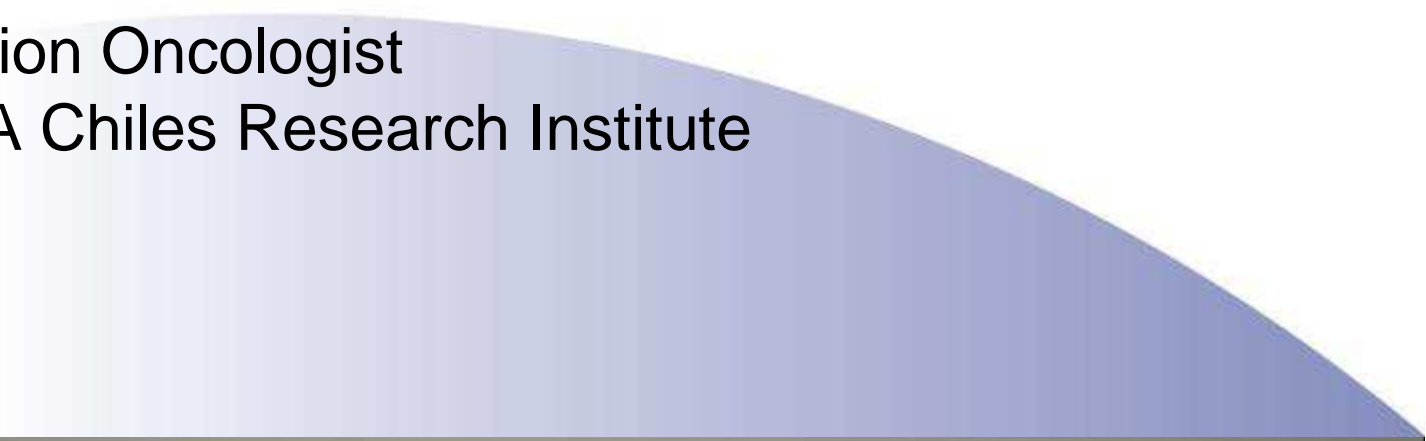


The Emerging Role of Combination Tumor Immunotherapy with Radiation

Marka Crittenden M.D. Ph.D.
Radiation Oncologist
Earle A Chiles Research Institute

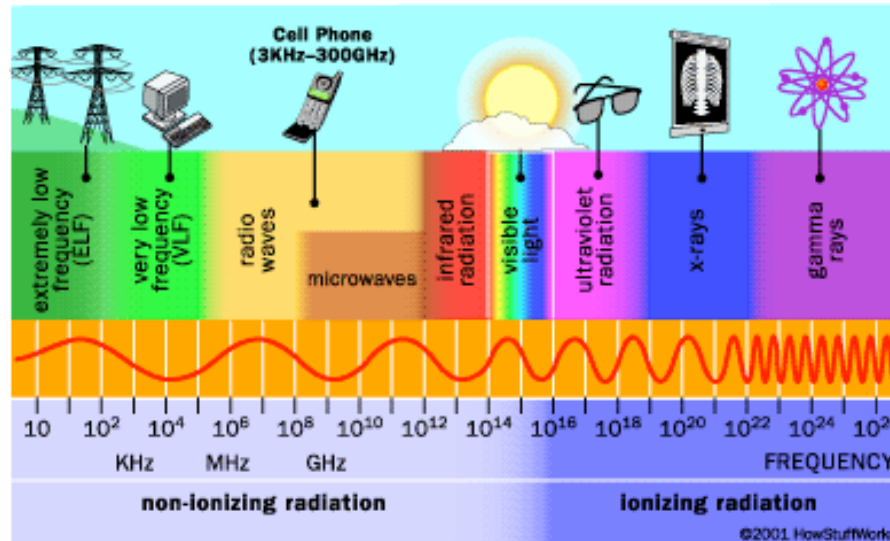


Presentation Outline

- Overview of Radiation
 - Radiation and Immune System
 - Radiation and Immunotherapy Preclinical Examples
 - Radiation and Immunotherapy Clinical Examples
 - Multiple Choice Questions
- 

Radiation Oncology

- Uses radiation to treat disease (specifically cancer)
- *Radiation* is energy that comes from a source and travels through some material or through space in the form of a wave or a particle.

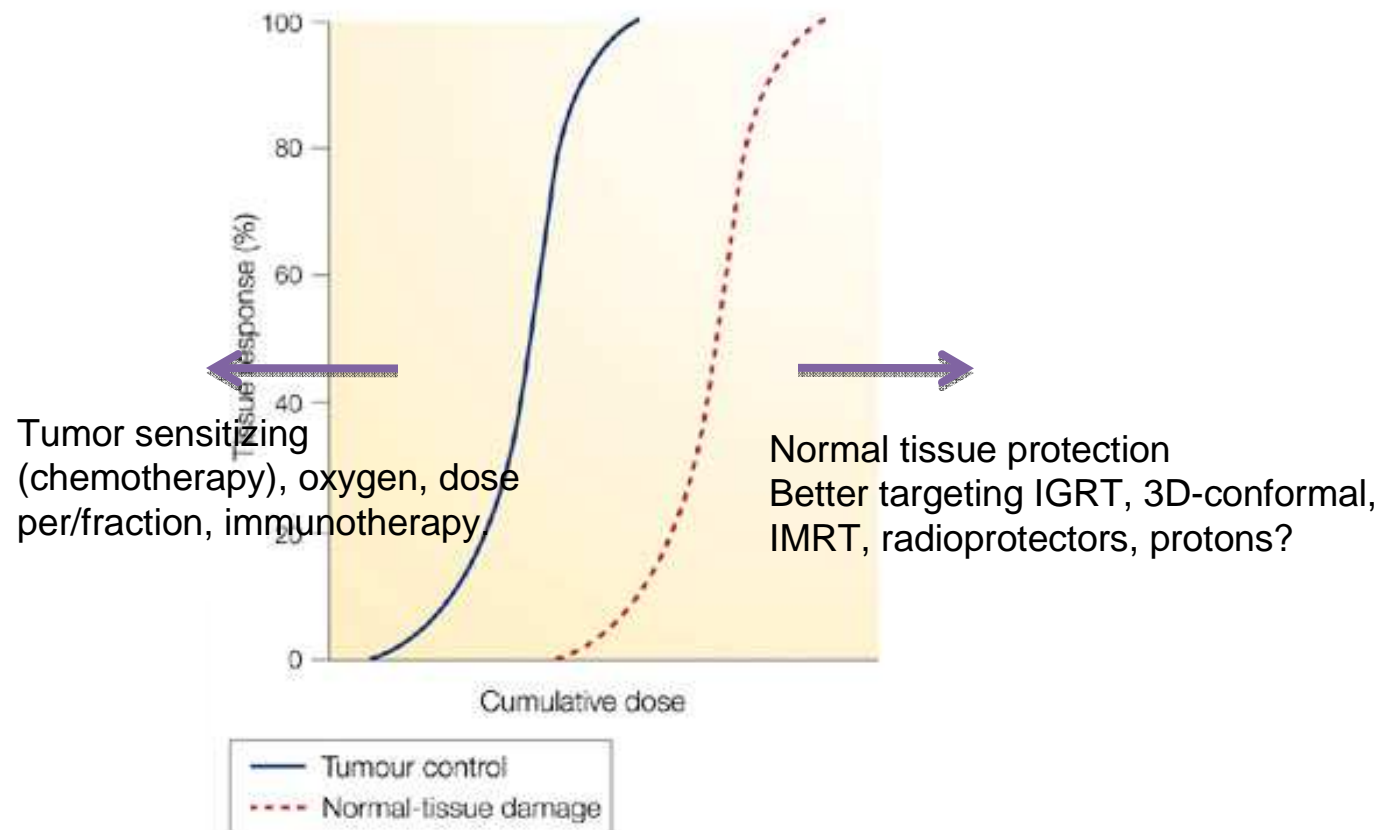


Overview of Radiation

- Radiation Therapy uses ionizing radiation (x-rays, electrons, protons, neutrons, gamma rays) to focally treat tumors.
- Local modality with both a direct cytotoxic effect on cancer cells and indirect effect on stromal tissue.
- Therapeutic Ratio-fundamental principle of radiation



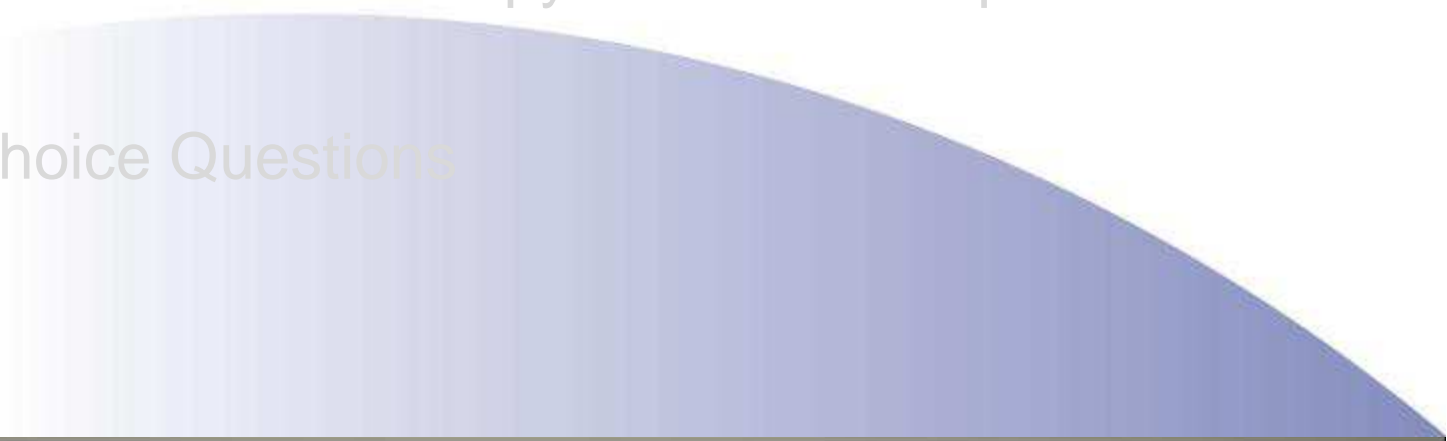
Therapeutic Ratio

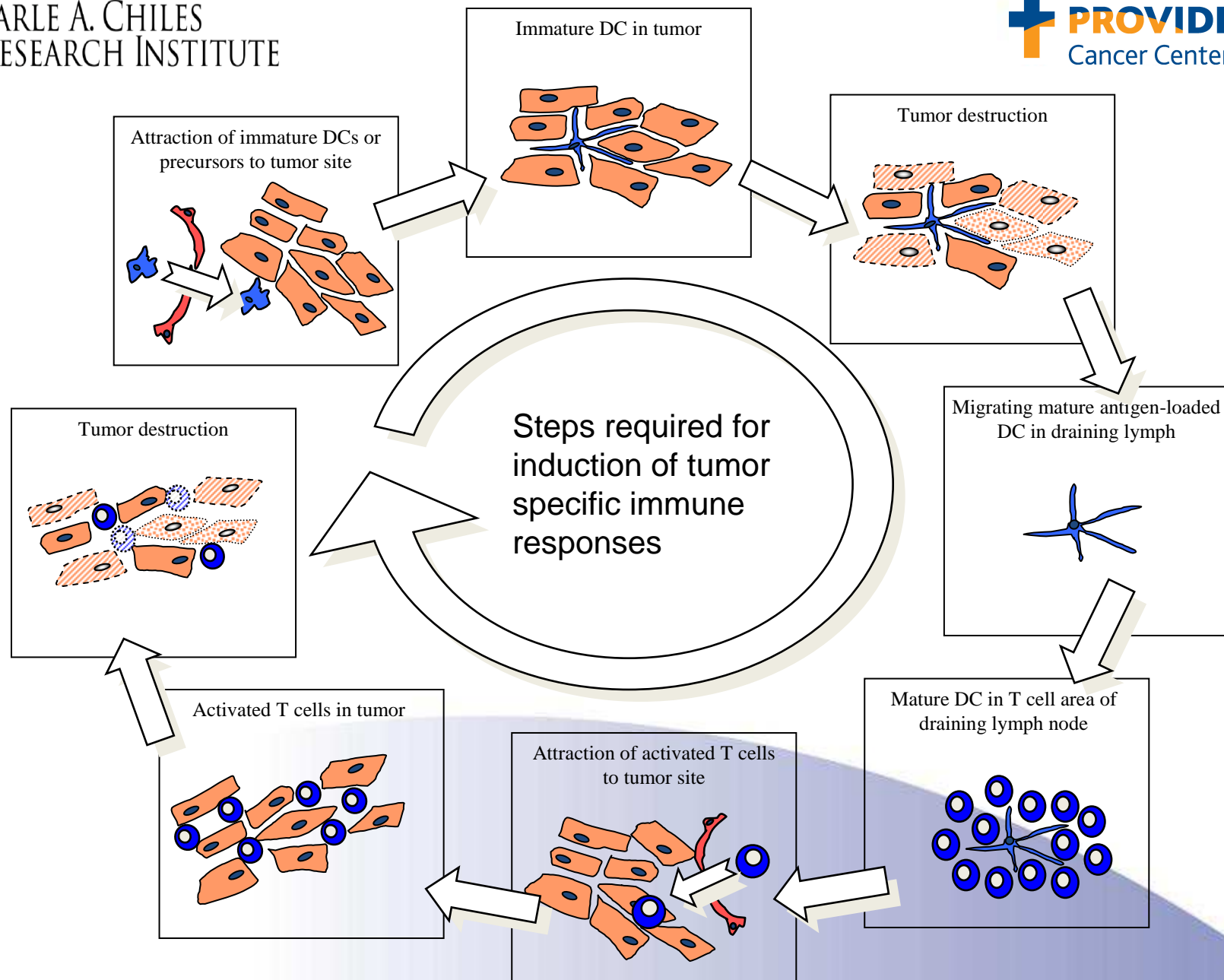


Fractionation

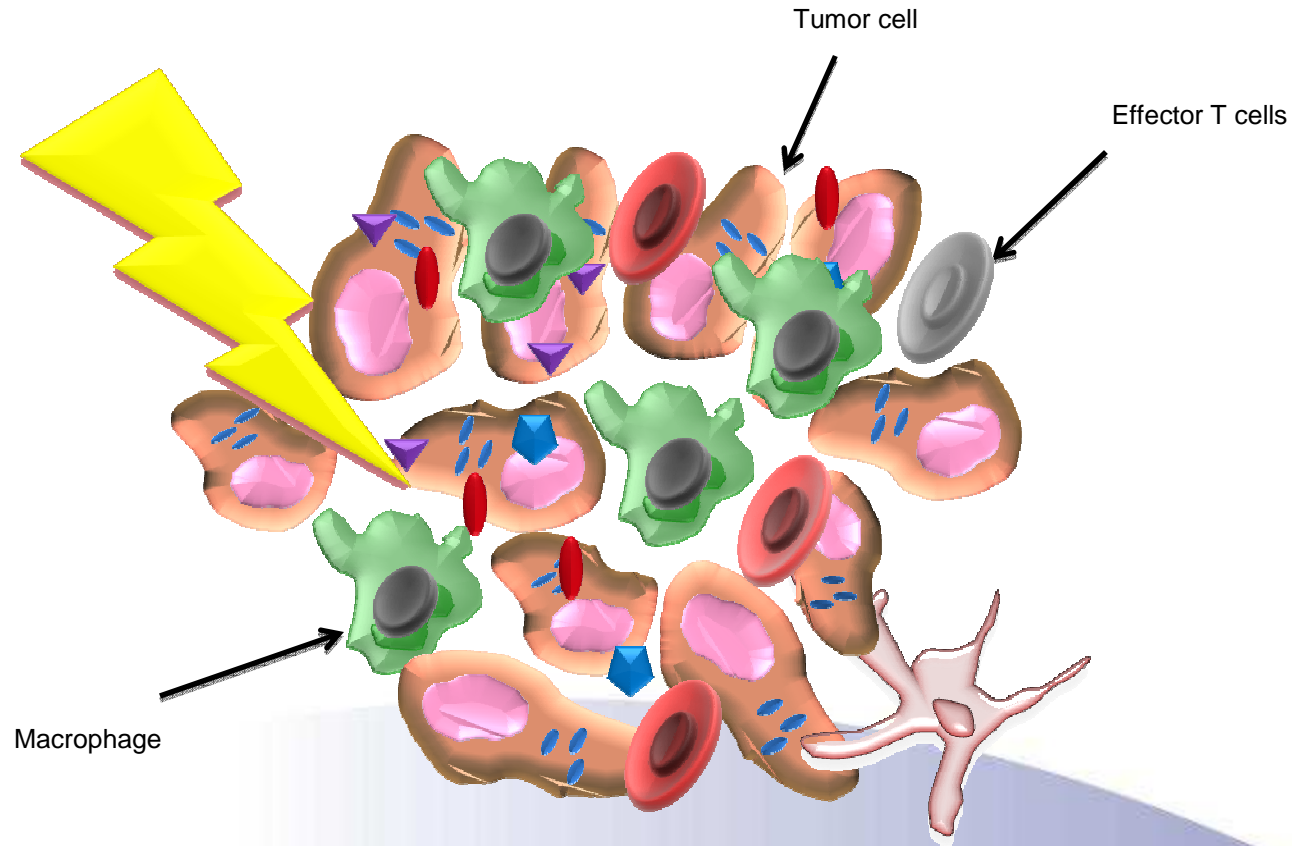
	Standard Fractionation	Hypofractionation
Duration	5-8 weeks (28-40 treatments)	1-2 weeks (<5 treatments)
Dose	1.8-2.0 Gy per fraction	5-40Gy per fraction
Field Size	Large Fields including normal tissue	Tight small fields minimizing normal organs
Duration per fraction	2-10 min	45 min -1 hr
Toxicity	Acute>Chronic	Chronic>Acute
		SBRT, SABR, Gamma Knife, radiosurgery, Cyberknife

Presentation Outline


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- 



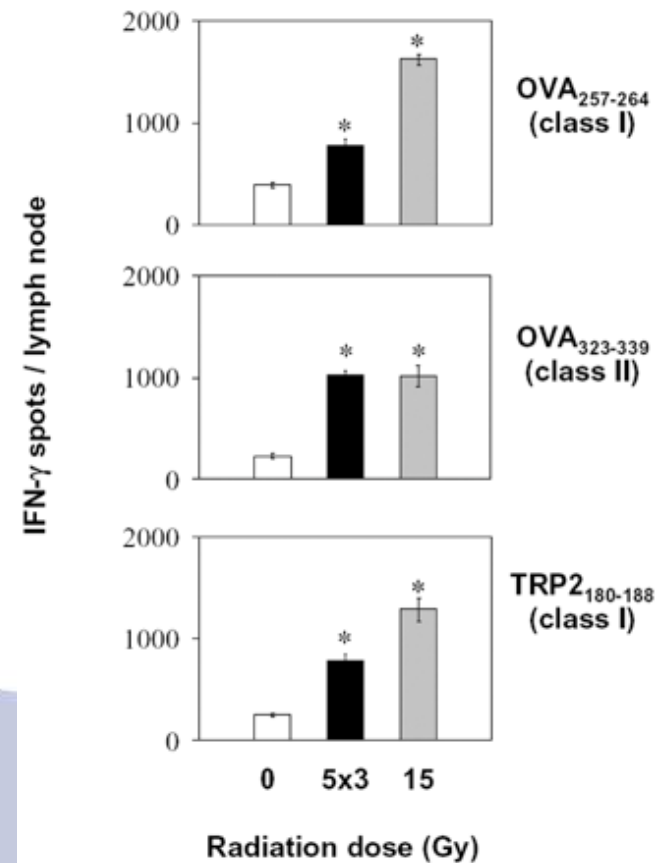
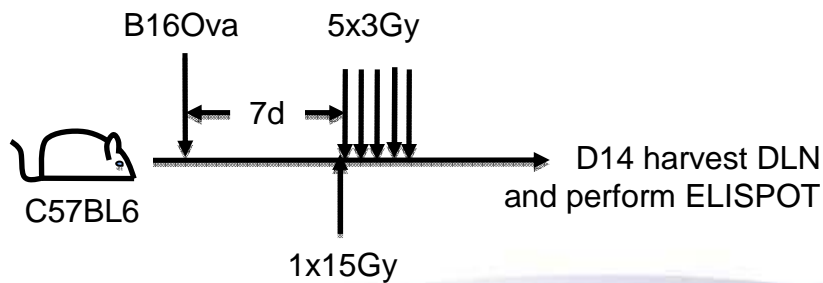
Rationale for radiation and immunotherapy



Mechanisms of Synergy between Radiation and Immune Response

- Tumor antigen release and increased priming
 - Tumor adjuvant release (DAMPS)
 - Deletion of anergic and regulatory T cells and activation of T cells
 - Antigen processing machinery upregulation
 - Cytokine and chemokine induction
 - Enhanced Immune cell trafficking
- 

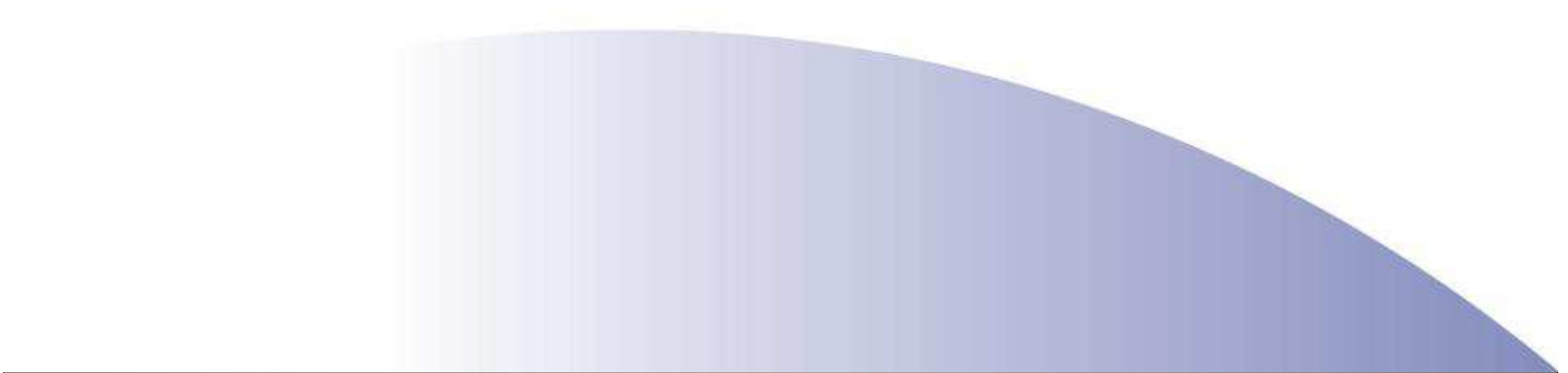
Tumor antigen release and enhanced priming in preclinical mouse models

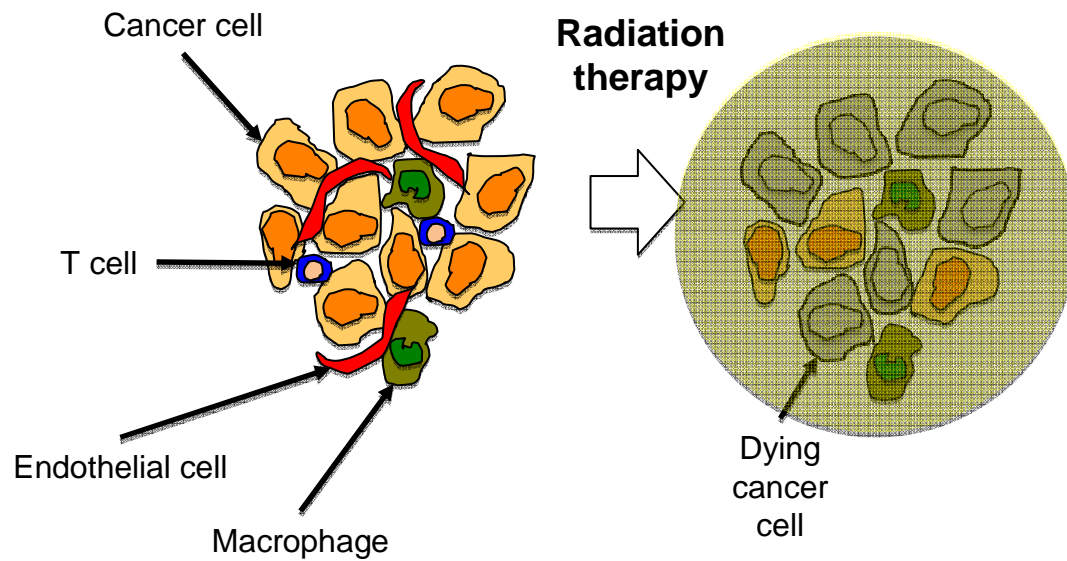


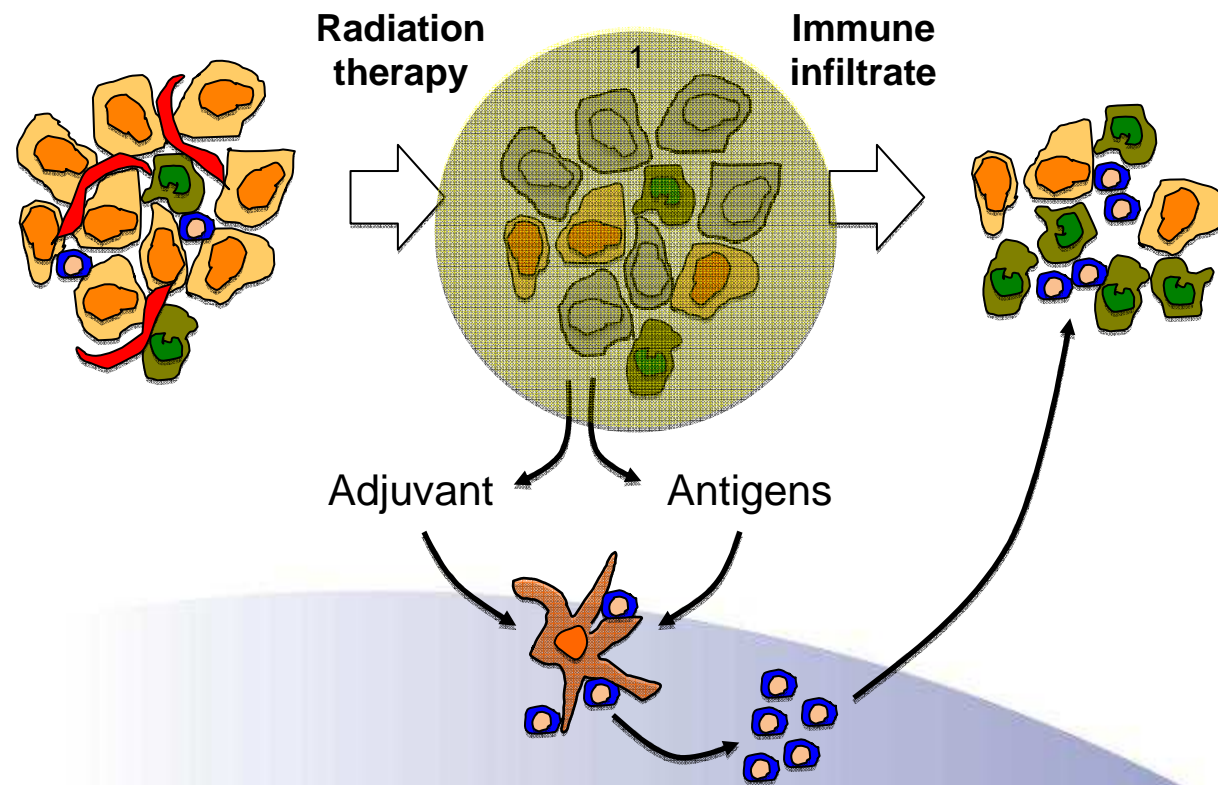
Lugade et al. The Journal of Immunology June 15, 2005 vol. 174 no. 12 7516-7523

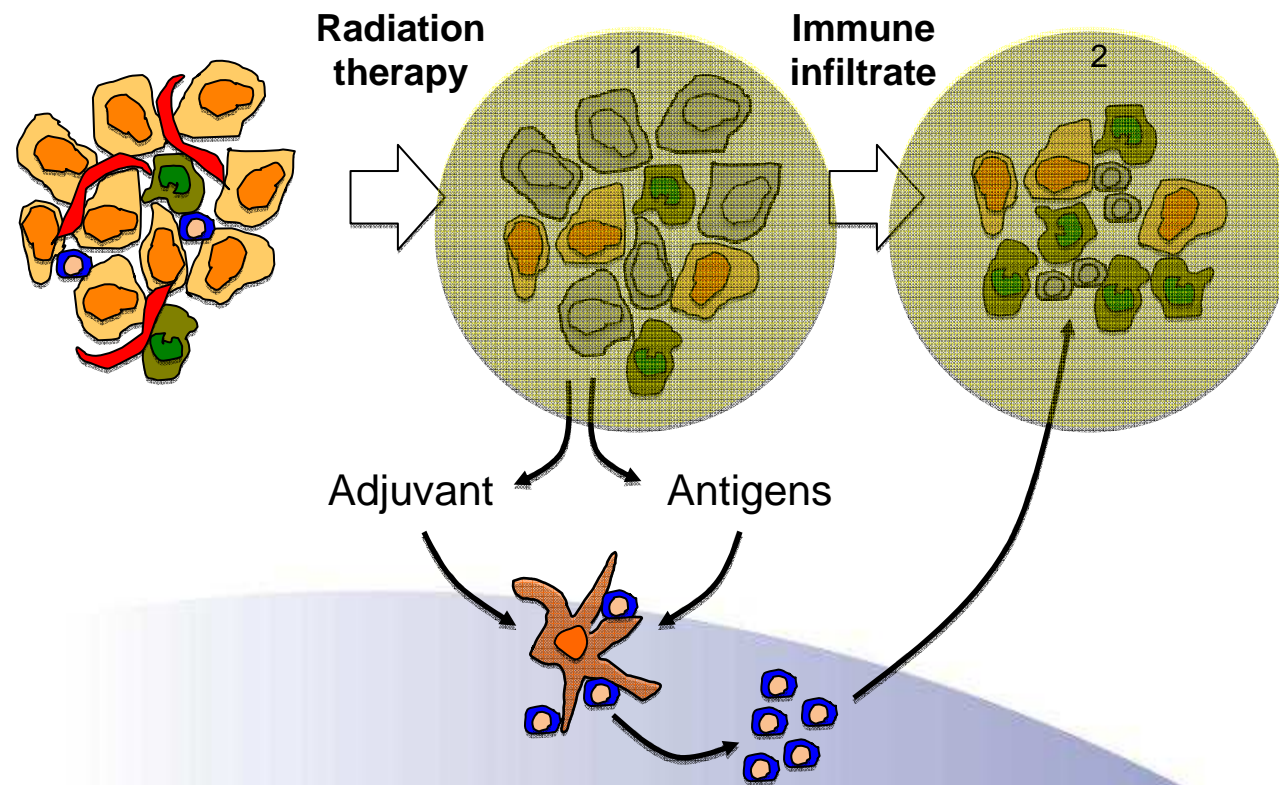
Fractionation Interlude

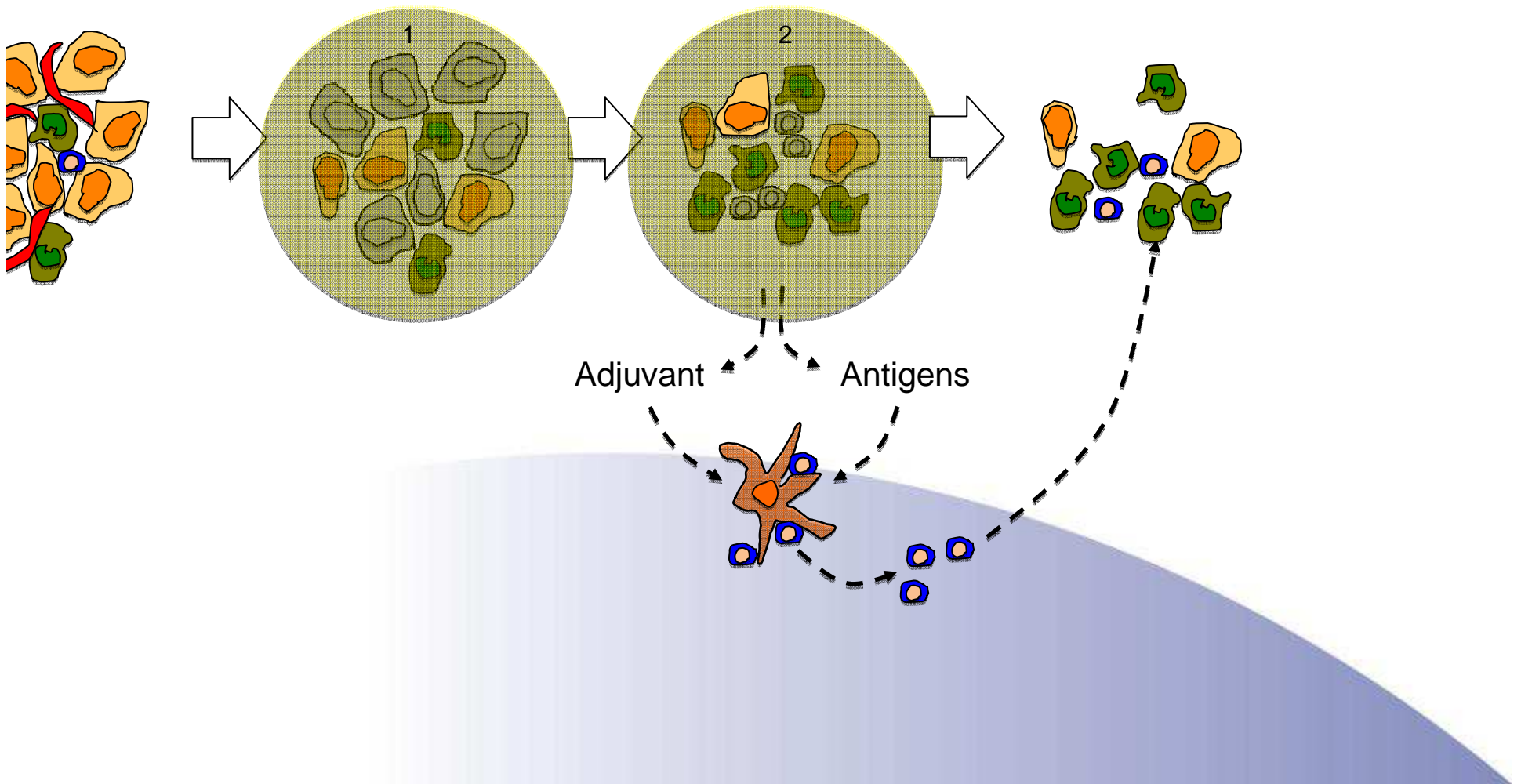
- Is hypofractionated radiation better than standard fractionation radiation?

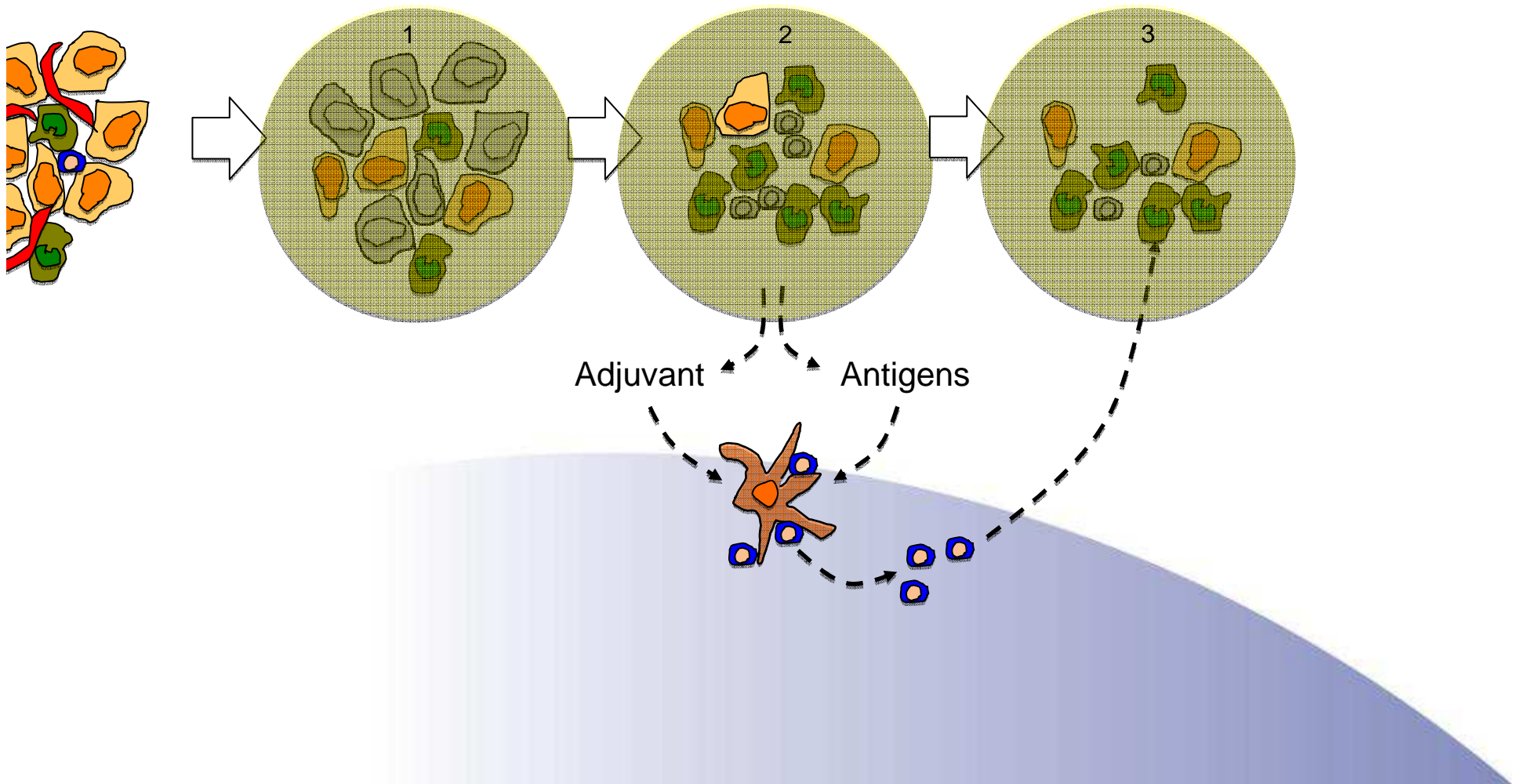


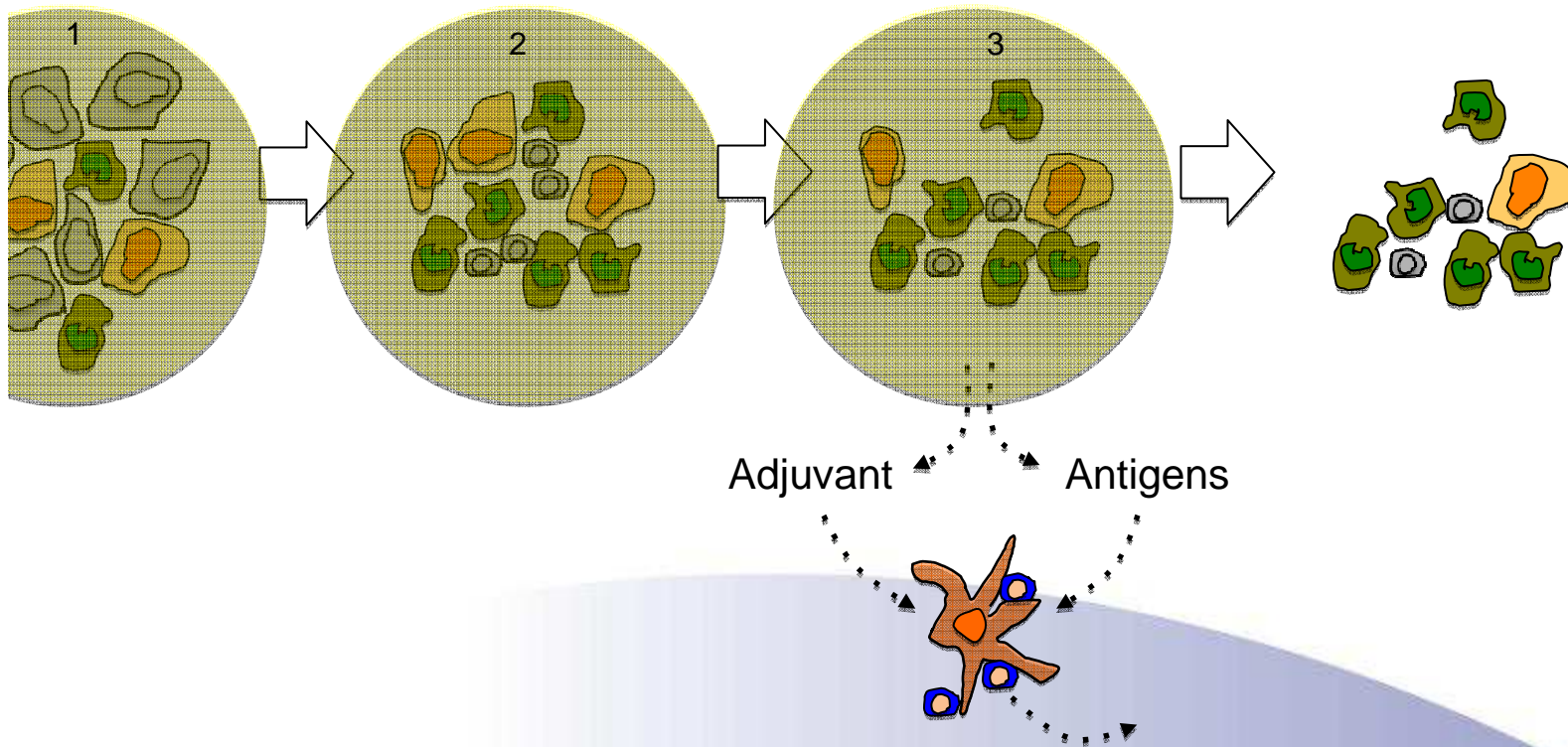


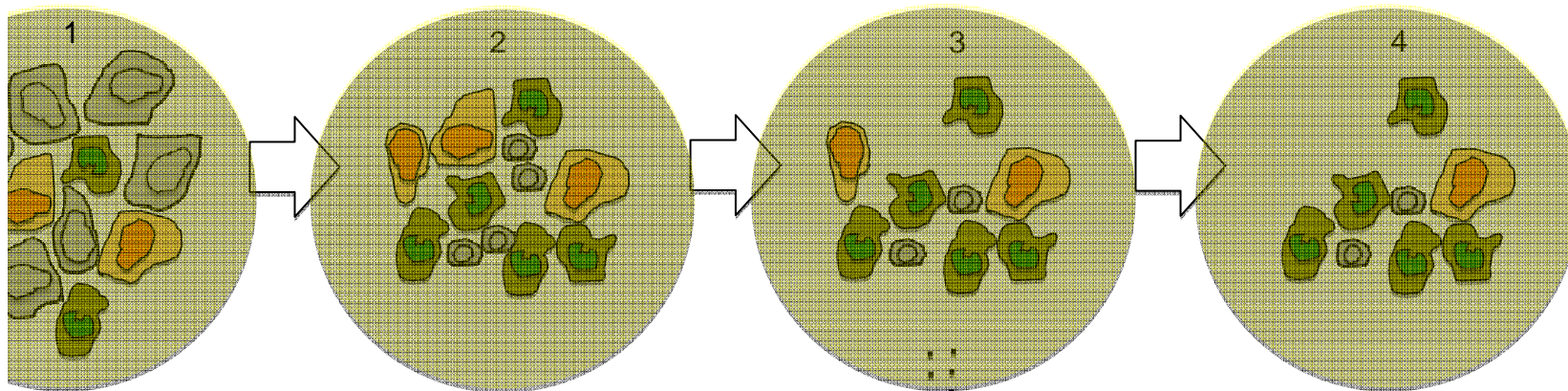




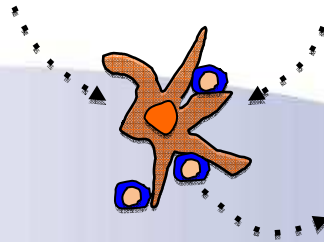


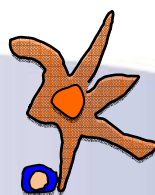
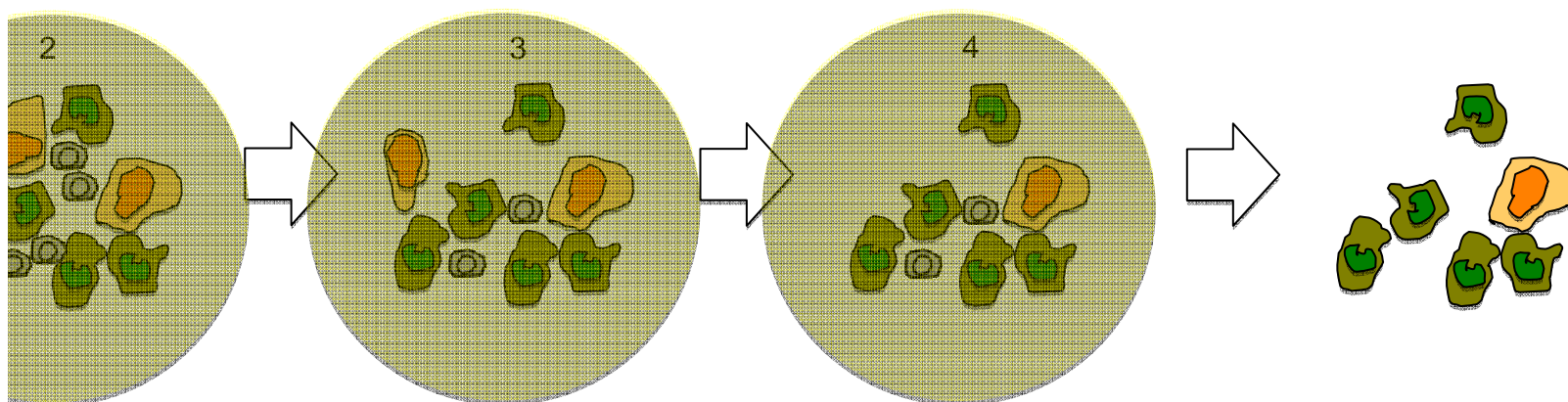


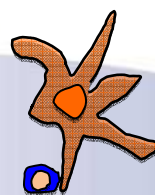
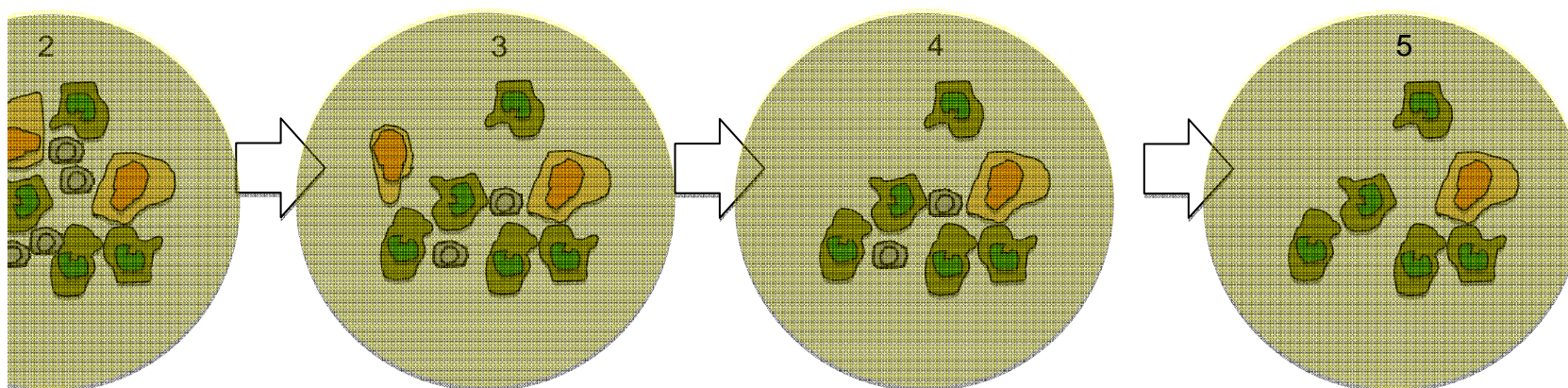




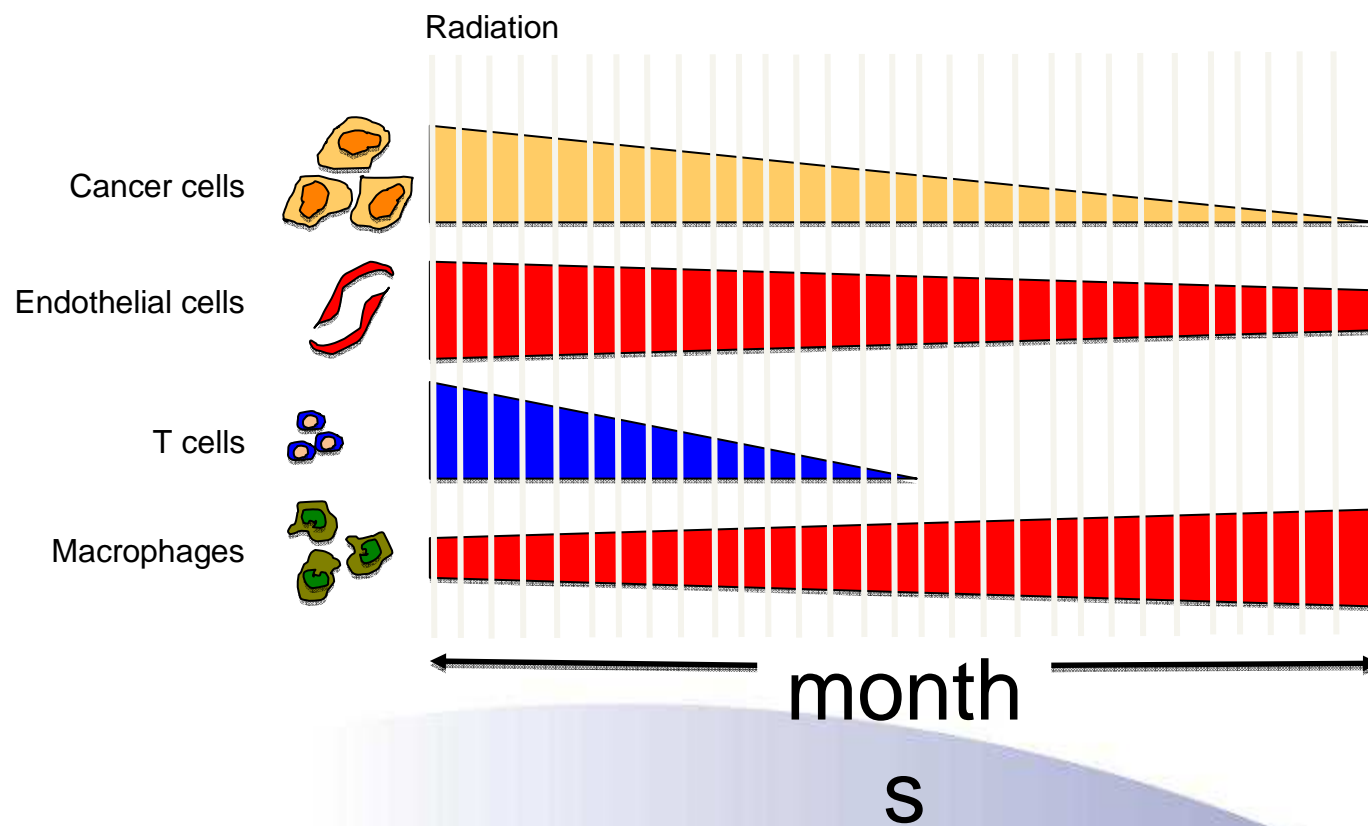
Adjuvant Antigens

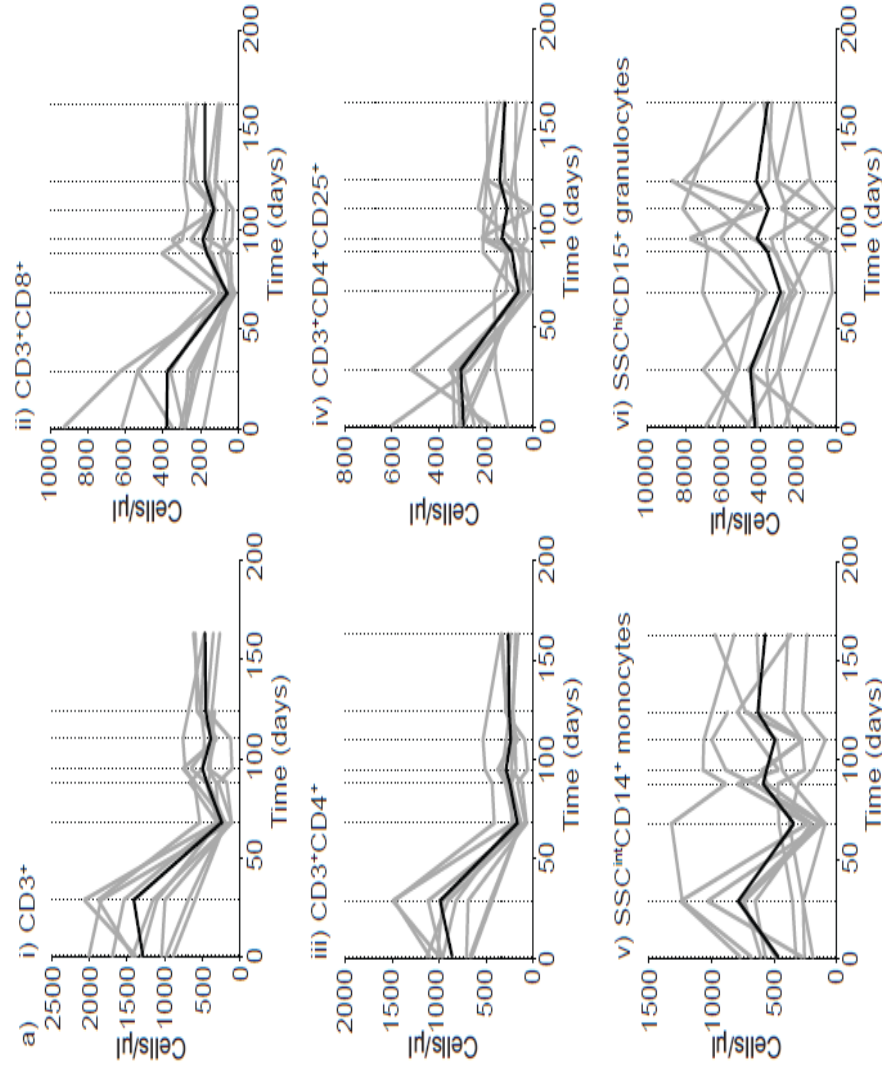






Conventional fractionation






Fractionation Interlude

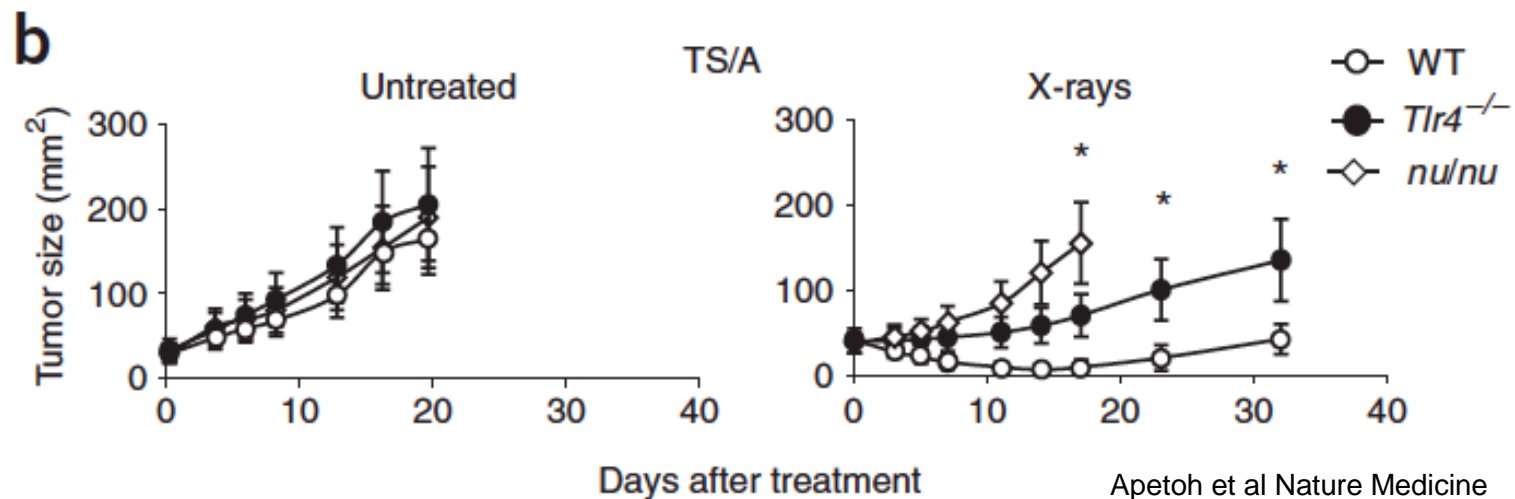
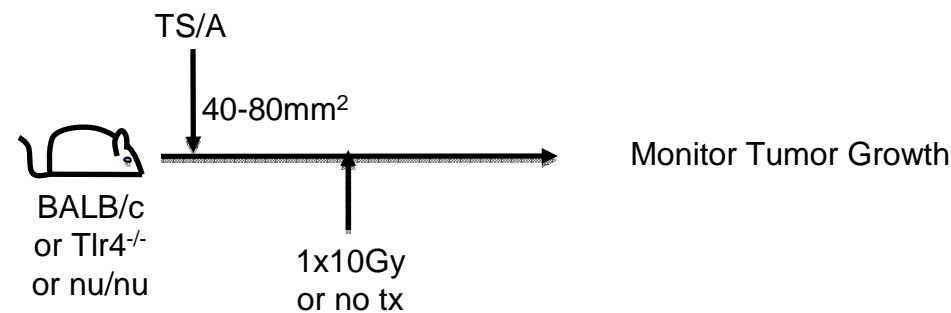
- Is hypofractionated radiation better than standard fractionation radiation for combination with immunotherapy?
- Given the sensitivity of lymphocytes to radiation standard radiation may not be the best
 - 1970s reports showing prolonged lymphopenia following standard fractionation for breast and lung cancer.



Mechanisms of Synergy between Radiation and Immune Response

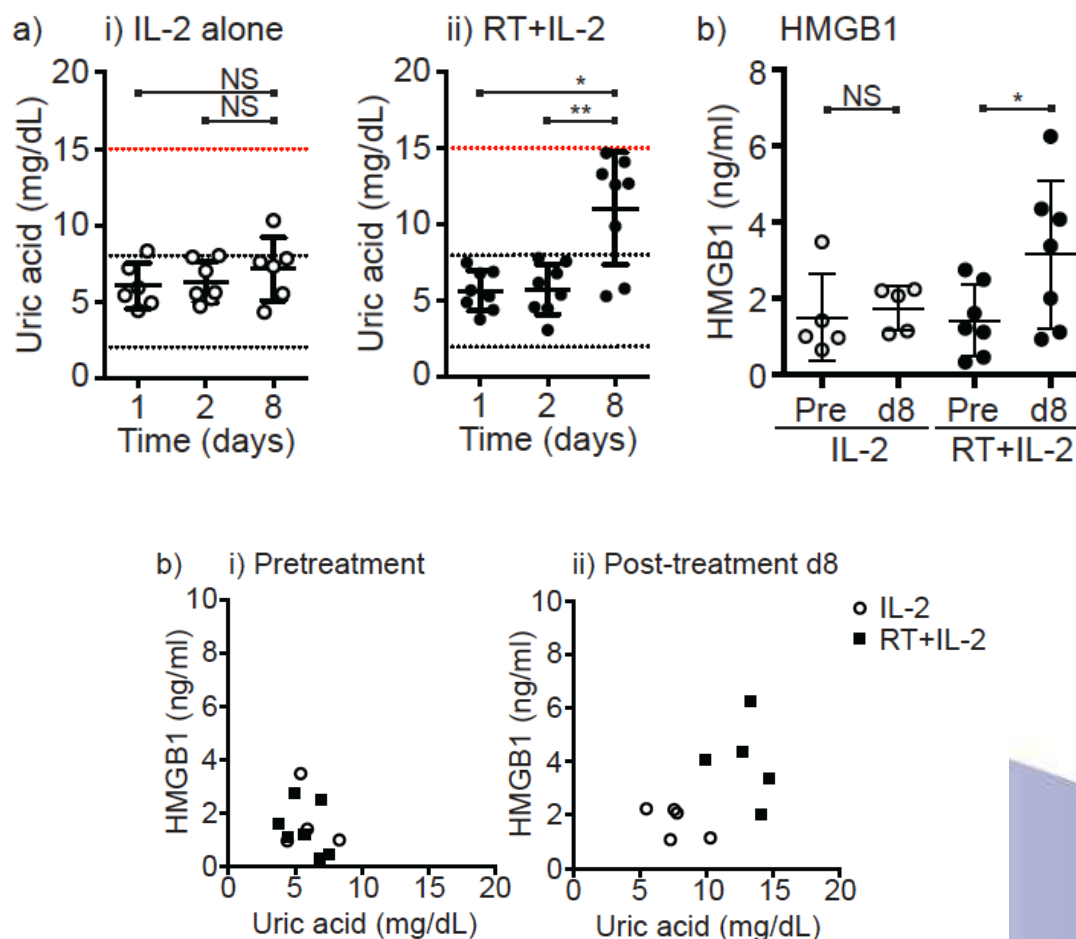
- Tumor antigen release and increased priming
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 - Deletion of anergic and regulatory T cells and activation of T cells
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 - Cytokine and chemokine induction
 - Enhanced Immune cell trafficking
- 

Tumor adjuvant release in preclinical mouse models

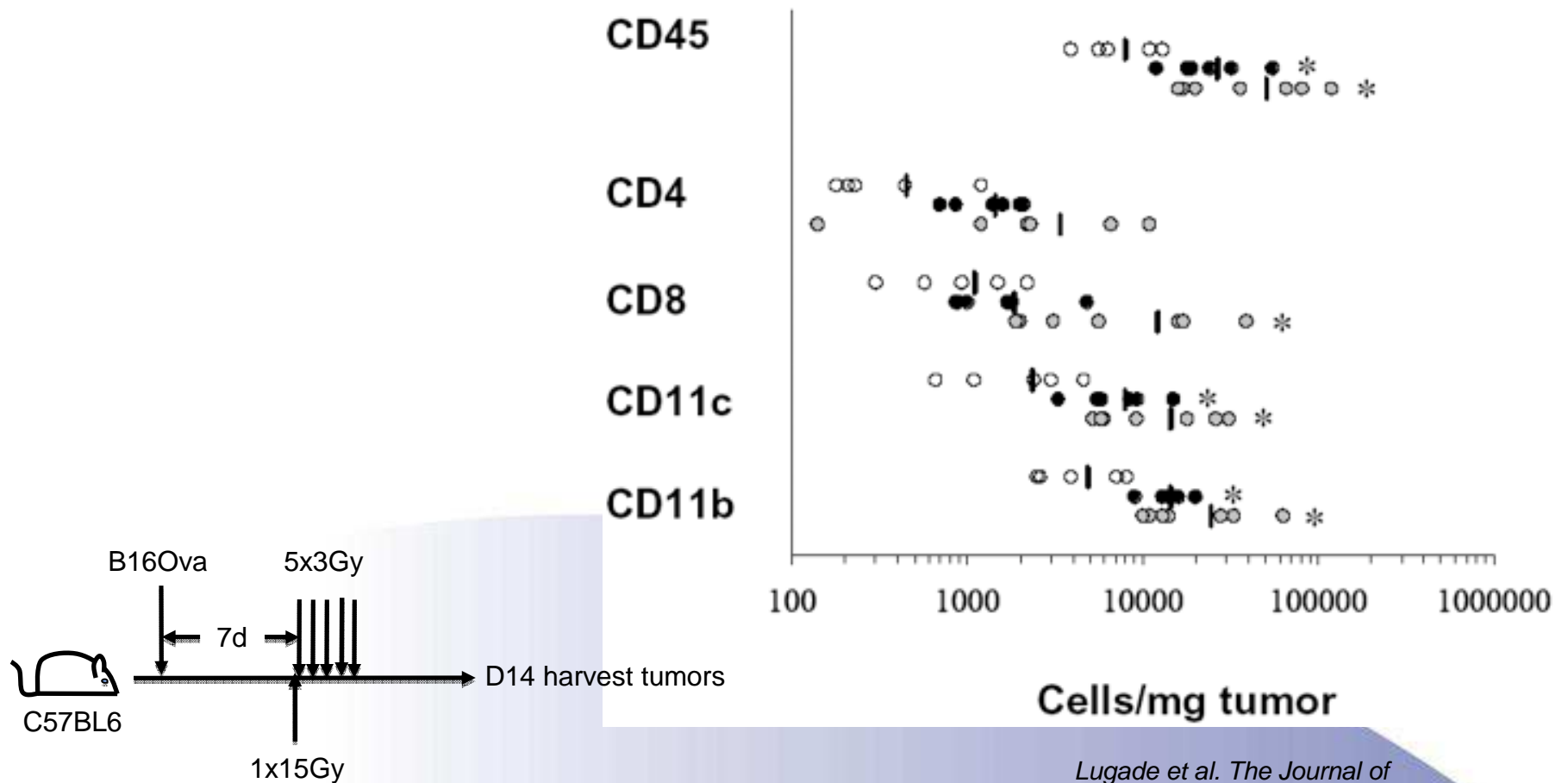


Apetoh et al Nature Medicine
September 2007 Vol. 13 1050-1059

Adjuvant release in patients following high dose RT

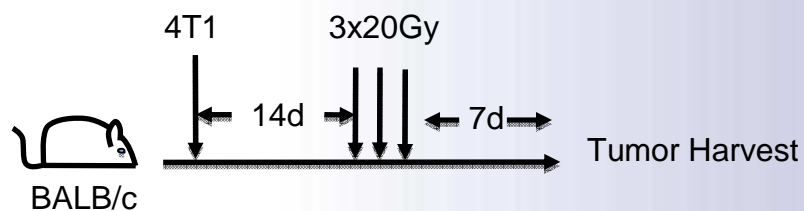
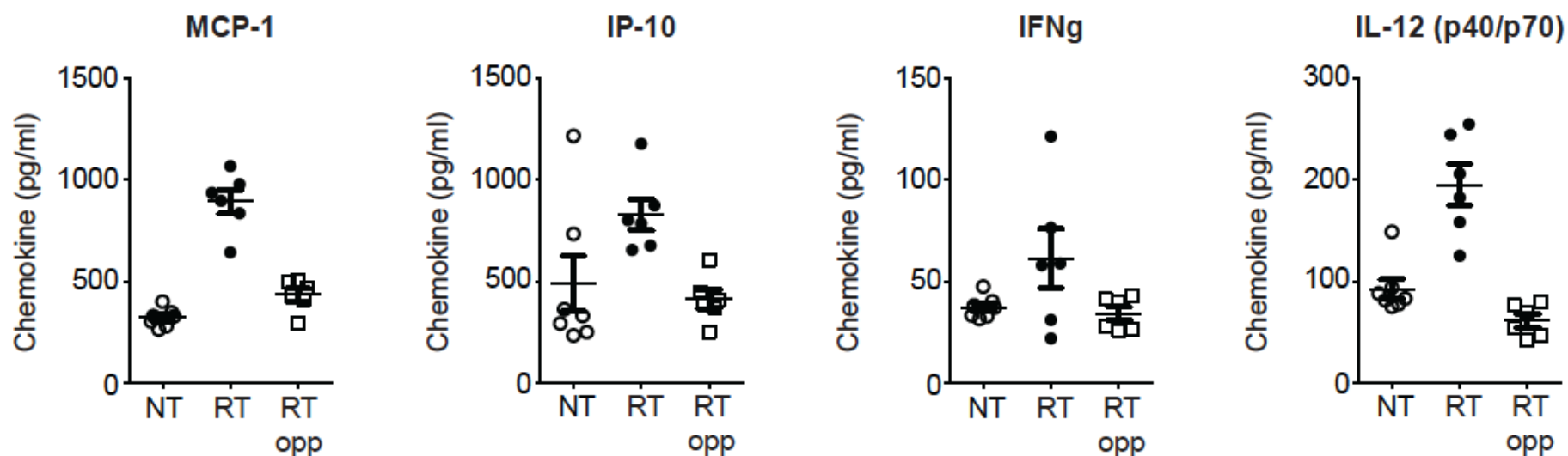


Radiation recruits immune cells to irradiated tumors

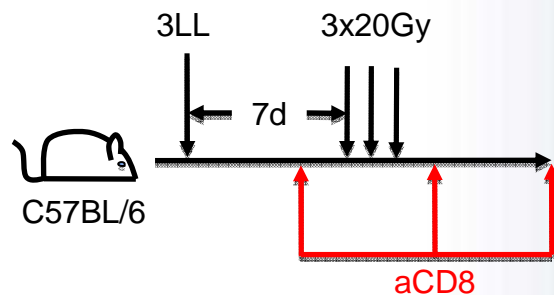
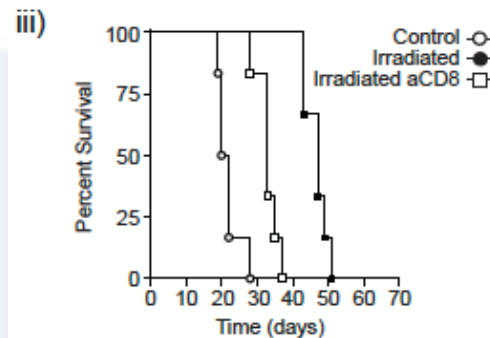
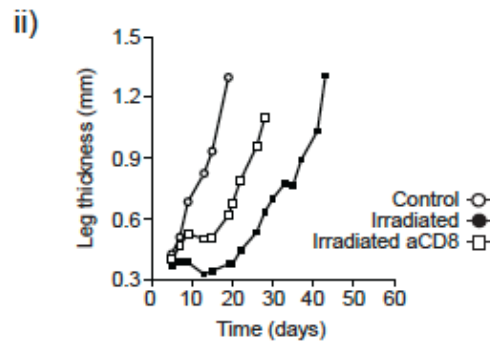
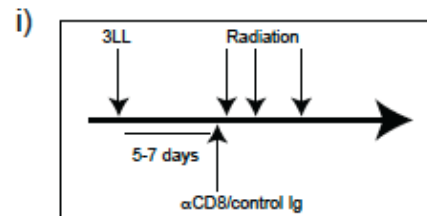


Lugade et al. *The Journal of Immunology* June 15, 2005 vol. 174 no. 12 7516-7523

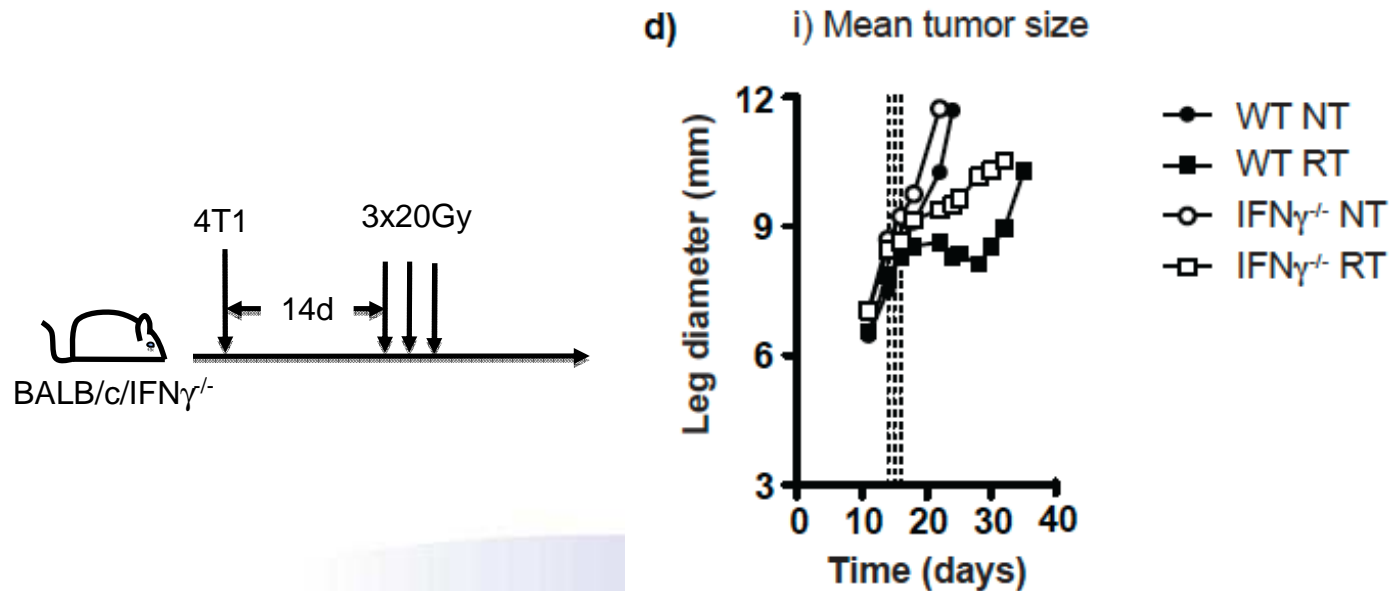
T cell attracting chemokines in tumors following RT in mouse tumor models



T cells are important in radiation therapy



IFN γ ^{-/-} with radiation therapy



Mechanisms of Synergy between Radiation and Immune Response

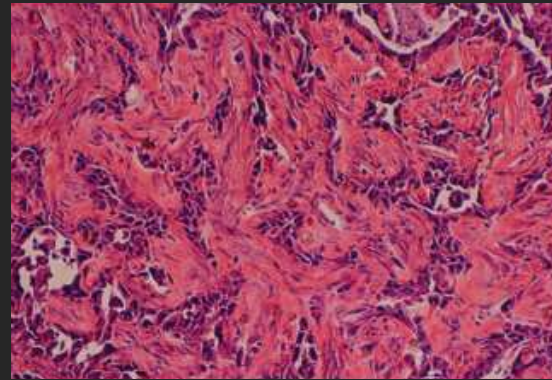
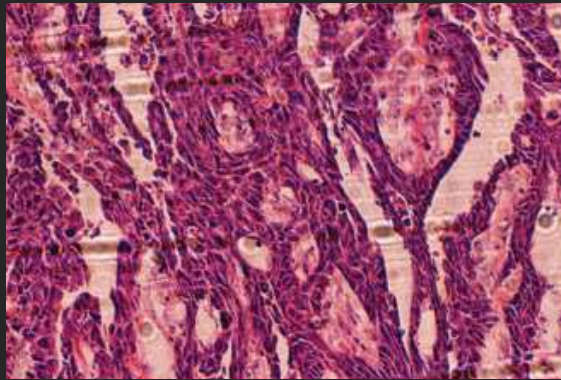
- Tumor antigen release and increased priming
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-
- IS IT ALL GOOD?

Stromal proliferation following radiation

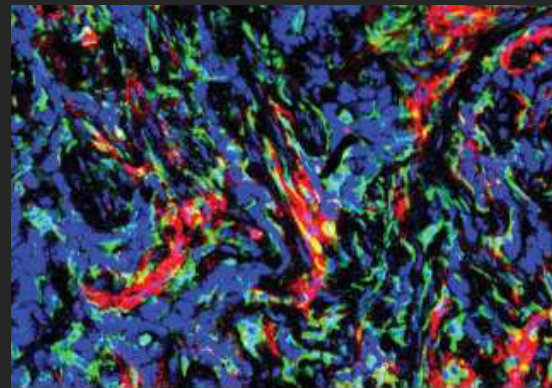
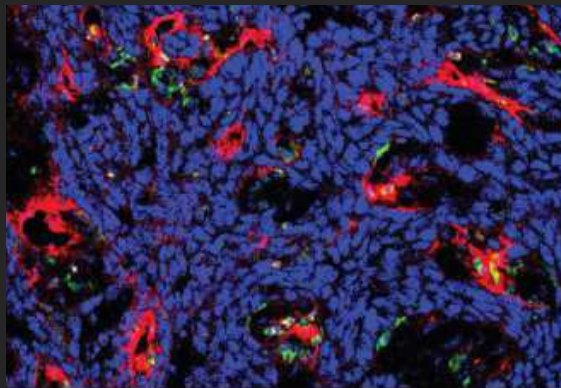
NT

RT

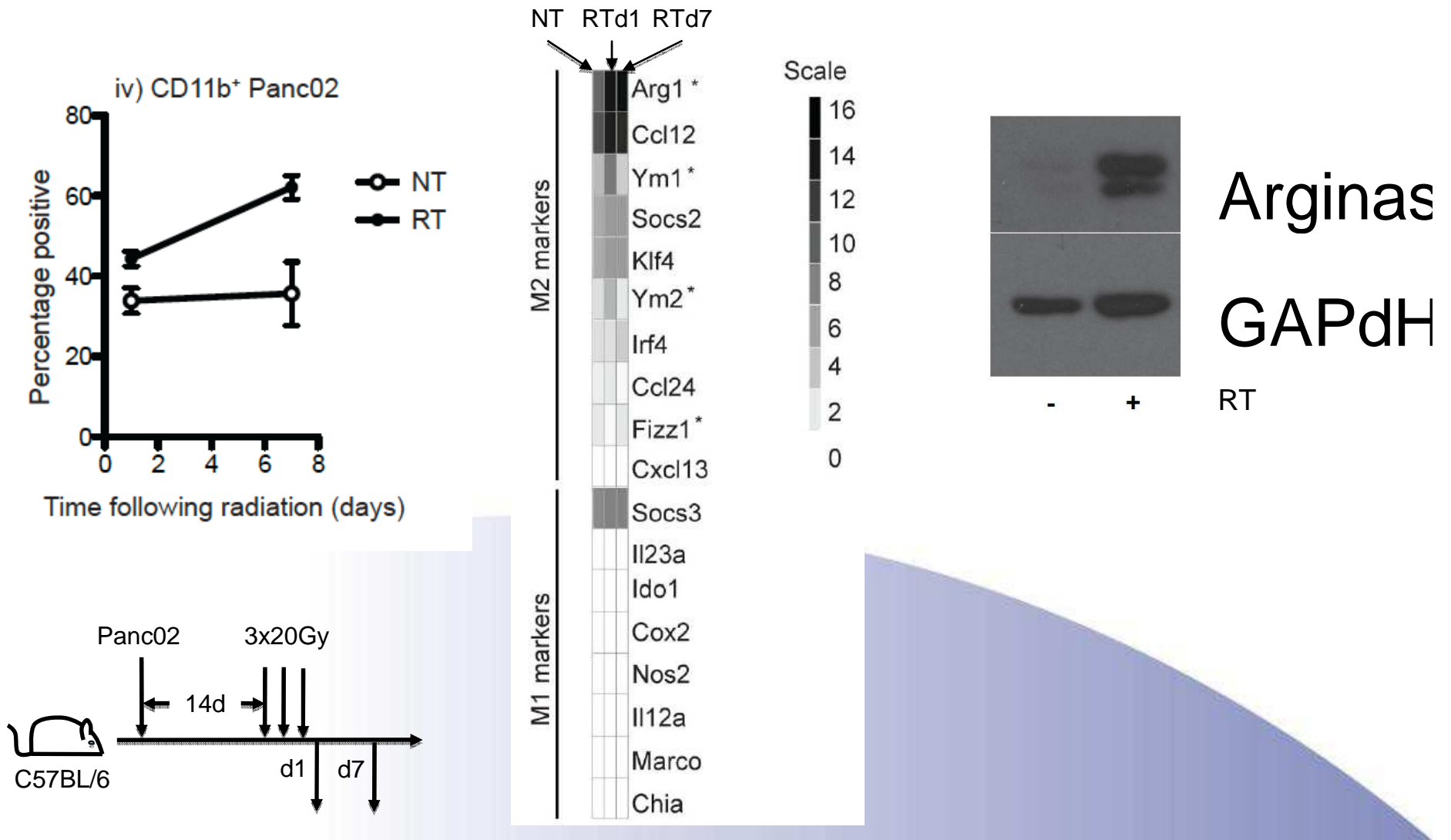
H&E



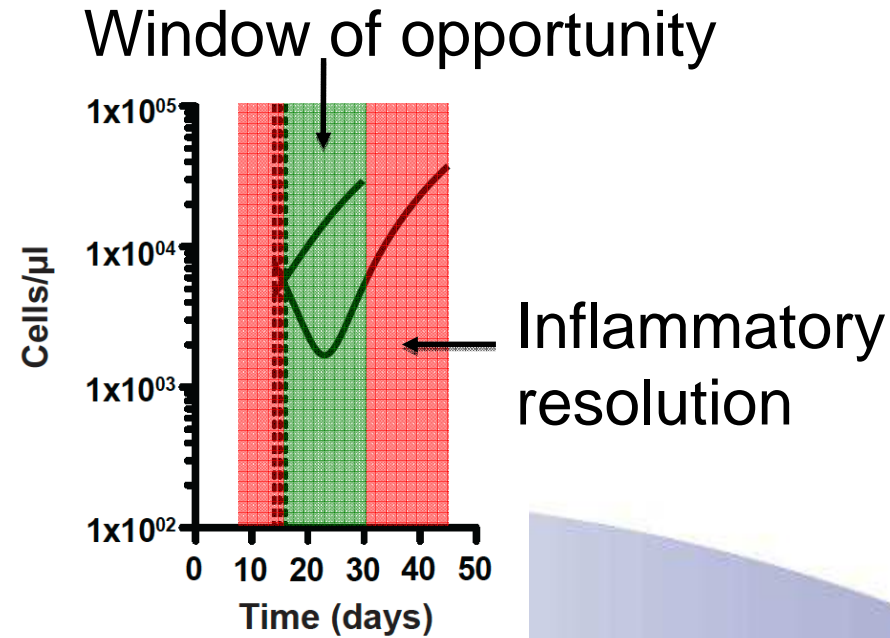
F4/80-FITC
VWF-PE
DAPI



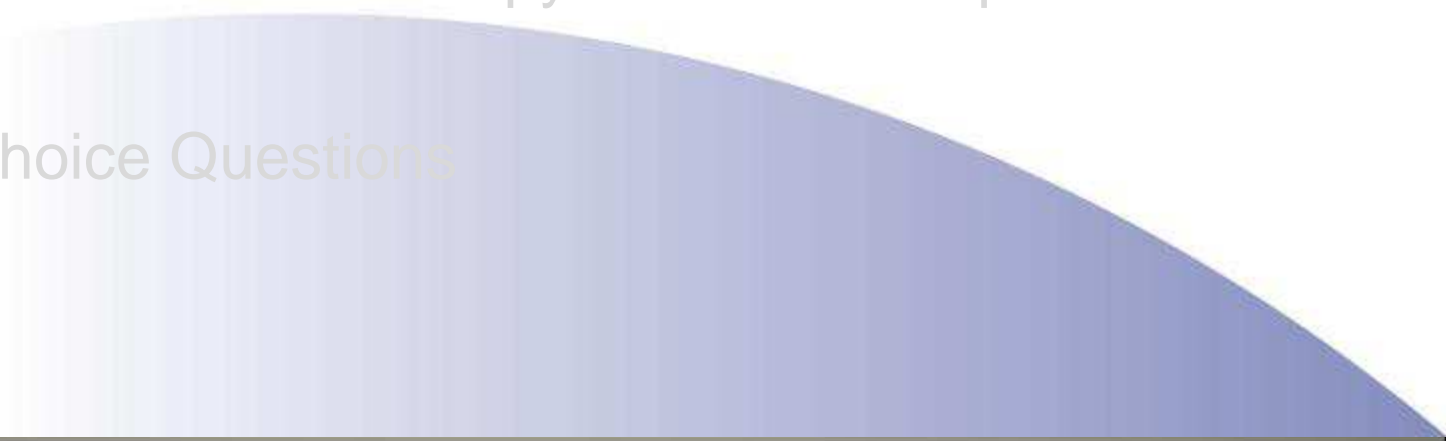
M2 differentiation of tumor macrophages



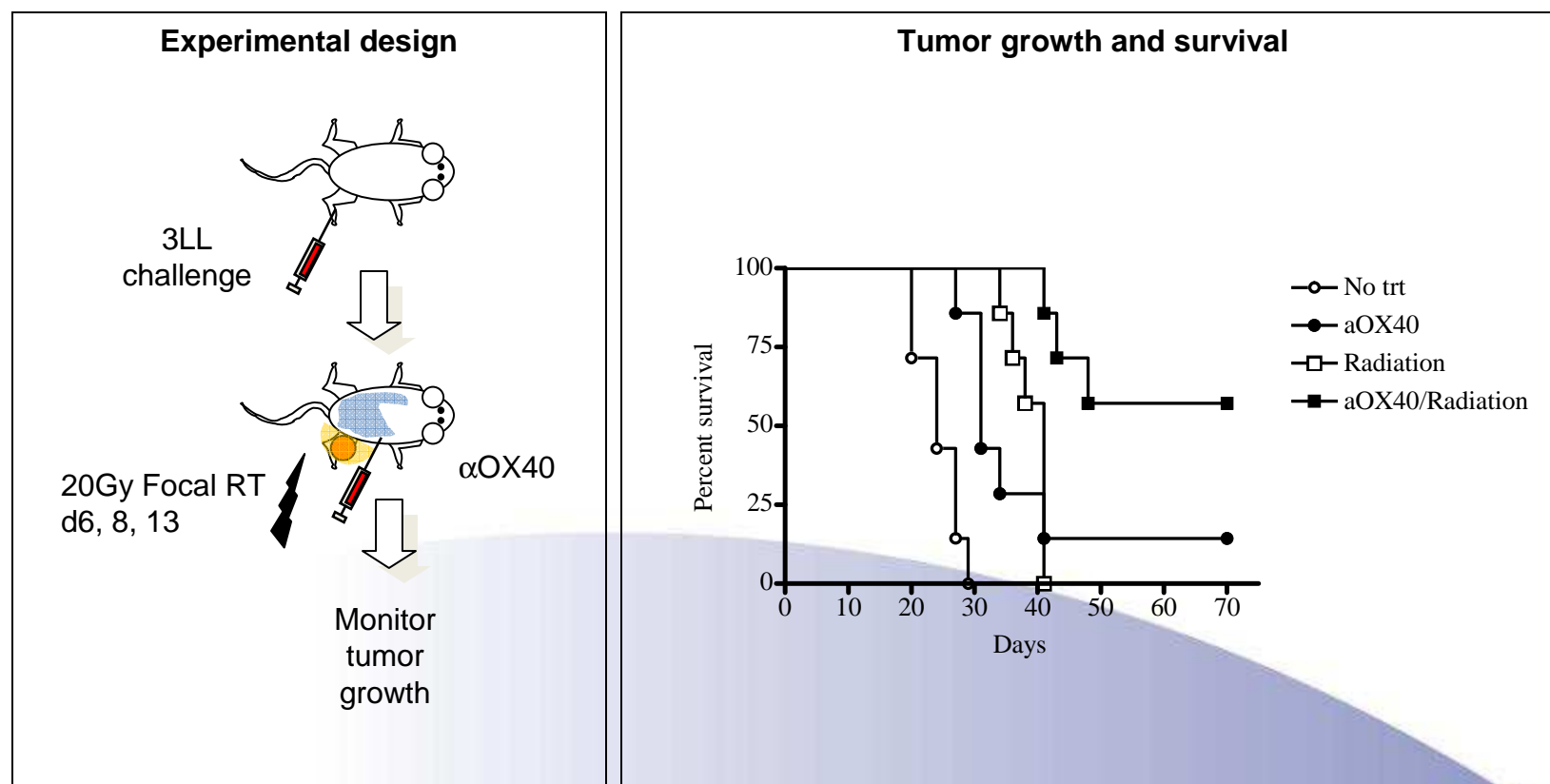
Immunotherapeutic window post-RT



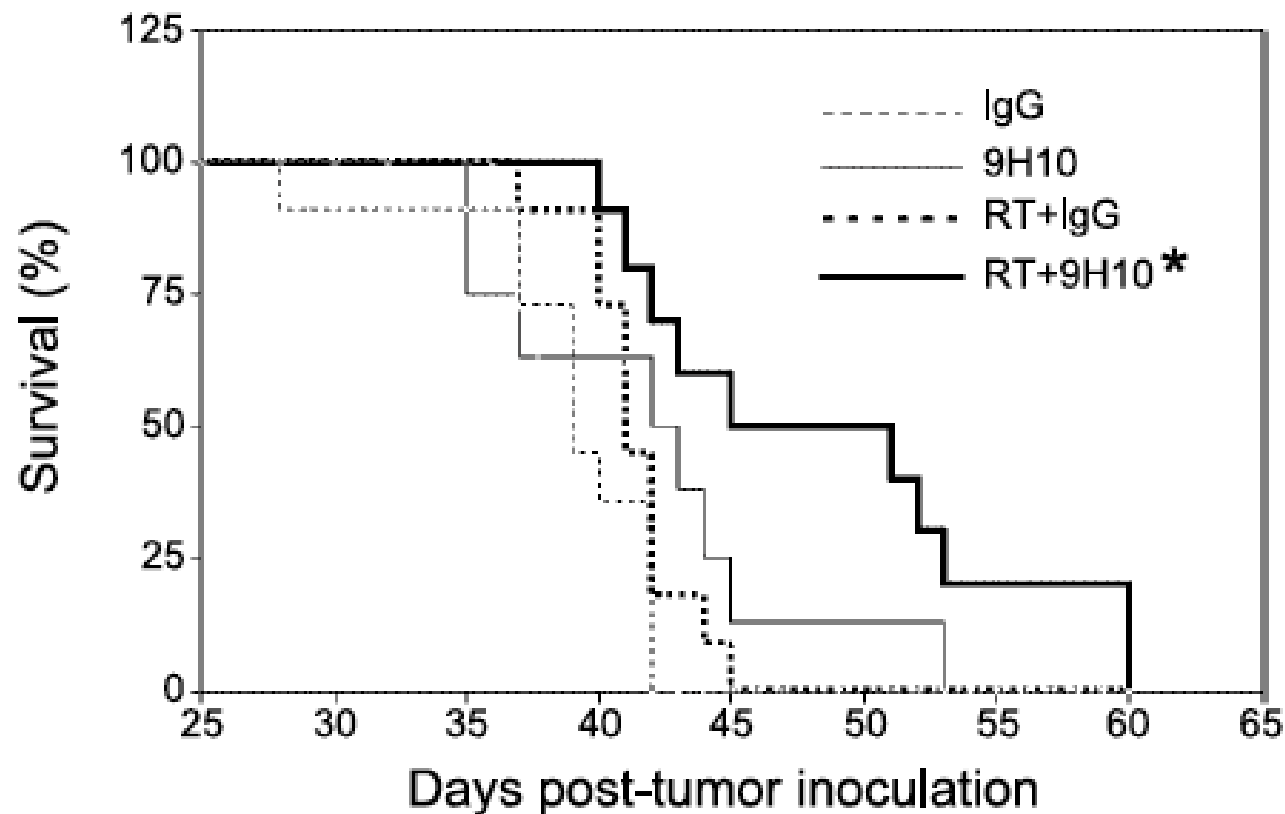
Presentation Outline

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- 

Hypofractionated RT plus anti-OX40 agonist antibody

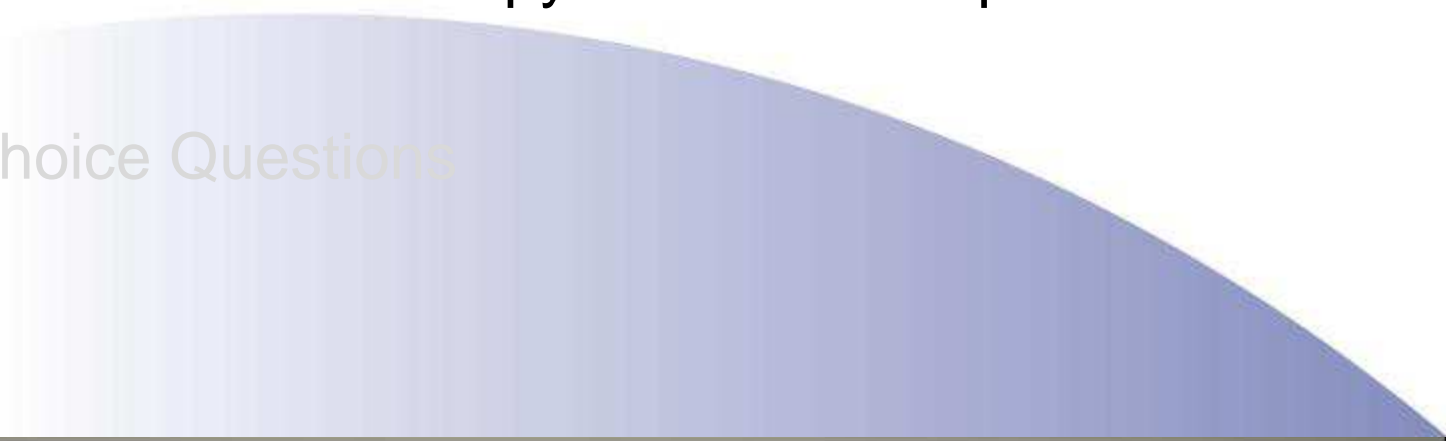


Hypofractionated RT plus anti-CTLA-4 antagonist antibody

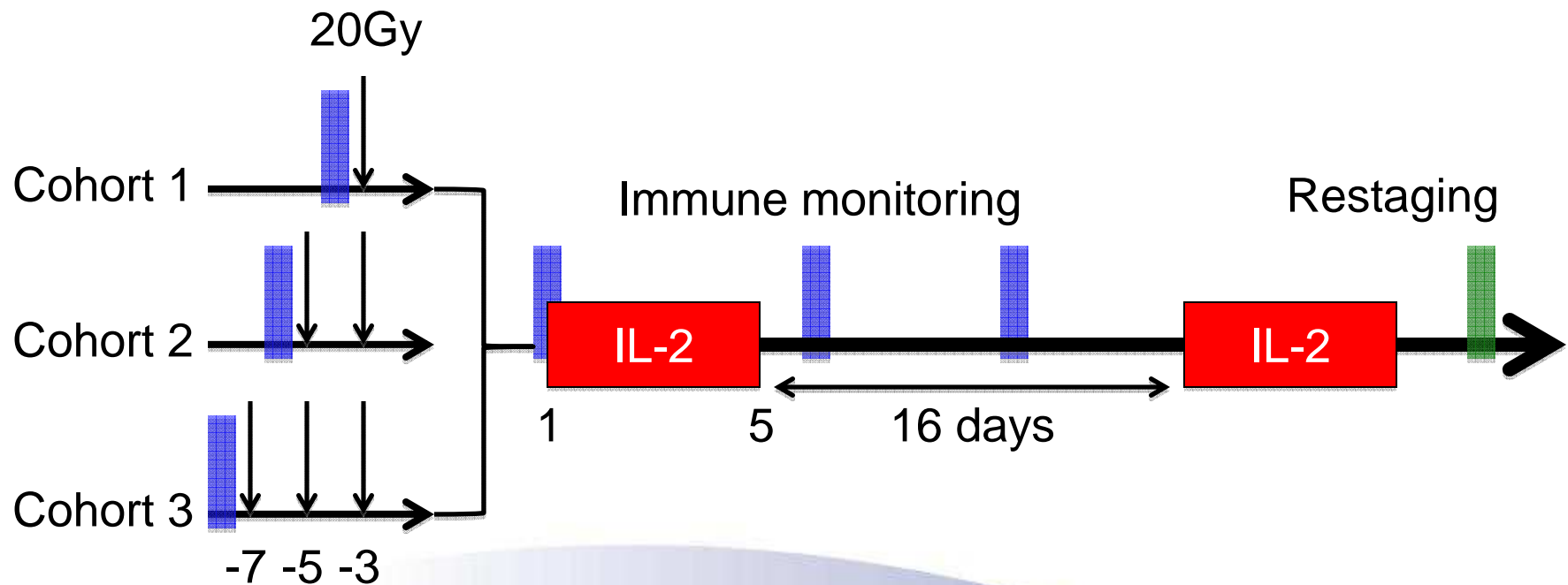


*Demaria et al Clin Cancer
Res January 15, 2005 11;
728*

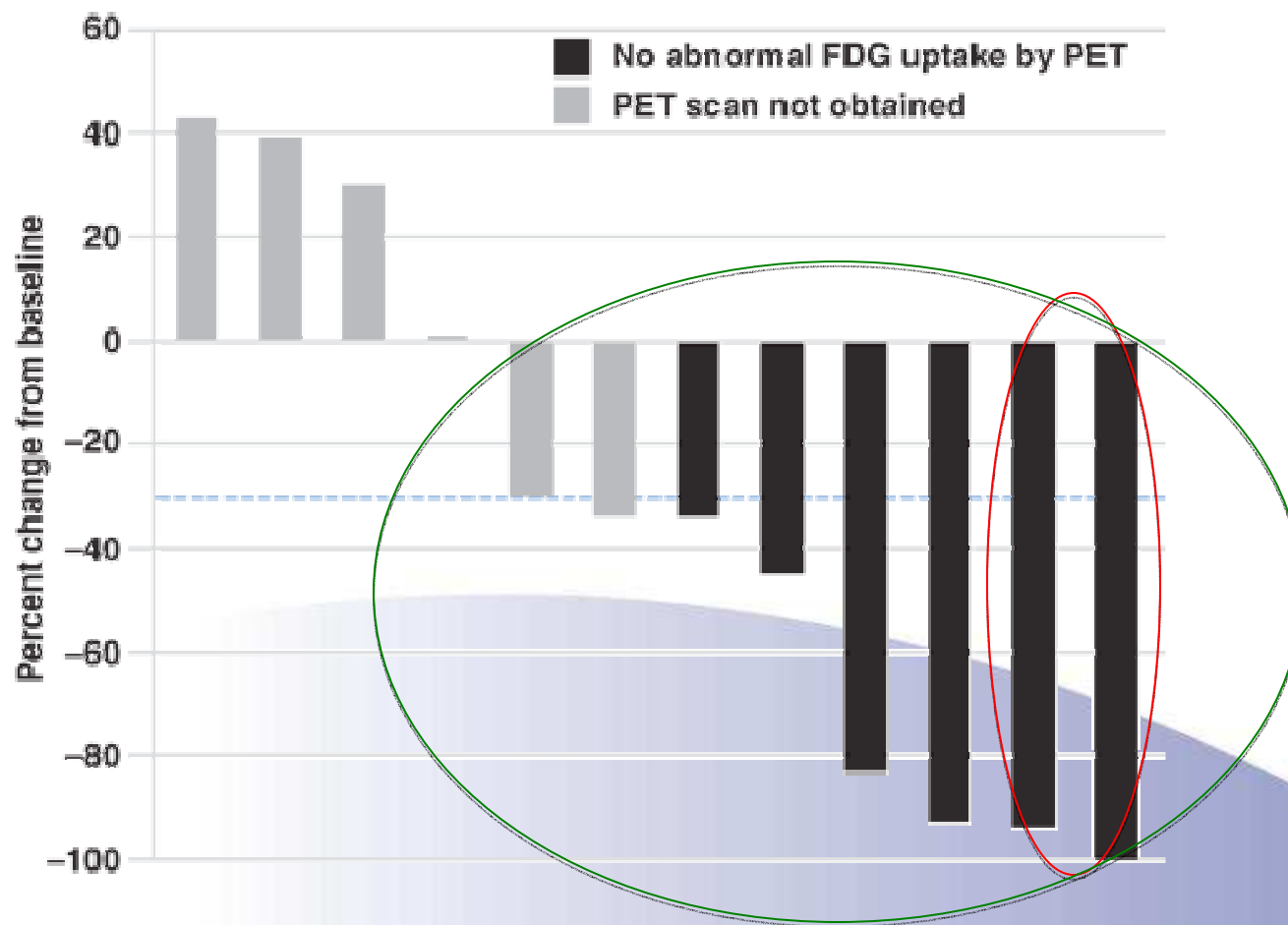
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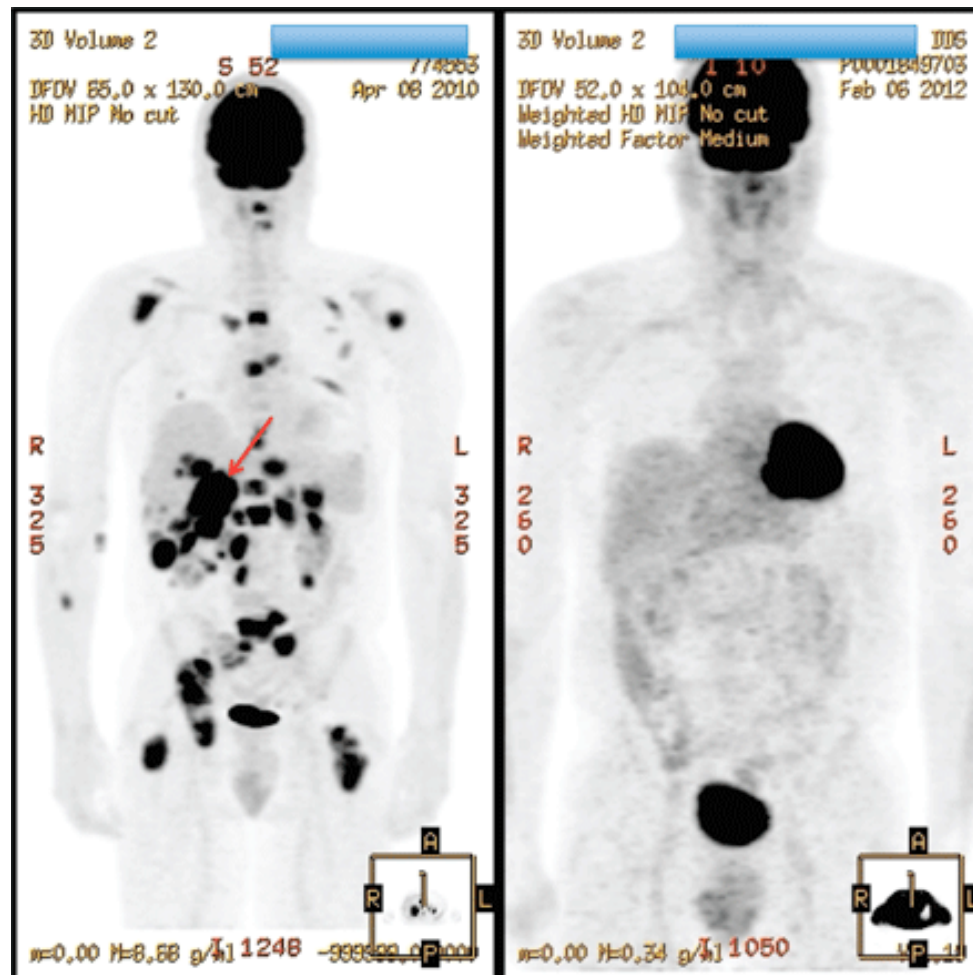
Protocol design



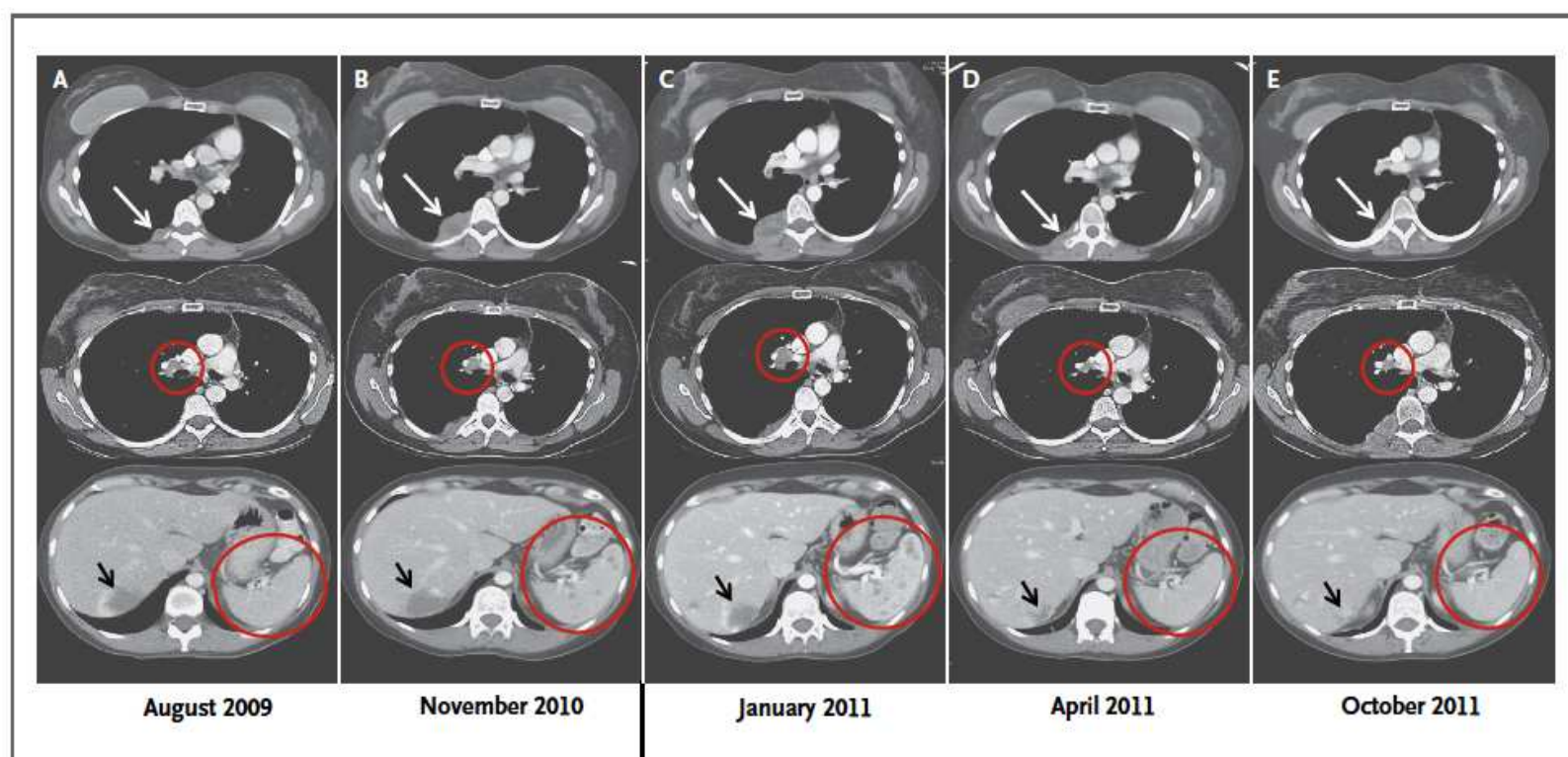
Response rates exceed historic rates with IL-2 alone



Radiation and high dose IL-2



Systemic response in patient treated with radiation and Ipilimumab



↑
Radiation 9.5Gy x 3

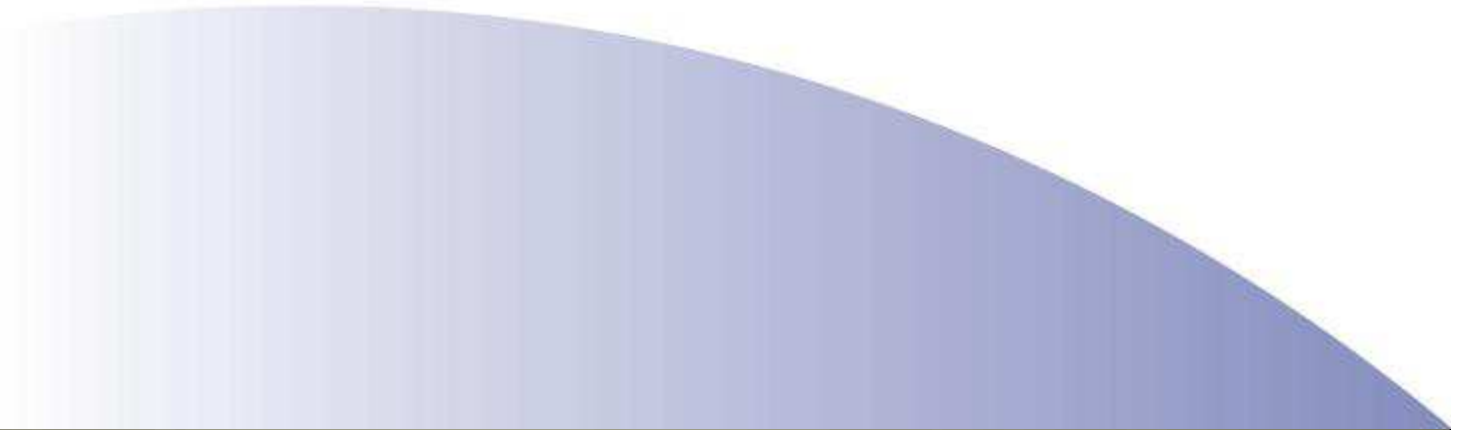
Postow et al N Engl J Med. 2012
Mar 8;366(10):925-31

Presentation Outline

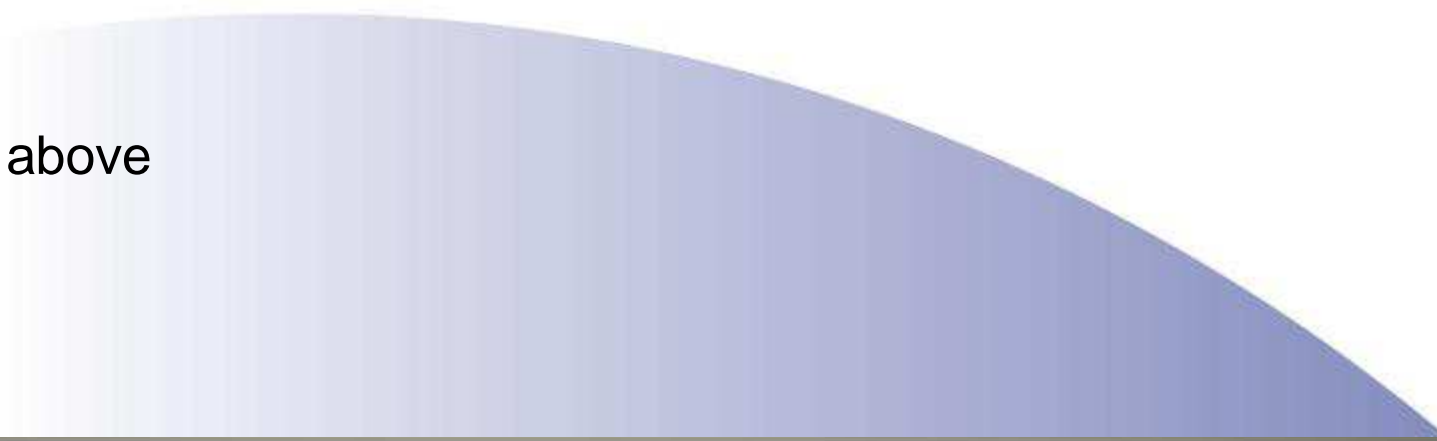
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- 

Question 1

- Hypofractionated radiation involves larger doses of radiation typically >5 Gy delivered in fewer fractions compared to standard radiation.
- A) True
- B) False



Question 2

- Which of the following are proposed mechanisms for radiation and immune system synergy?
 - A) Enhanced antigen release following radiation
 - B) Enhanced adjuvant release following radiation
 - C) Enhanced cytokine and chemokine release following radiation
 - D) All of the above
- 

Question 3

- Which of the following are proposed mechanisms for radiation and immune system synergy?
 - A) Tumor cells
 - B) Lymphocytes
 - C) Endothelial cells
 - D) All of the above – depends on dose
- 