IDEAL TIMING OF IMMUNOTHERAPY AND RADIATION IN MURINE TUMOR MODELS

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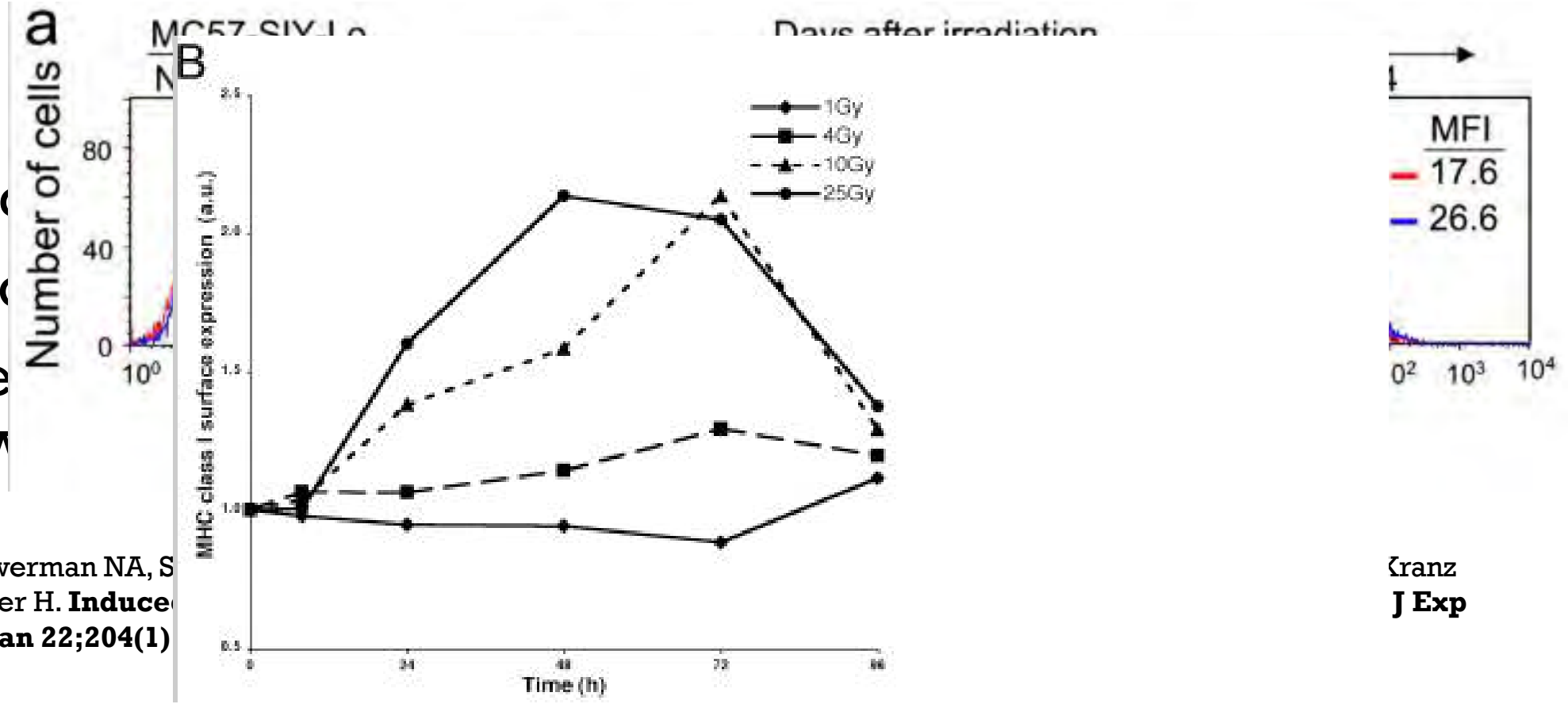
Oregon Health & Science University
EACRI at Providence Portland Medical Center

DISCLOSURES

- None

RATIONALE FOR POST-RADIATION IMMUNOTHERAPY

- RT inc
- RT inc
- Some
  follow



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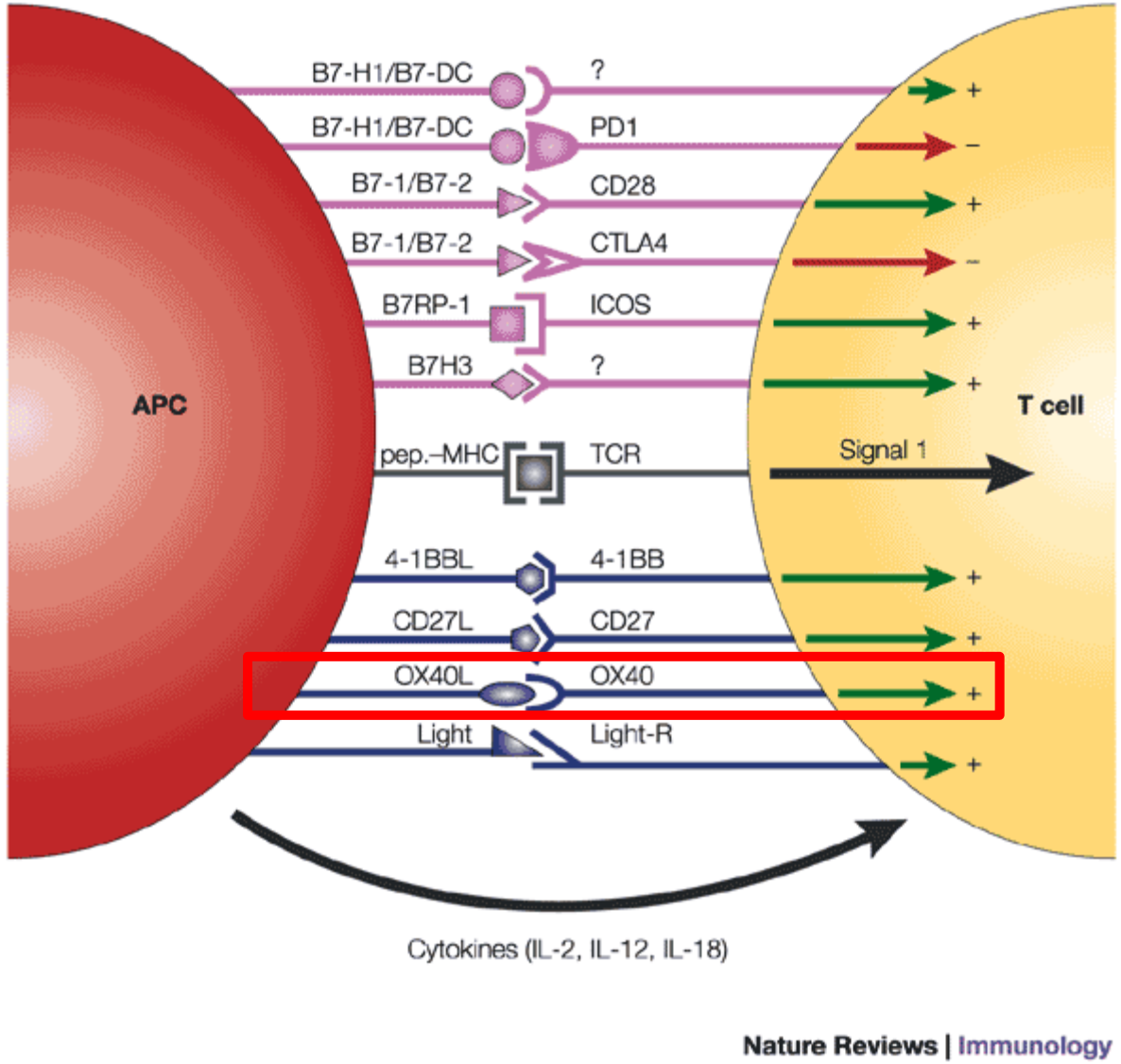
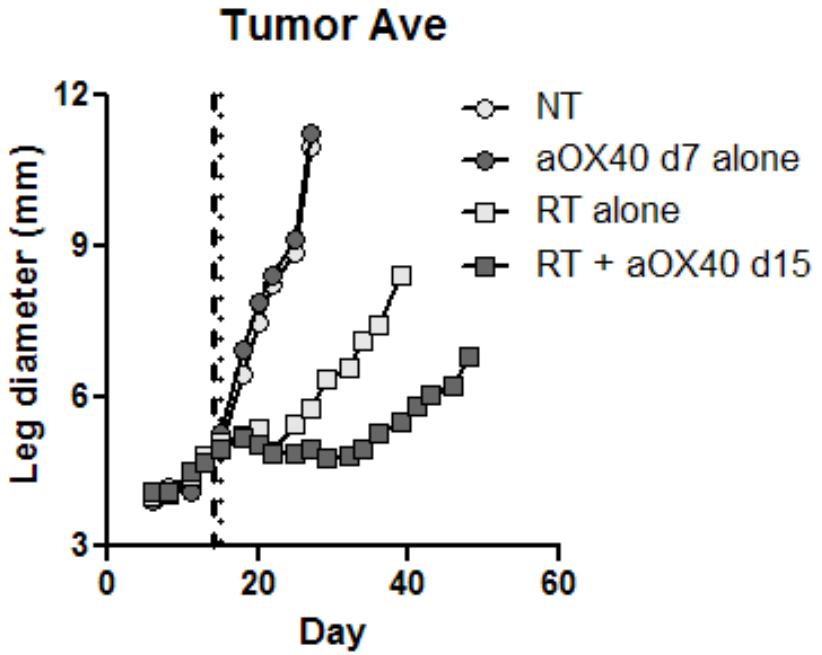
αOX40 AND RADIATION

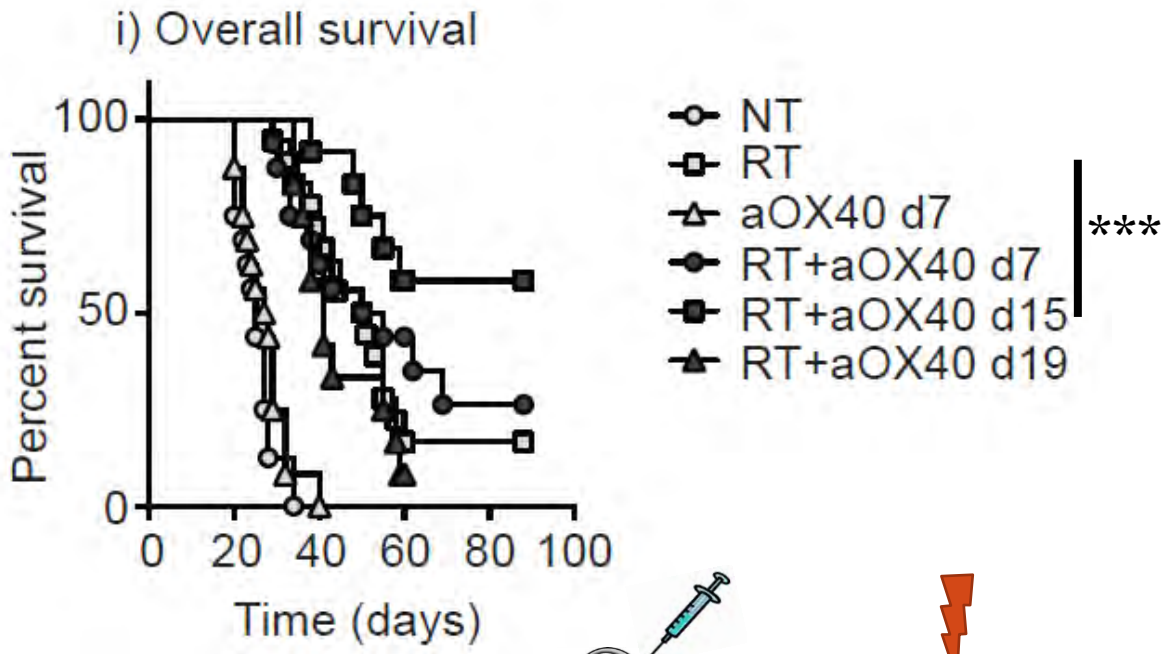
POTENTIAL IMMUNE THERAPY TARGETS

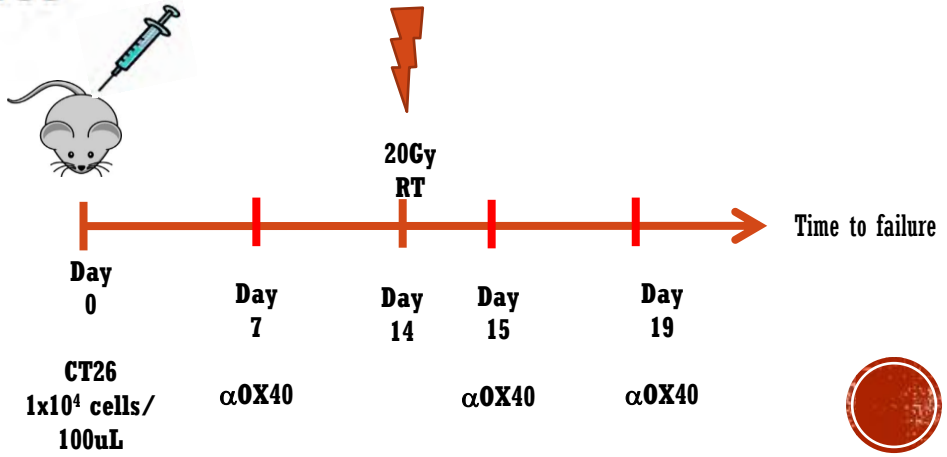


Pardoll DM. Nature Reviews Immunology 2, 227-238 (April 2002)

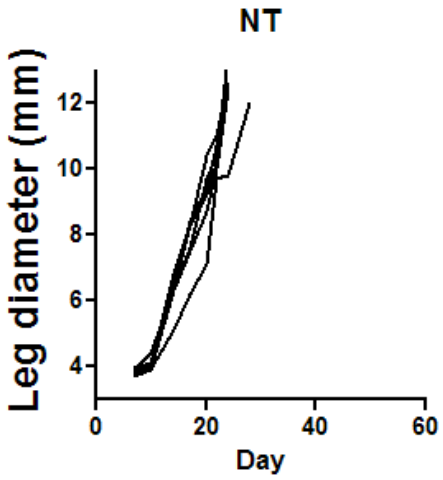
αOX40 AGONIST SHORTLY AFTER RADIATION PROMOTES TUMOR CLEARANCE

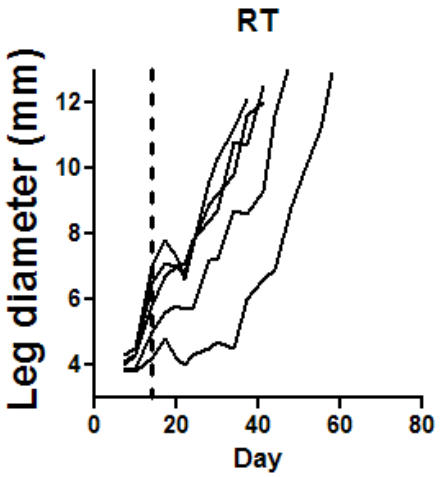


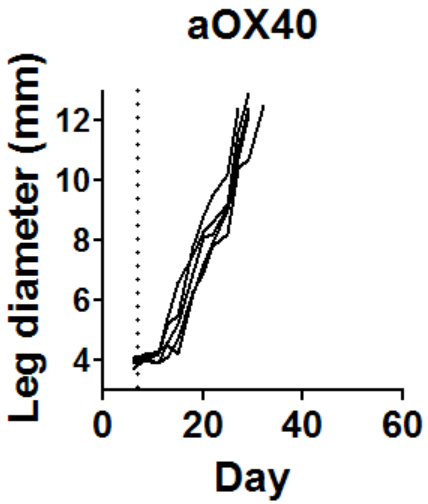


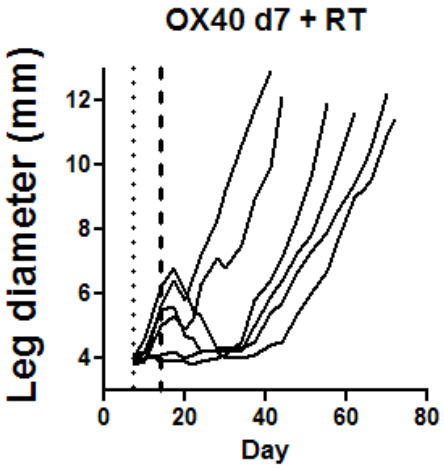


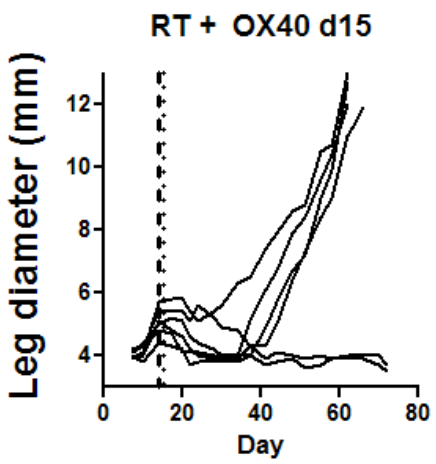
αOX40 AGONIST AFTER RADIATION YIELDS TUMOR CLEARANCE

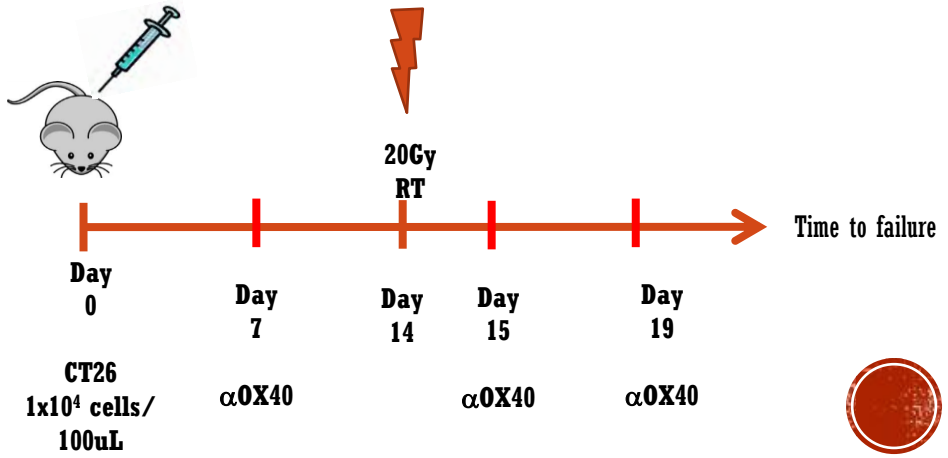




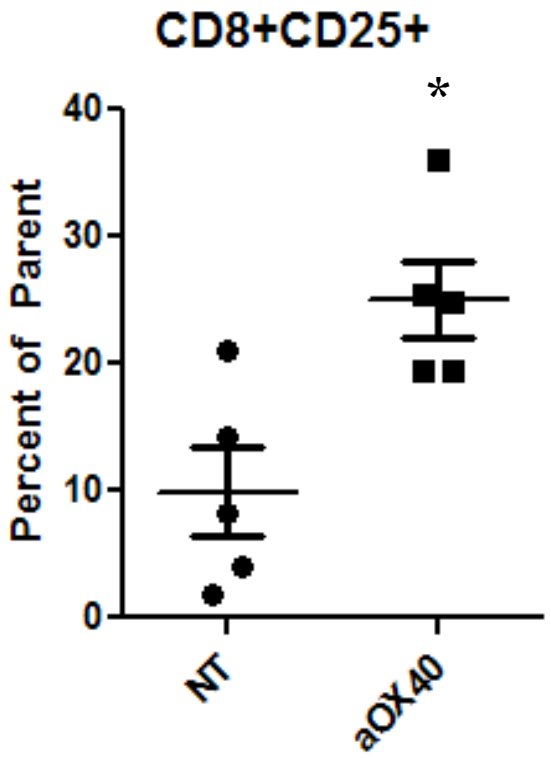


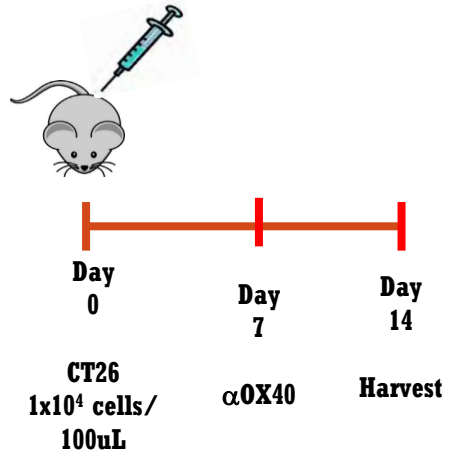






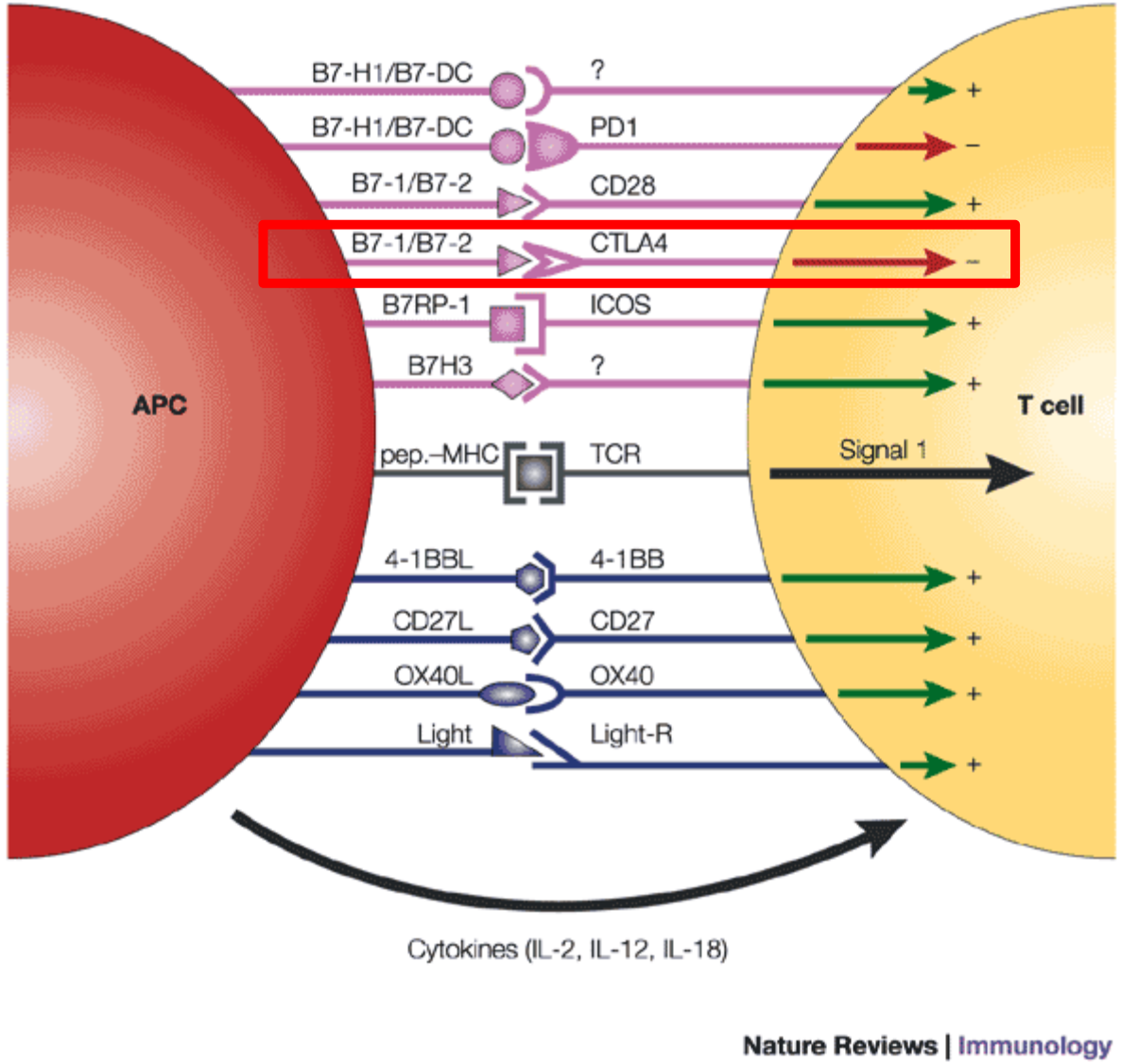
αOX40 INCREASES ACTIVATED CD8 T CELLS





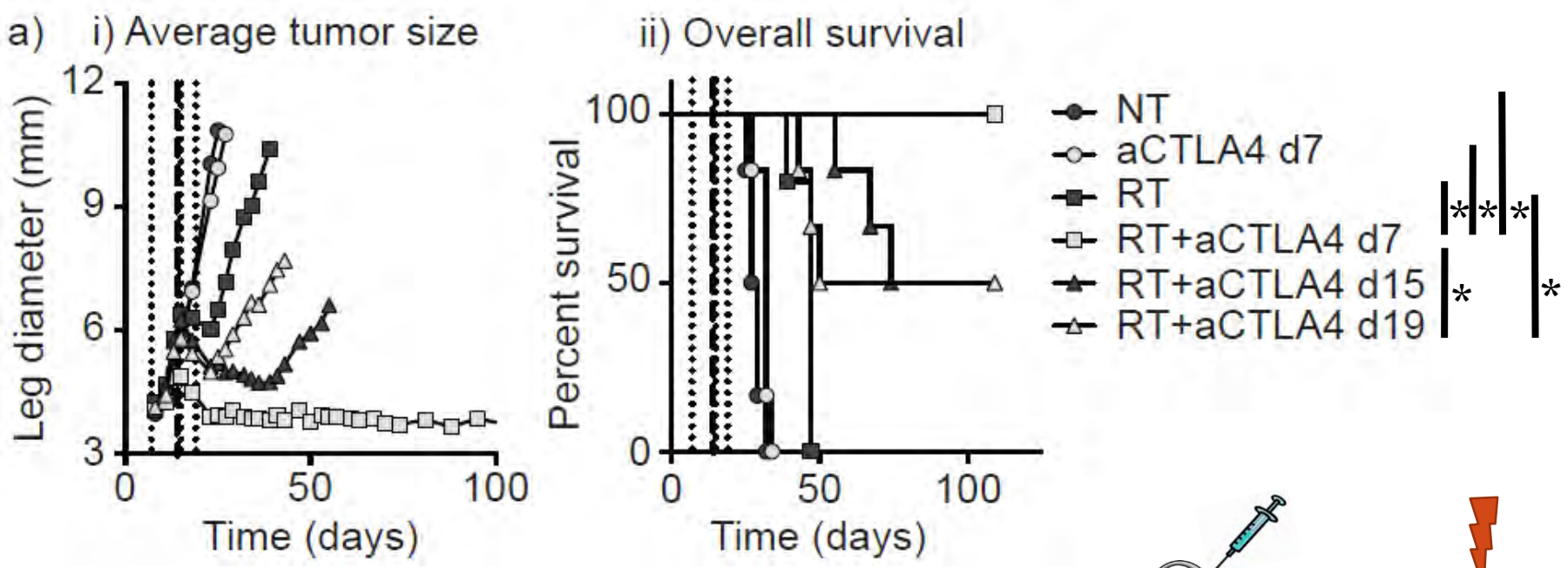
αCTLA4 AND RADIATION

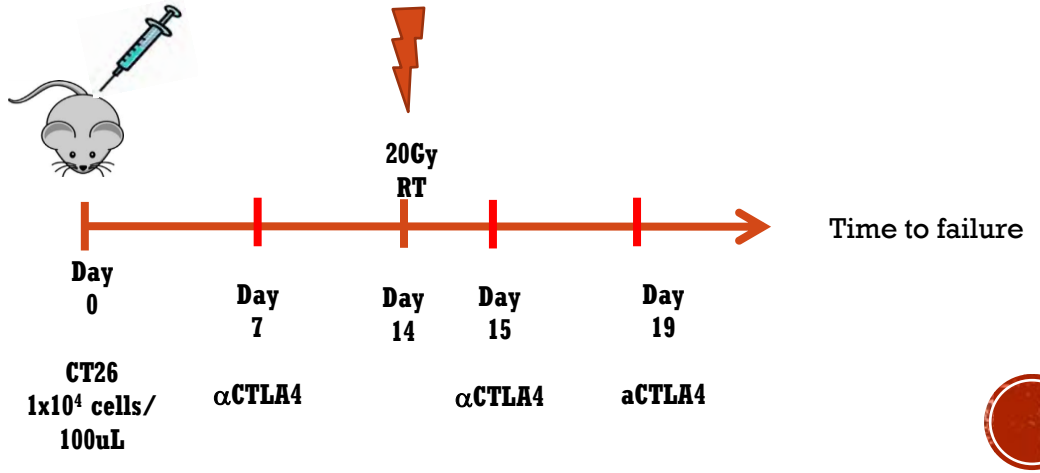
POTENTIAL IMMUNE THERAPY TARGETS



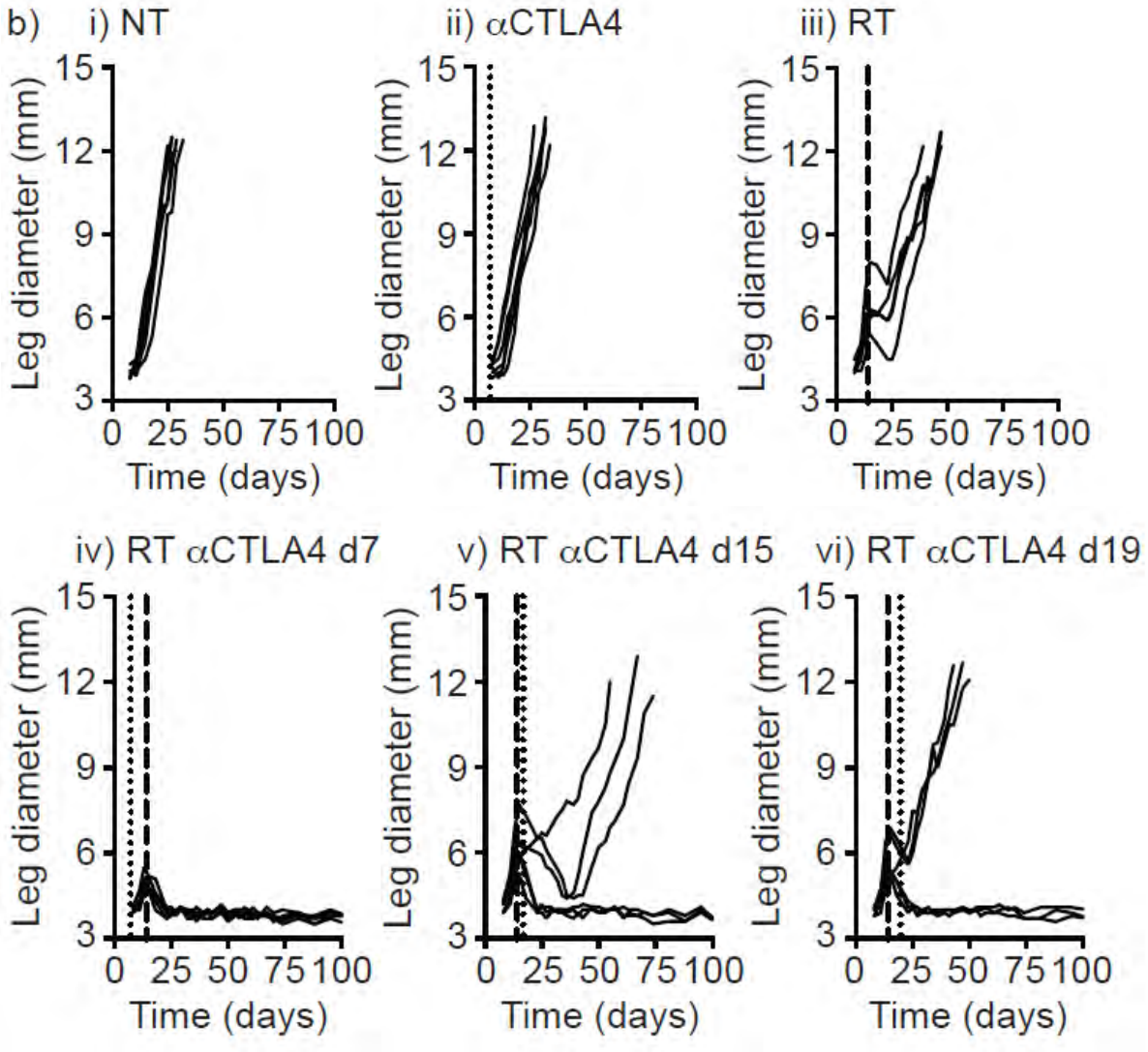
Pardoll DM. Nature Reviews Immunology 2, 227-238 (April 2002)

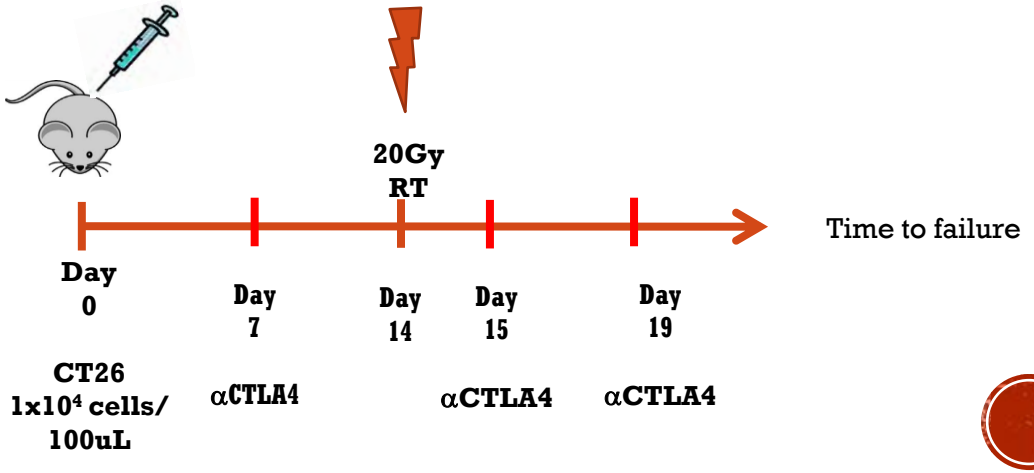
PRETREATMENT WITH αCTLA4 RESULTED IN TUMOR CLEARANCE



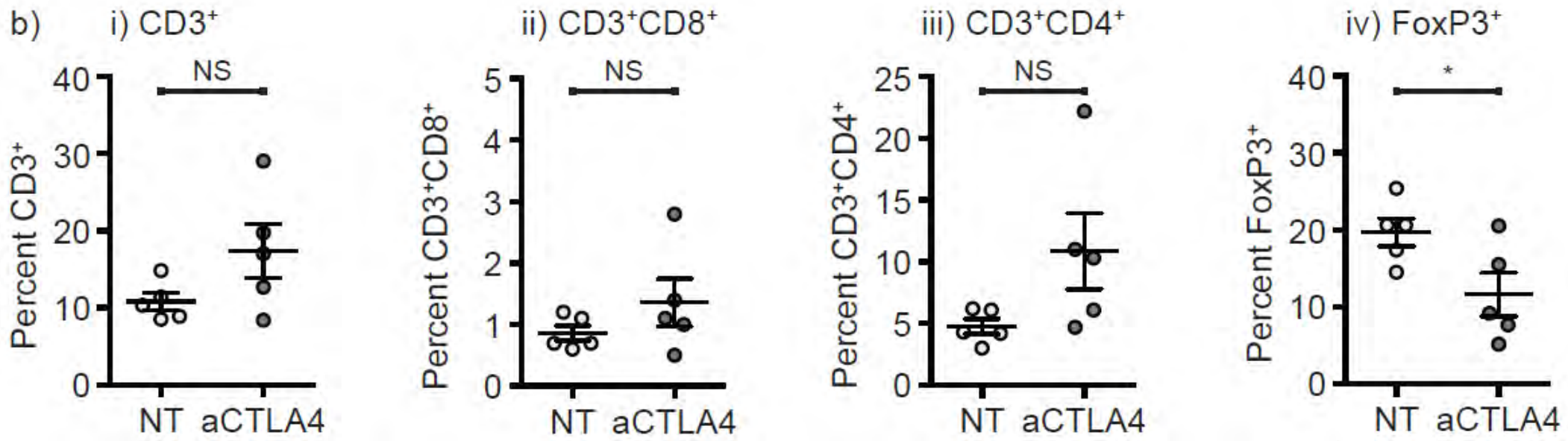


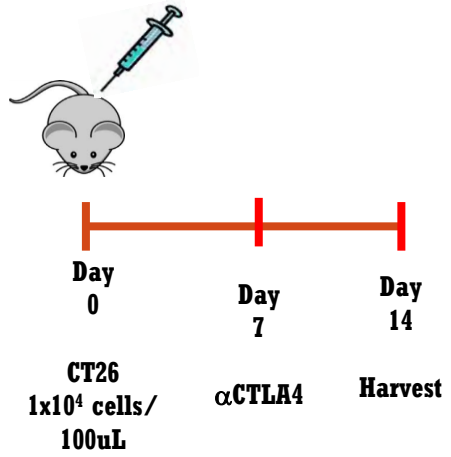
αCTLA4 PRETREATMENT YIELDED BEST RESULTS



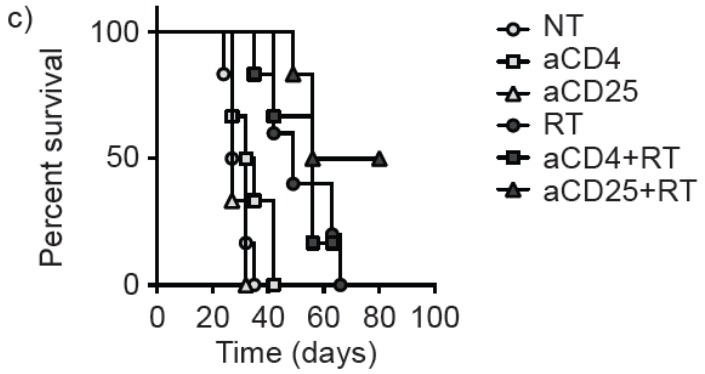


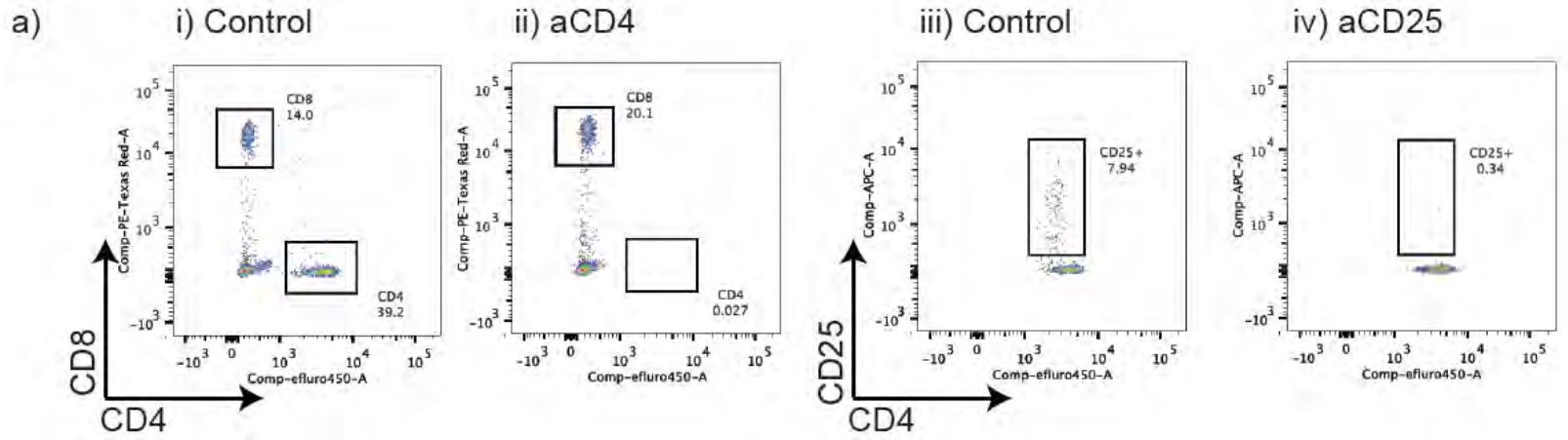
αCTLA4 ADMINISTRATION DECREASED T_{REG} INFILRATE

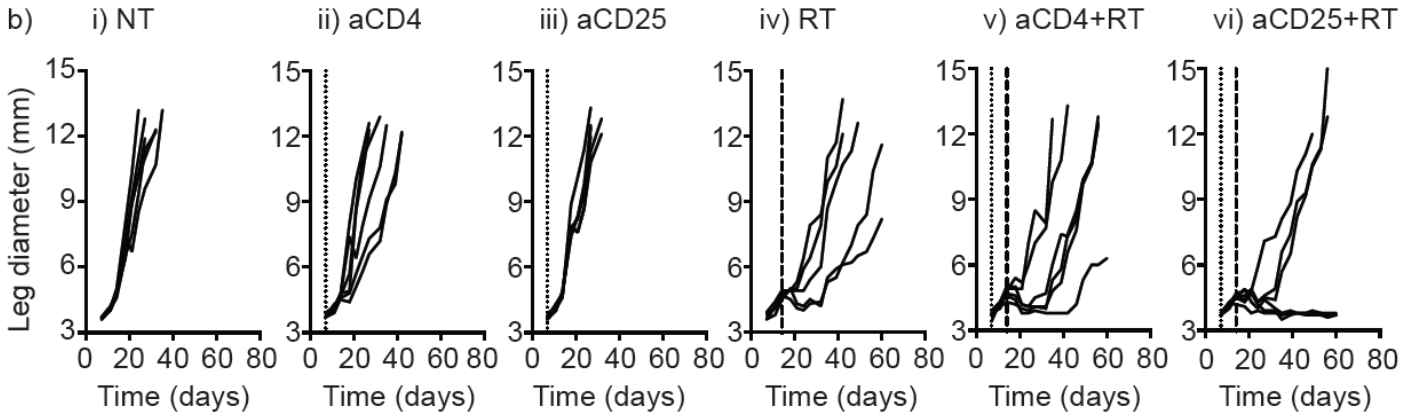


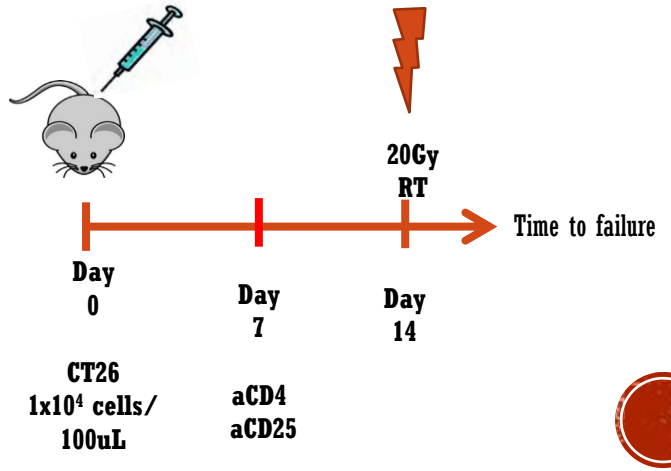


TARGETED T CELL DEPLETION PARTIALLY RECAPITULATES CTLA4 PRETREATMENT PHENOTYPE

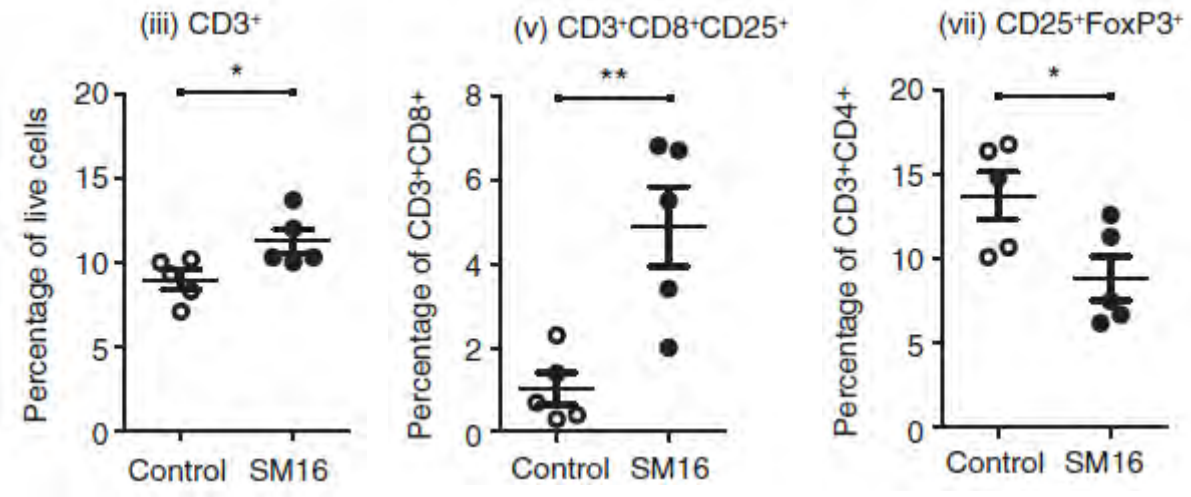


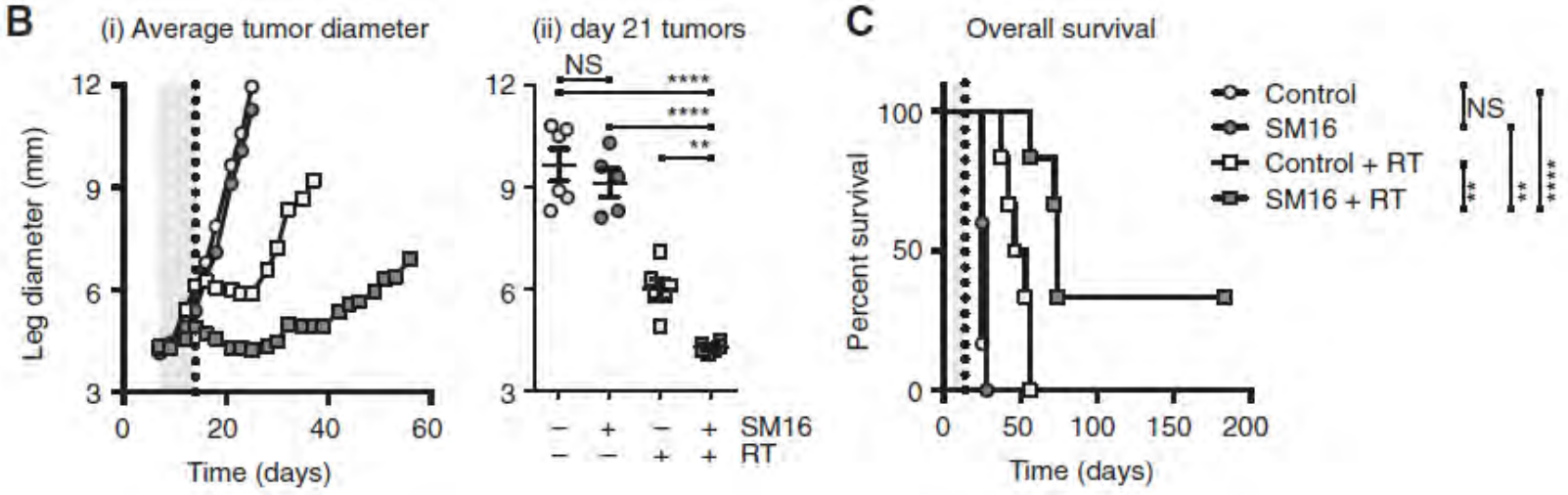


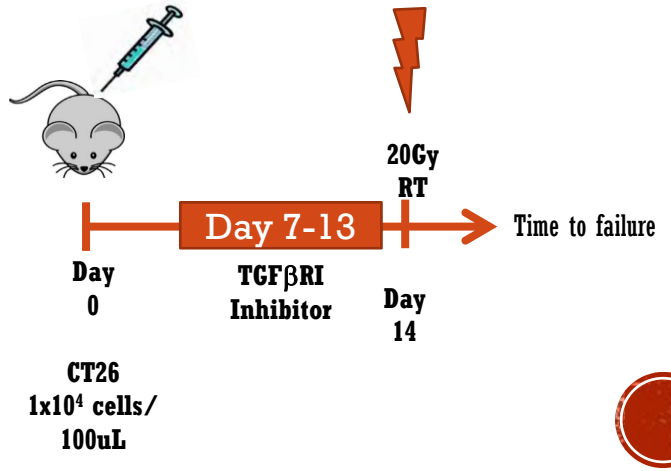




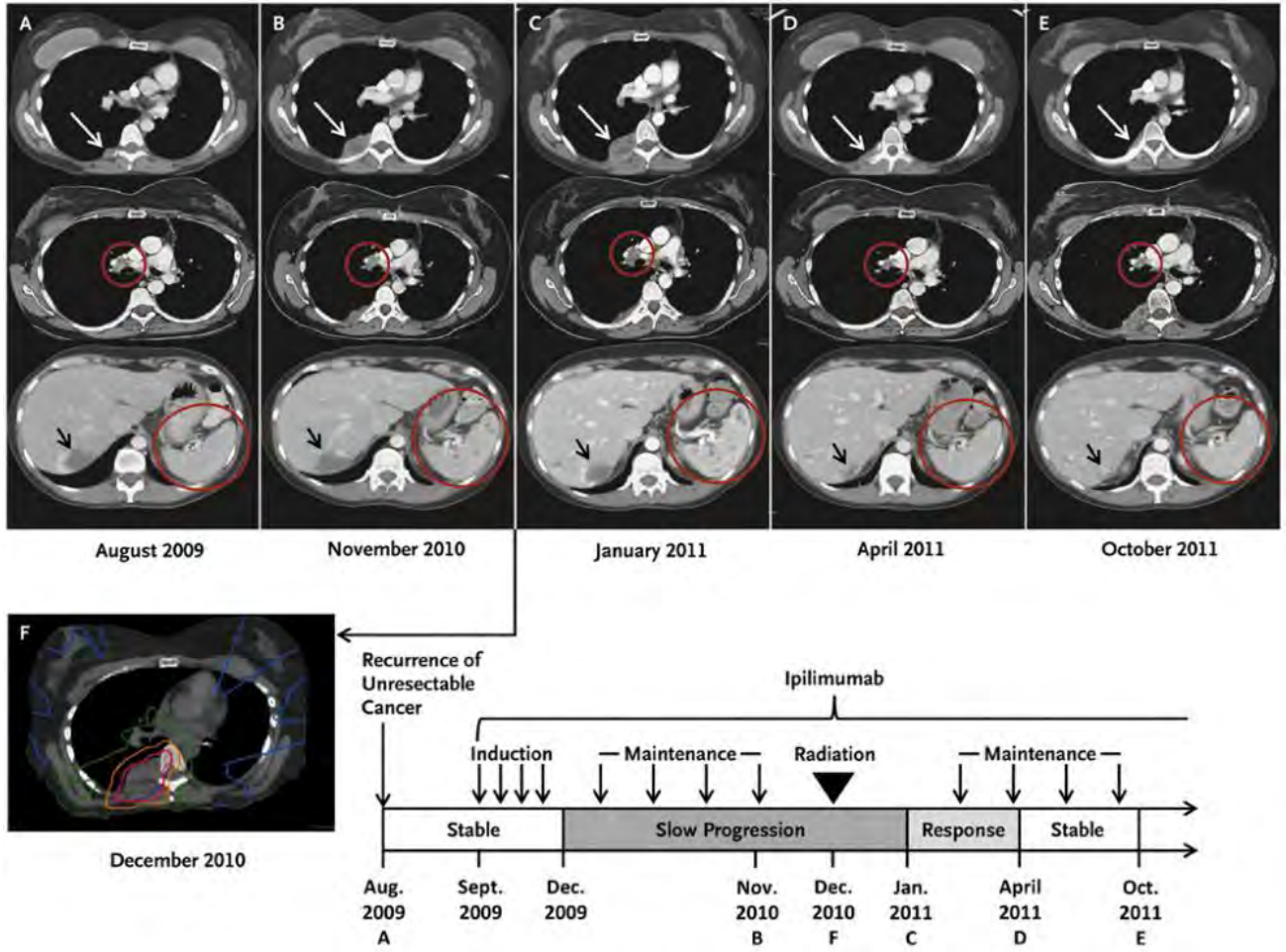
PRETREATMENT WITH TGFβRI INHIBITOR ALSO DEPLETES T_{REGS} AND RESULTS IN TUMOR CLEARANCE







ANECDOTAL EVIDENCE FOR PRETREATMENT IPILUMIMAB



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

SUMMARY

Postow, M. A. *et al.* Immunologic correlates of the abscopal effect in a patient with melanoma. *The New England journal of medicine* **366**, 925–31 (2012).

ANECDOTAL EVIDENCE FOR PRETREATMENT IPILUMIMAB

Translational Oncology
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A Systemic Complete Response of Metastatic Melanoma to Local Radiation and Immunotherapy

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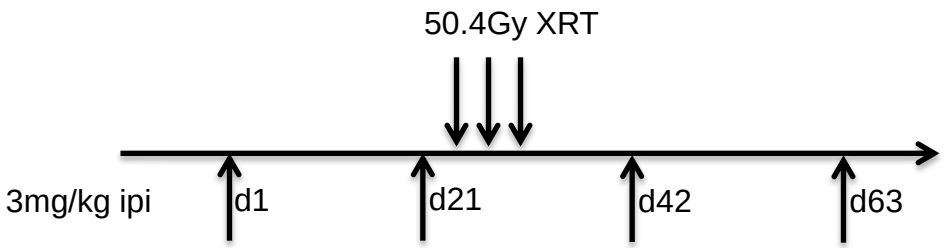
*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA; †Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA; ‡Department of Dermatology, Stanford University School of Medicine, Stanford, CA



International Journal of Radiation Oncology biology • physics
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Brief Report

The Abscopal Effect Associated With a Systemic Anti-melanoma Immune Response

Emily F. Stamell, MD,* Jedd D. Wolchok, MD, PhD,†,‡,§,‖ Sacha Gnjatic, PhD,‡,§ Nancy Y. Lee, MD,¶ and Isaac Brownell, MD, PhD**,††

*Division of Dermatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York; †Melanoma and Sarcoma Service, Department of Medicine, ‡Ludwig Institute for Cancer Research, and §Ludwig Center for Cancer Immunotherapy, Memorial Sloan-Kettering Cancer Center, New York, New York; ‖Weill-Cornell Medical College, New York, New York; ¶Department of Radiation Oncology and **Dermatology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York; and the ††Dermatology Branch, National Cancer Institute, Bethesda, Maryland

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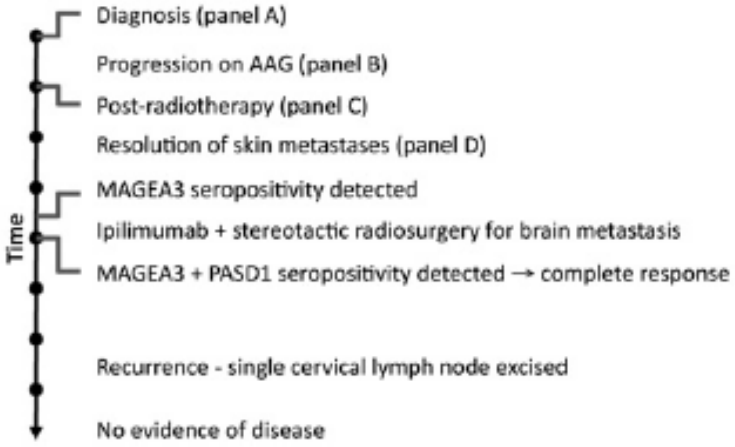

ONGOING IPILUMIMAB + RT TRIALS

Clinical trial	SIte	Start date	Pre-RT	Concurrent/ post-RT	Cancer	RT dosing	Additional therapy
NCT00861614	Bristol-Myers Squibb	May-09		x	Prostate	Not specified	
NCT01557114	Gustave Roussy, Paris	Mar-11		x	Melanoma	5Gyx3, 6Gyx3, 8Gyx3	
NCT01449279	Stanford University	Oct-11		x	Melanoma	Palliative	
NCT01565837	Comprehensive Cancer Centers of Nevada	Aug-12	x		Melanoma	SART	
NCT01711515	NCI	Oct-12		x	Cervical	Fractionated	Cisplatin
NCT01703507	Thomas Jefferson University	Nov-12		x	Melanoma	Whole brain/SRS	
NCT01689974	New York University	Jan-13		x	Melanoma	6Gyx5	
NCT01935921	NCI	Apr-13		x	H&N	Fractionated	Cetuximab
NCT01860430	University of Pittsburgh	Apr-13		x	H&N	Fractionated	Cetuximab
NCT01996202	Duke University	Nov-13			Melanoma	Not specified	
NCT01970527	University of Washington	Mar-14		x	Melanoma	SBRTx3	
NCT02115139	Grupo Español Multidisciplinar de Melanoma	Apr-14	x		Melanoma	Whole brain 3Gyx10	
NCT02107755	Ohio State University	Apr-14	x		Melanoma	SABR	
NCT02097732	University of Michigan	Apr-14	x		Melanoma	SRS	

CONCLUSIONS

- αOX40
  - Ideal timing shortly after RT
  - Proposed mechanism
    - Increases activated CD8 T cells
    - Provides co-stimulatory agonist in window of radiation-induced increased antigen presentation
- αCTLA4
  - Pre-treatment provides the best environment for enhanced radiation efficacy
    - Still some enhanced efficacy following RT
  - Decreased Tregs may be responsible
- Together, indicates ideal timing may differ by immunotherapy and mechanism of action

ACKNOWLEDGEMENTS

- Earle A. Chiles Research Institute at Providence Portland Medical Center
  - Gough/Crittenden Lab
    - Marka Crittenden, MD, PhD
    - Michael Gough, PhD
    - Jay Baird, PhD
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    - David Friedman
    - Talicia Savage
  - Akporiaye Lab
  - Redmond Lab
  - Bahjat Lab
  - Dan Haley
- OHSU Radiation Medicine
- ABR: B. Leonard Holman Research Pathway
- RSNA R&E Foundation Research Resident Award