiting
	Hoosier	02343952	Pembrolizumab	Time to distant relapse	II	83	1 year	Recruiting
	Rutgers/Penn/Yale	02621398	Pembrolizumab	Maximum tolerated dose (MTD)	I	30	1 year	Recruiting
Cytotoxic T-lymphocyte-associated protein 4	None							
MUC1 glycoprotein	START	00409188	Tecemotide (L-BLP25)	OS	III	1,513	Until progression	Completed
	INSPIRE	01015443	Tecemotide (L-BLP25)	OS	III	500	Until progression	Terminated
	START2	02049151	Tecemotide (L-BLP25)	OS	III	1,000	Until progression	Terminated
MUC1 glycoprotein and anti-VEGF	ECOG	00828009	Tecemotide (L-BLP25) and bevacizumab	Safety	II	55	Up to 34 courses	Recruiting

Berman et al. Transl Lung Cancer Res. 2016; 5(1):138-142

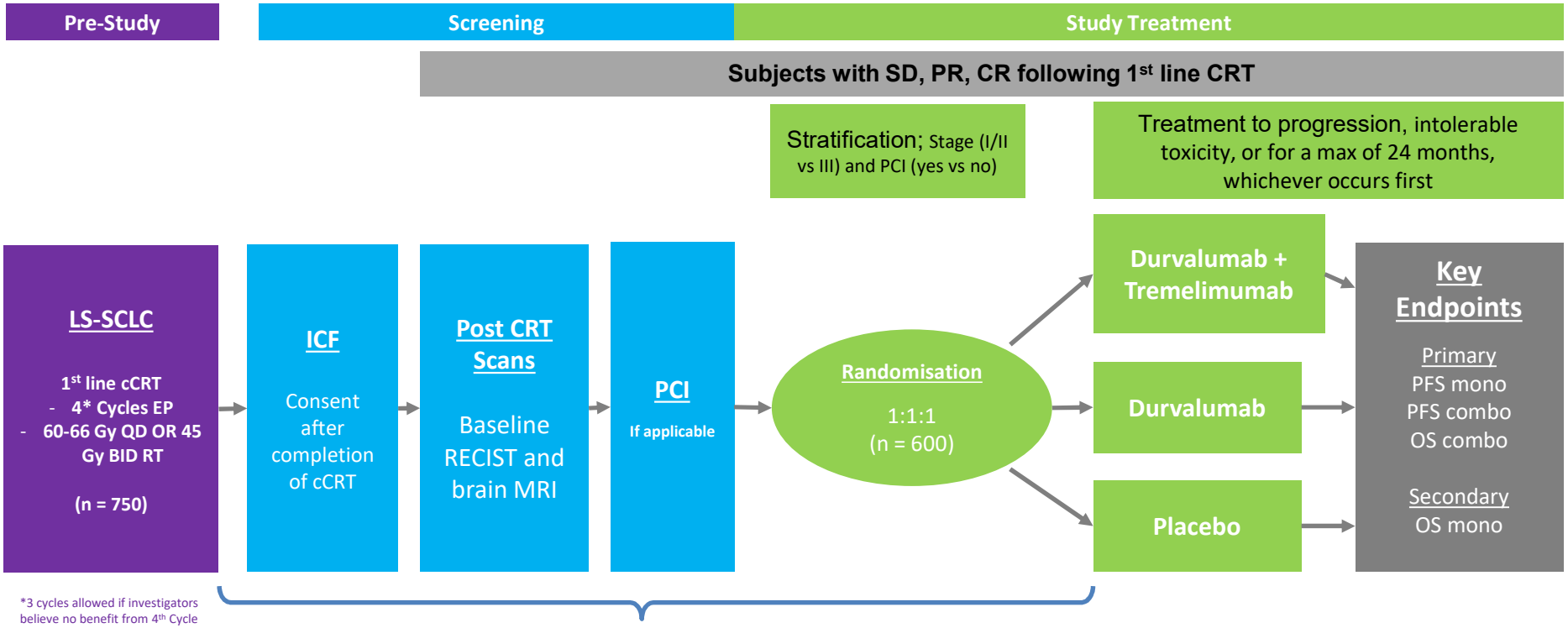
Pacific 4: Radiation -/+ IO for Early Stage NSCLC

Inclusion Criteria
- **Clinical Stage I/II node negative (T1 – T3 N0)**
- **Medically inoperable or refuse surgery**
- **ECOG PS 0-2**
- **All comers for histology and PDL-1 status**



Additional Key points
- NSCLC proven by histology / cytology
- Tissue submission mandated - Accepting FNA samples for translational analysis (in addition to usual core biopsy)
- Exploratory translational endpoint: ctDNA at baseline, at randomization, periodically during durva / placebo
- SOC SBRT taking place during screening. SBRT planning can occur before study enrollment
- Randomization within **7 days of completion of SOC SBRT**
- Limitation of T1ab patients (<2cm) due to relatively good prognosis, long timelines. However these patients still may recur → identify higher risk individuals

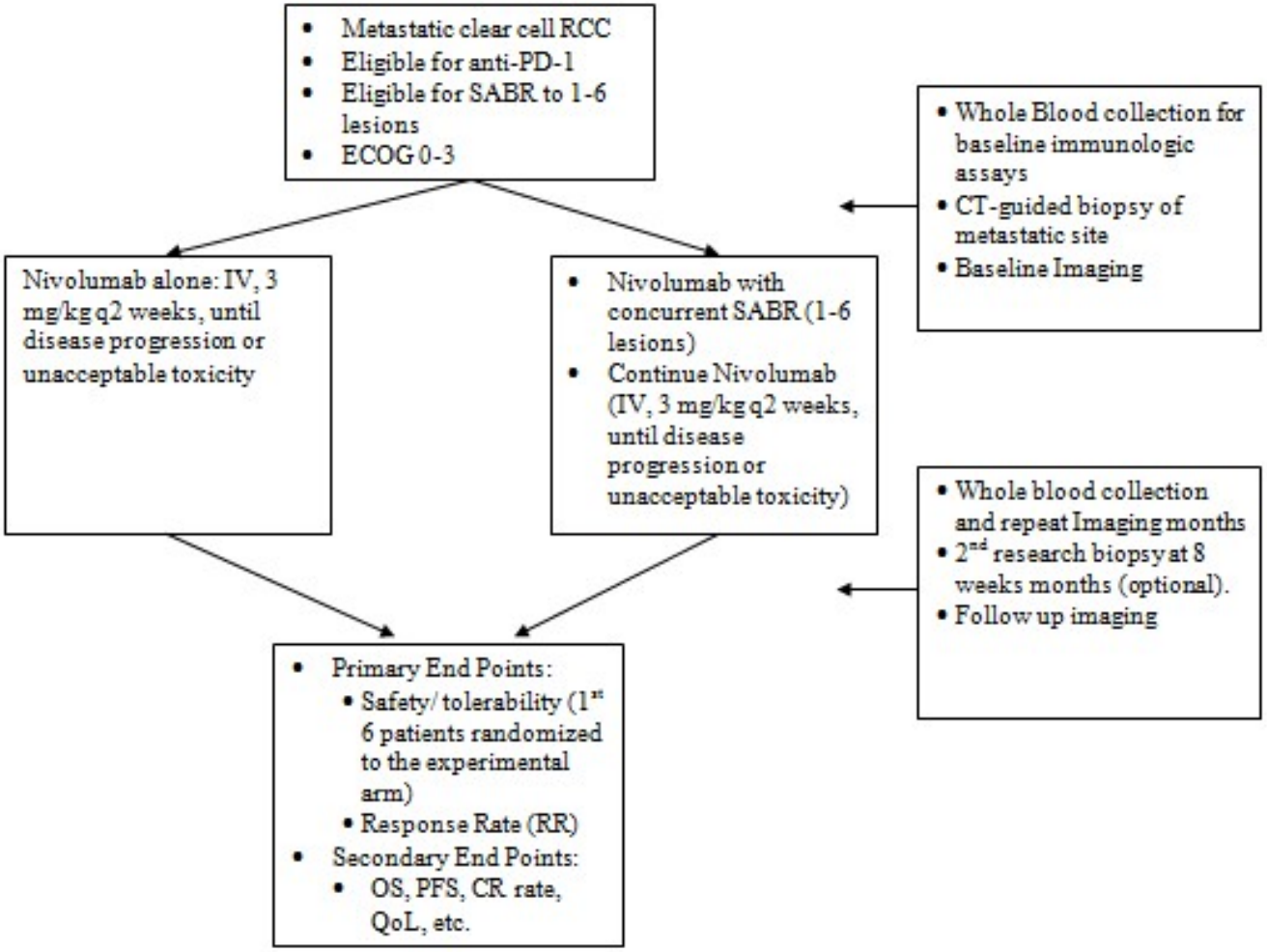
ADRIATIC: Radiation/Chemo and IO for Small Cell Lung Cancer



Maximum of 42 days from end of CRT to randomization **and** first dose of IP

Screening period starts on the last day of the final cycle of chemo (e.g. C4D21) or the last day of RT, whichever occurs later

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



1:2 Randomization: 58 and 29 patients

Radiation 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?

Radiation Trial Translational Correlates

- **Does Radiation induce/increase tumor-specific CTL?**
  - –ELISpot Assay
  - –T-cell proliferation Assay
  - –Cytotoxicity Assay
  - –Quantitate activation/proliferation markers for CD8+ cells

Next Generation Sequencing:

- Immune Repertoire Sequencing
- RNA sequencing
- Exome sequencing

Thank You
Questions/Suggestions?