Radiation Therapy And Immunotherapy

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Disclosures

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- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
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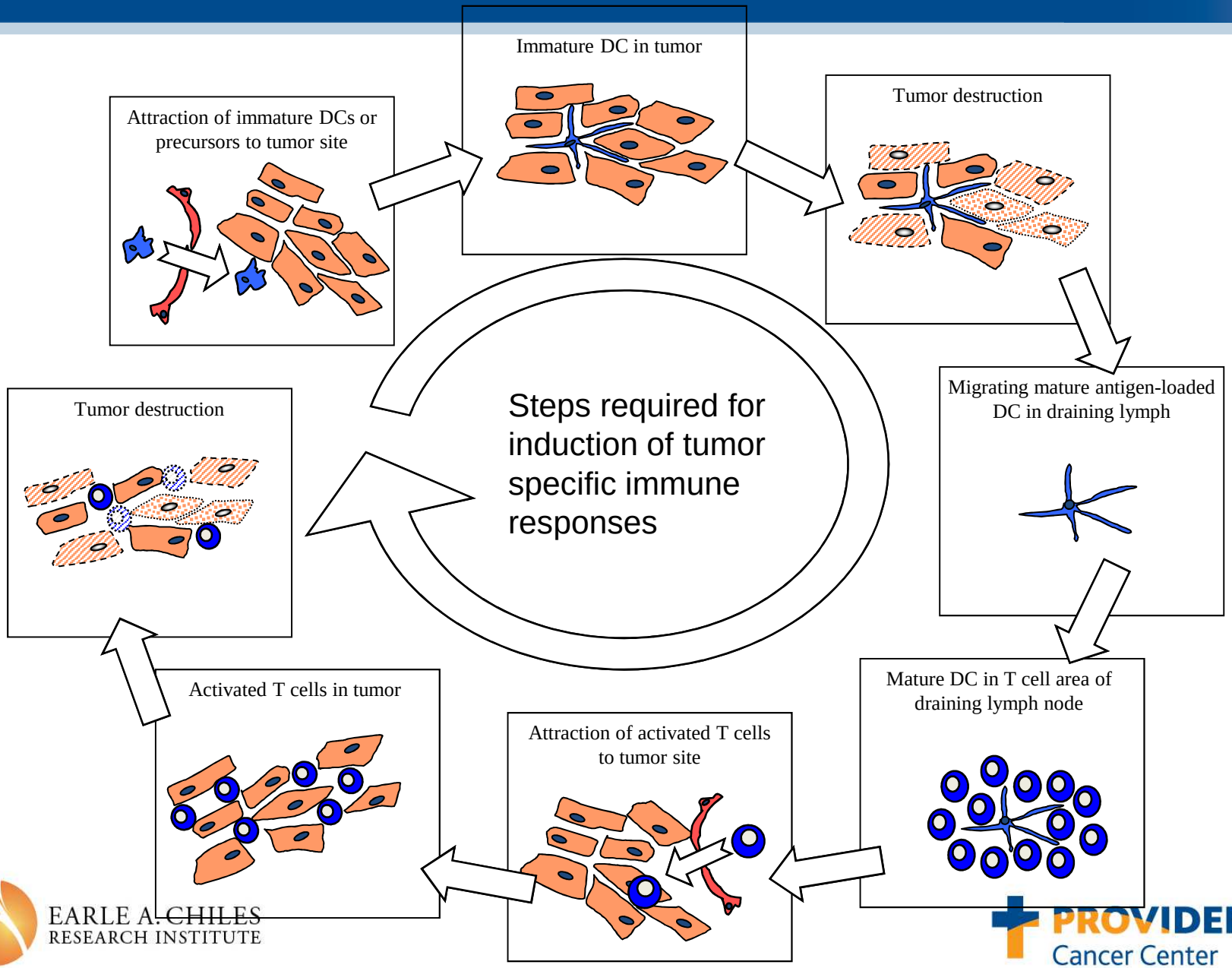
- Speakers Bureau: Prometheus



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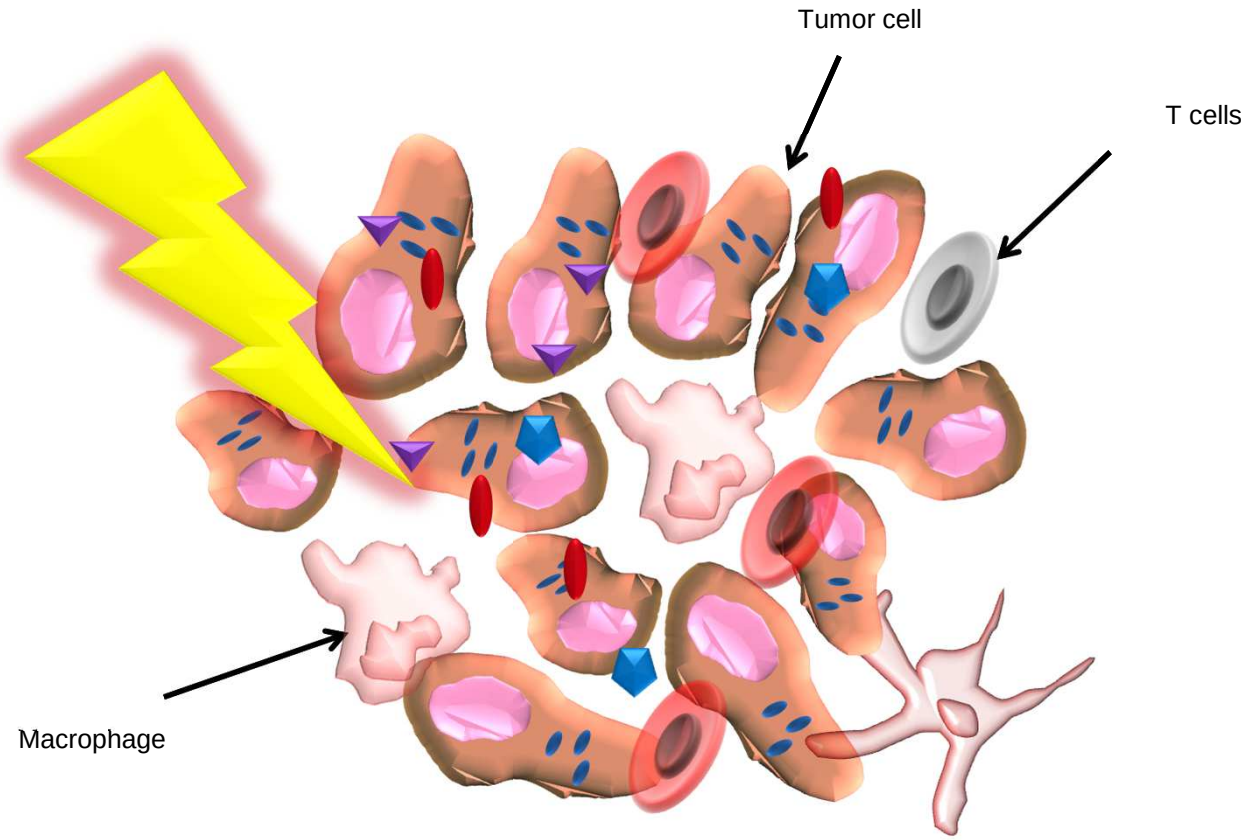
Rationale for Radiation and Immunotherapy



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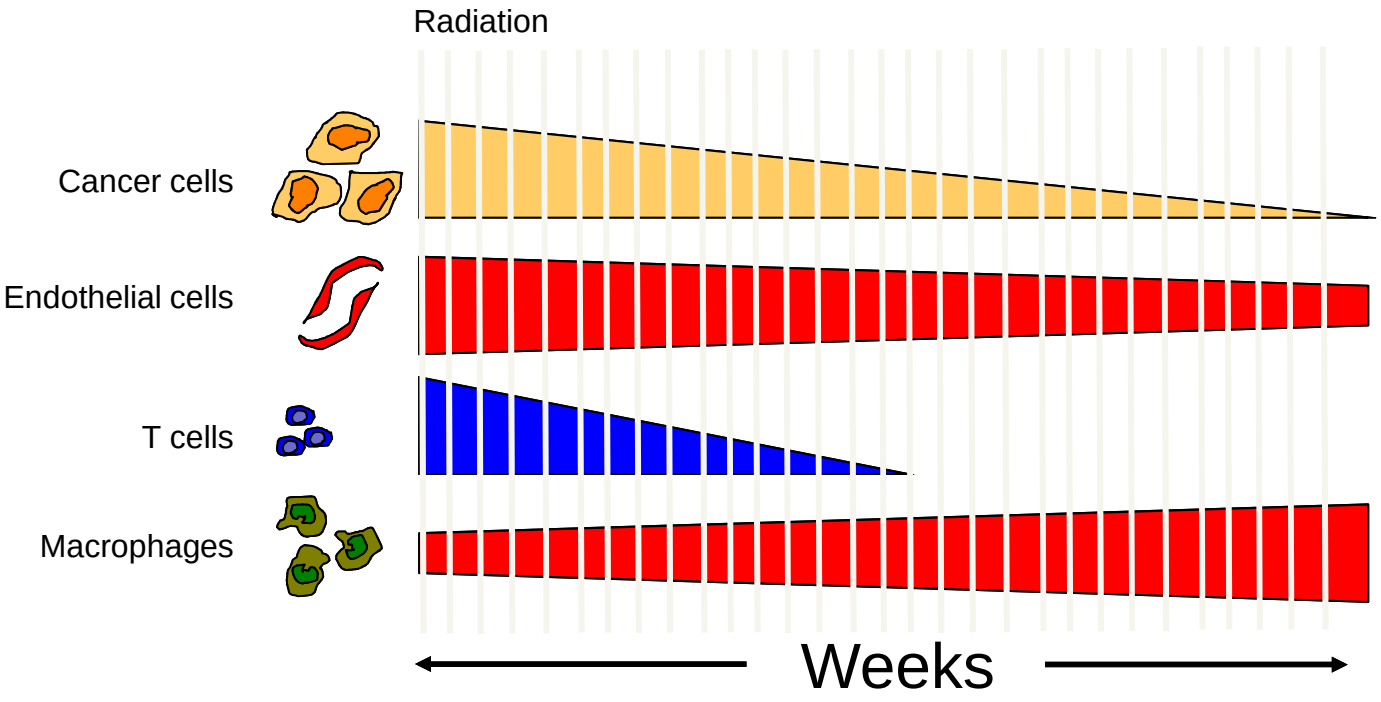
Is standard fractionation or hypofractionated more immunogenic?

Radiation 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

Conventional fractionation



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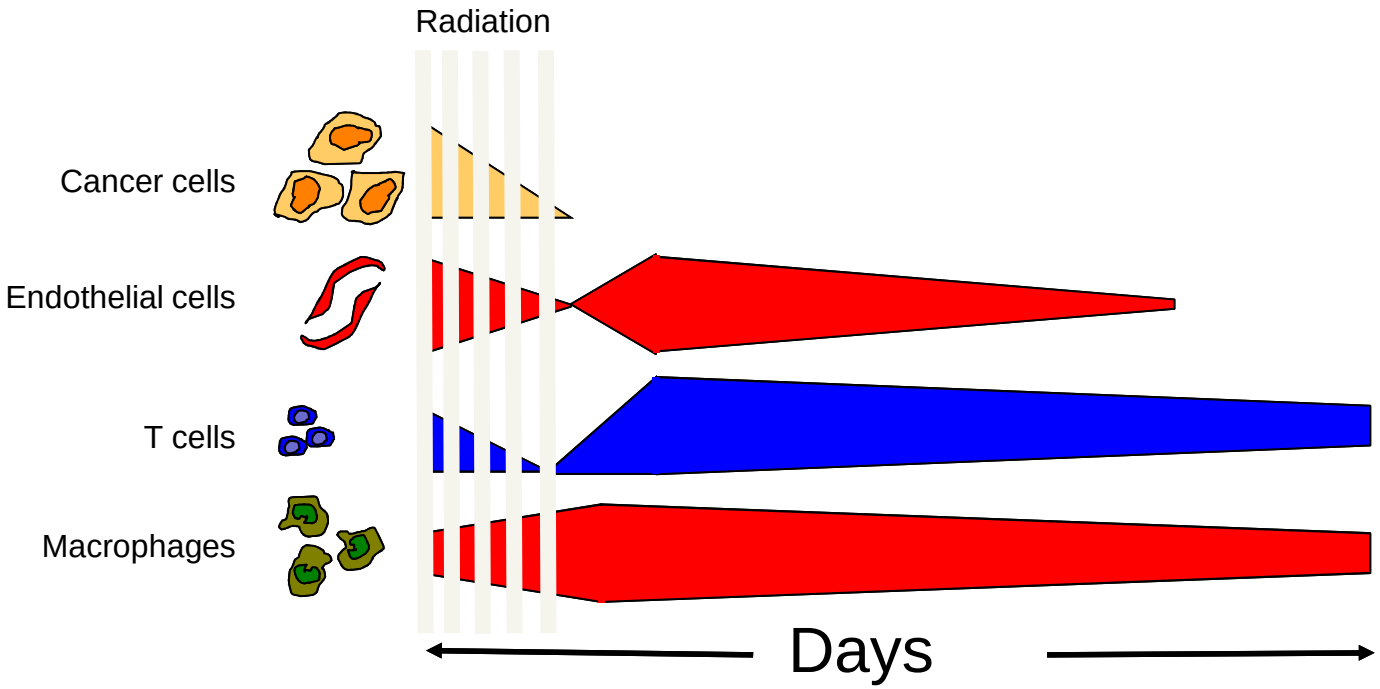
Hypofractionation



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Proposed Mechanisms of Synergy Between Radiation and Immunotherapy

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

RESEARCH ARTICLE

TUMOR RADIOTHERAPY

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

Steven K. Seung,[1,2]* Brendan D. Curti,[1,3]*† Marka Crittenden,[1,2] Edwin Walker,[1] Todd Coffey,[3] Janet C. Siebert,[4] William Miller,[1] Roxanne Payne,[3] Lyn Glenn,[3] Alexandru Bageac,[5] Walter J. Urba[1,3]

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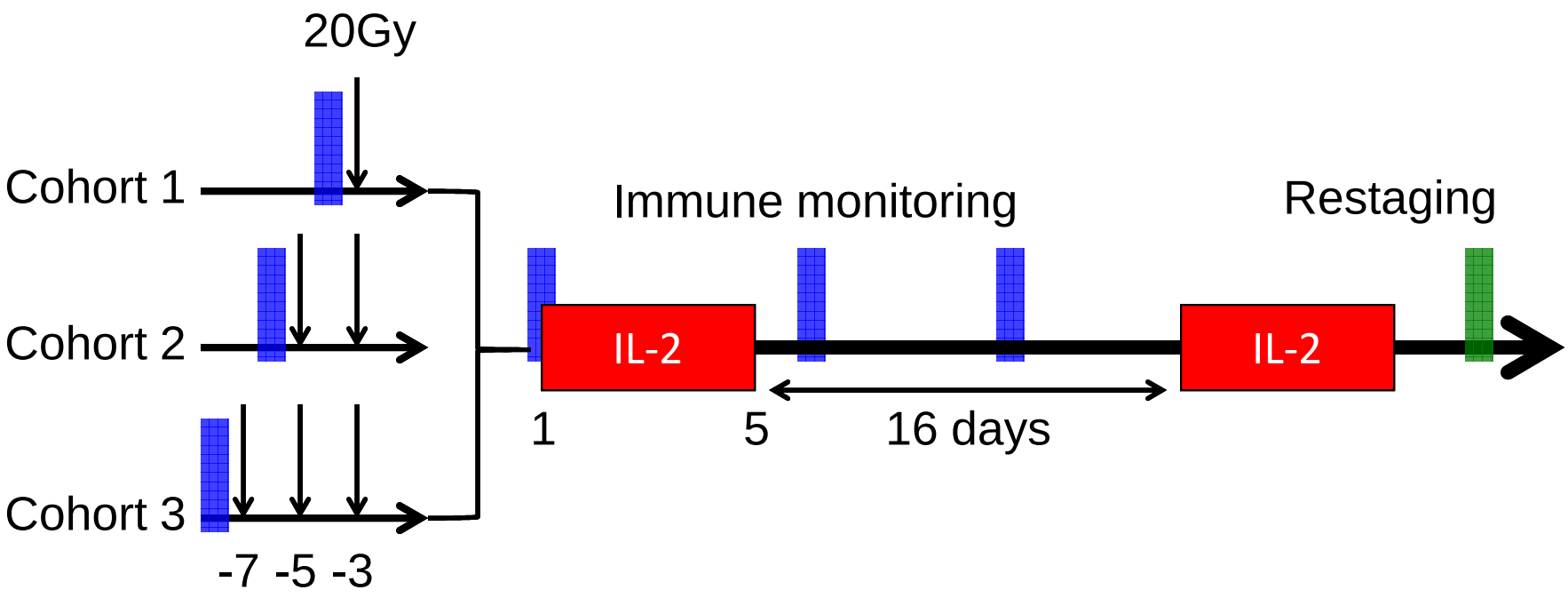
Protocol Design



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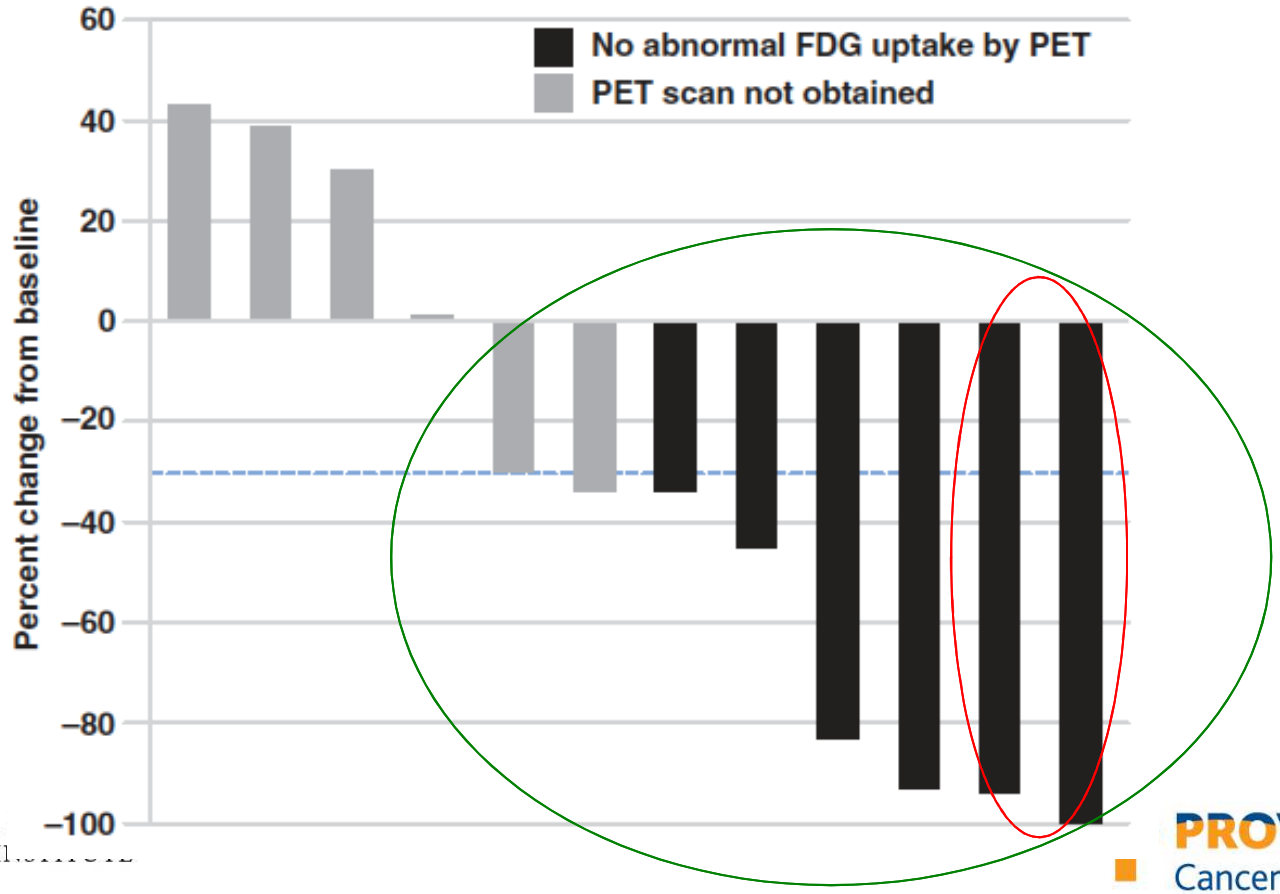
Response rates exceed historic rates with IL-2 alone



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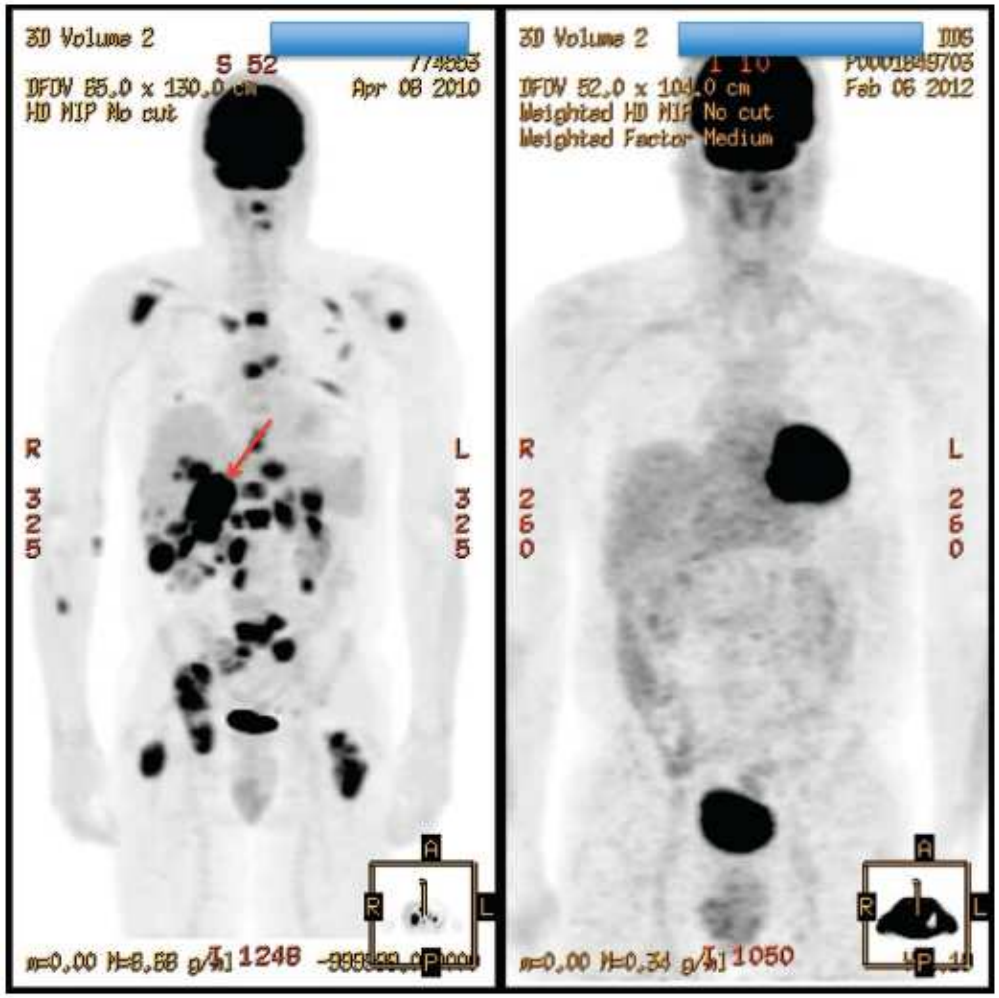
Melanoma Patient Anecdotes



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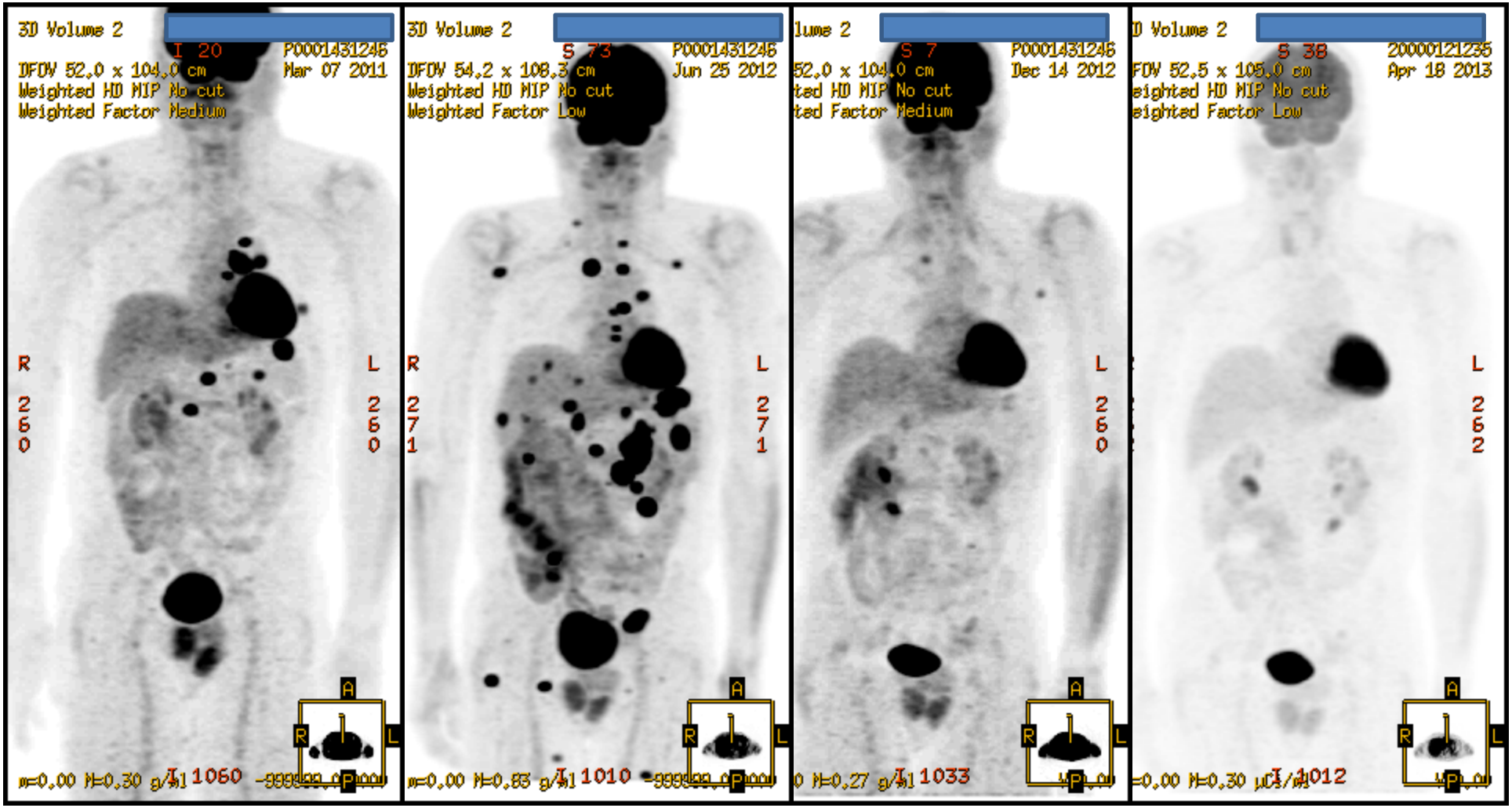
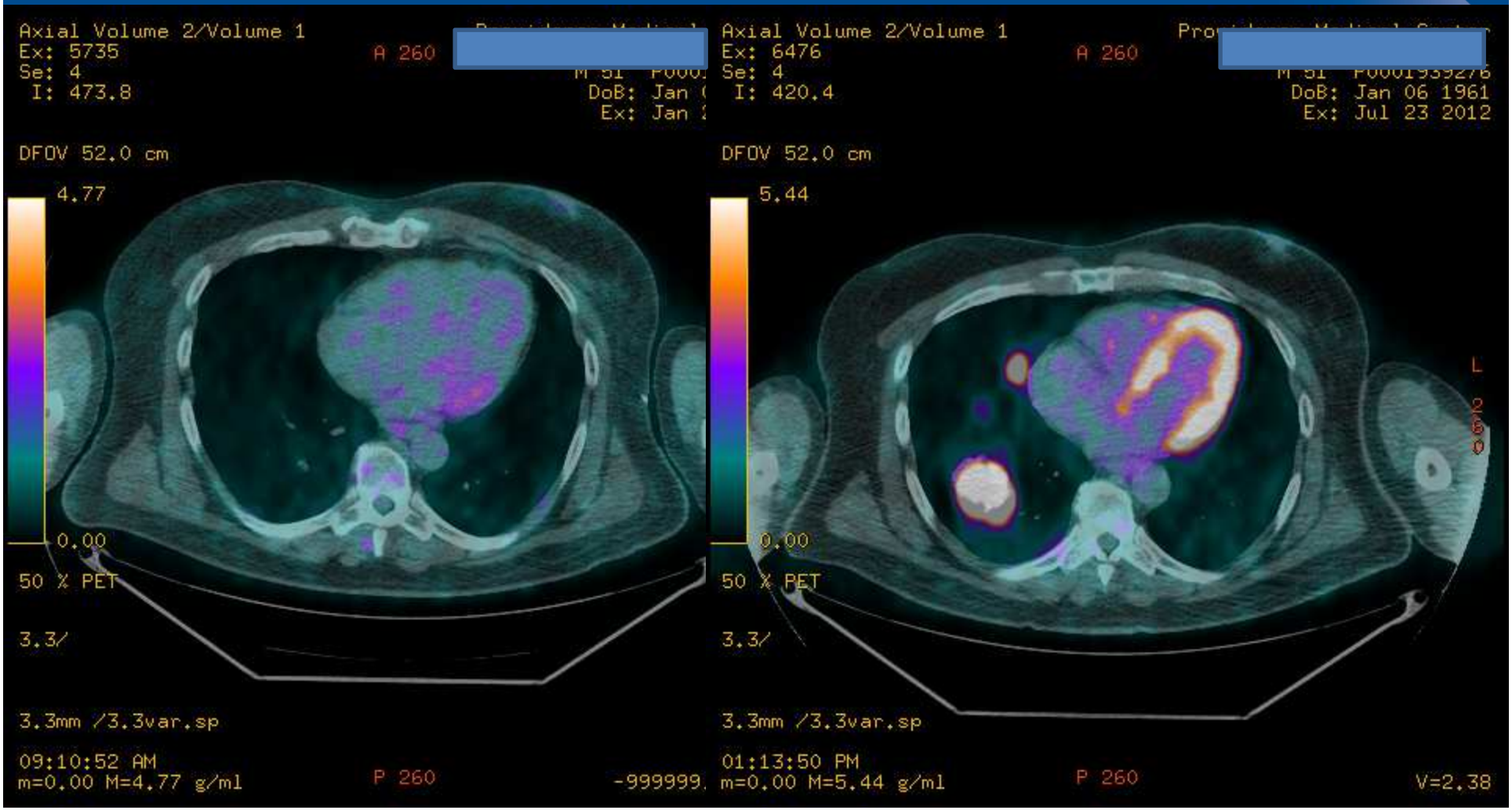


3/7/2011
Pre-Vemurafenib

6/25/2012
Post-Vem and Pre-IL-2

12/14/2012
After SBRT + IL-2 Cycle 4

4/18/2013
After SBRT + IL-2 Cycle 6



1/24/2012
Pre-IL2

7/23/2012
After Cycle 2 IL-2

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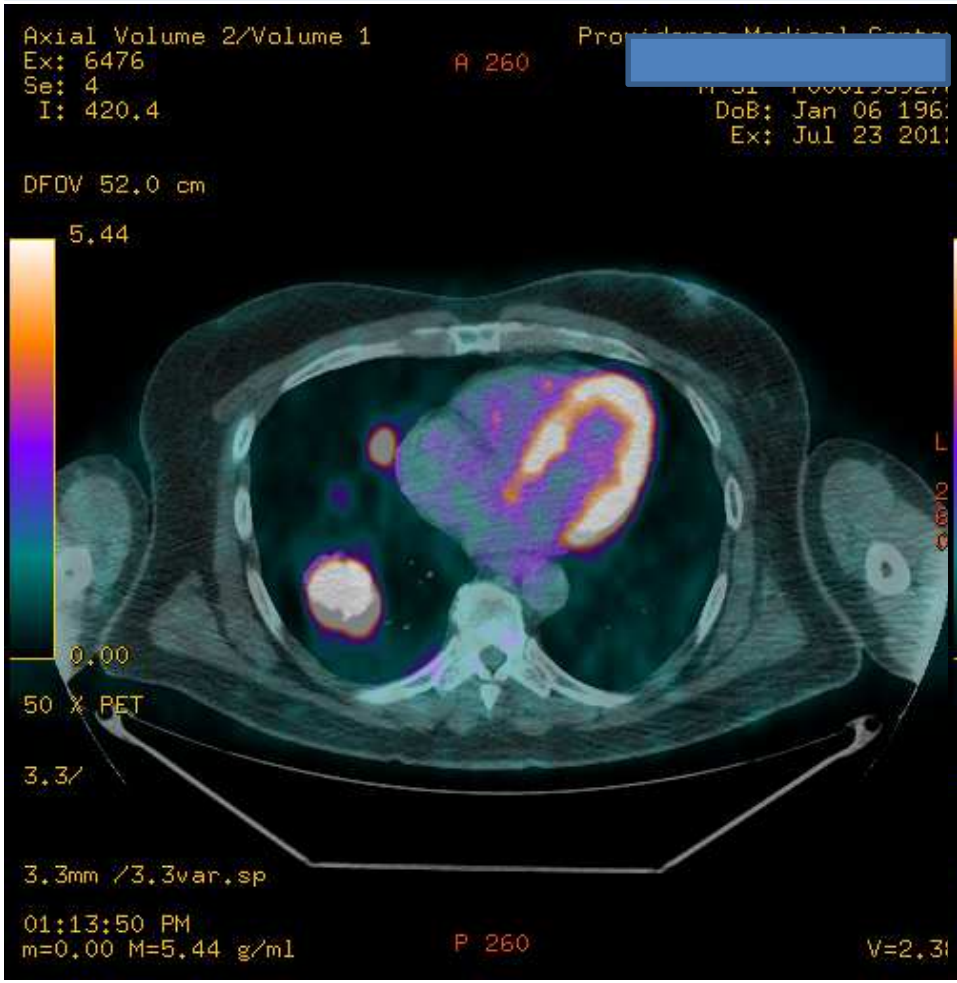
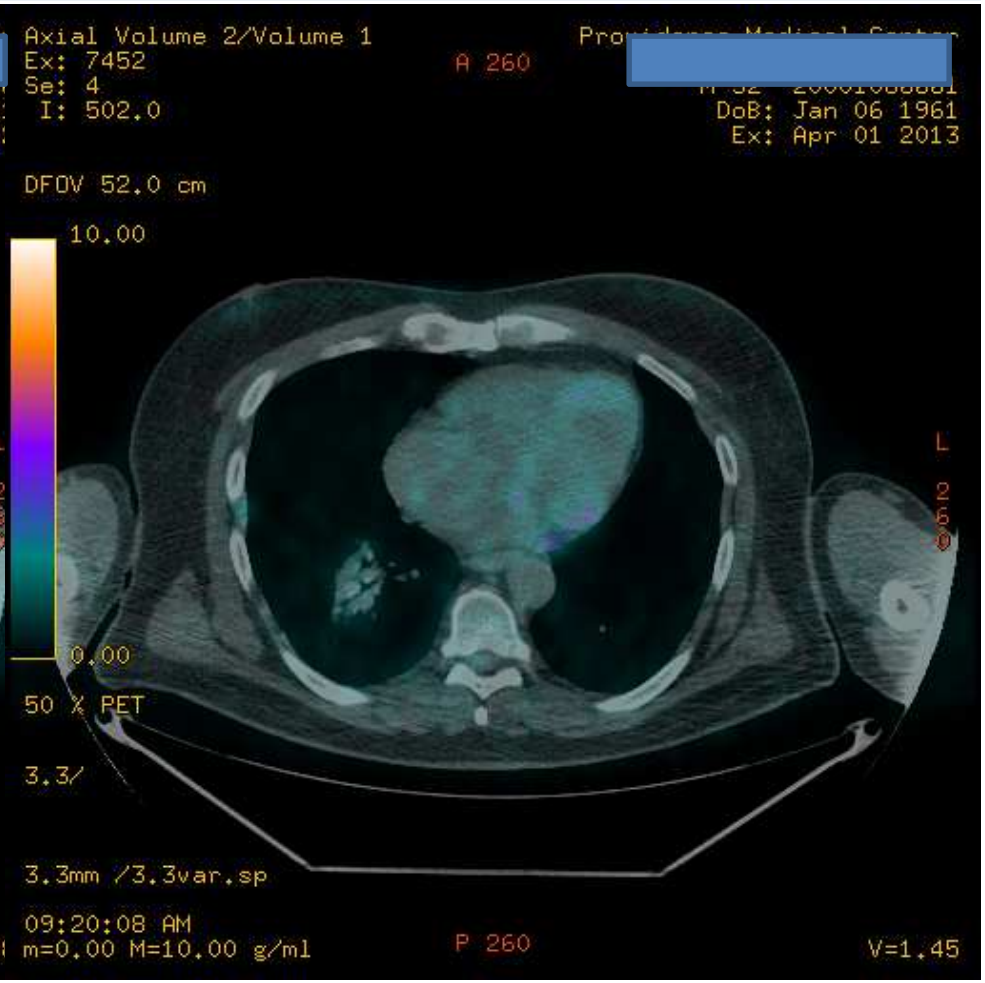


7/23/2012
After Cycle 2 IL-2



4/1/2013
After SBRT + IL-2

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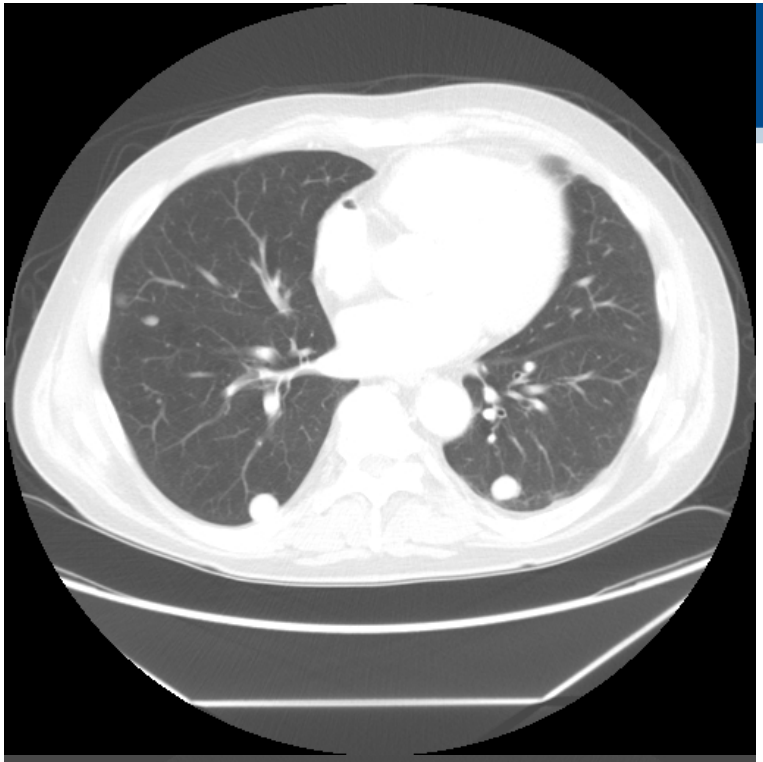
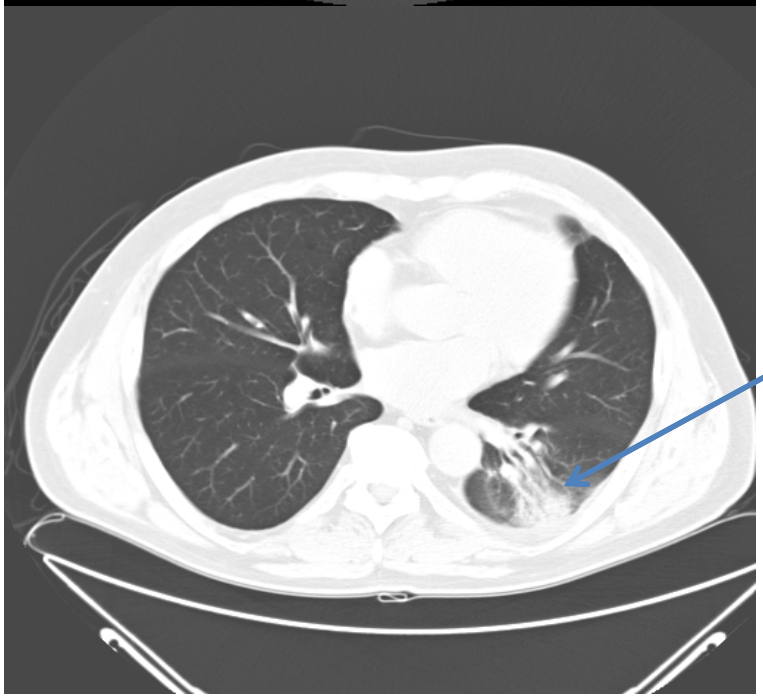
RCC Anecdotes

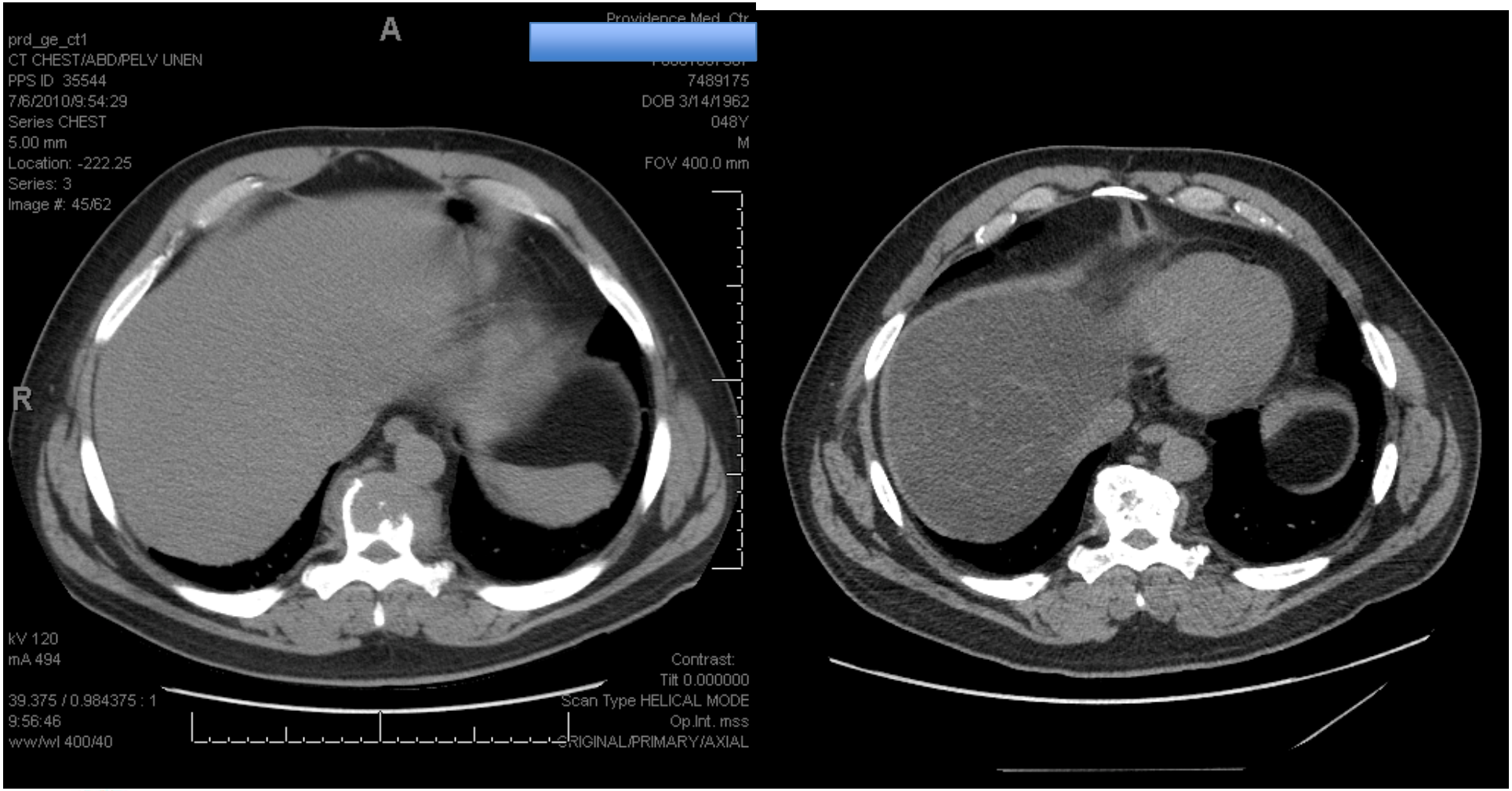


Before



Lesion tx'd with SBRT

After



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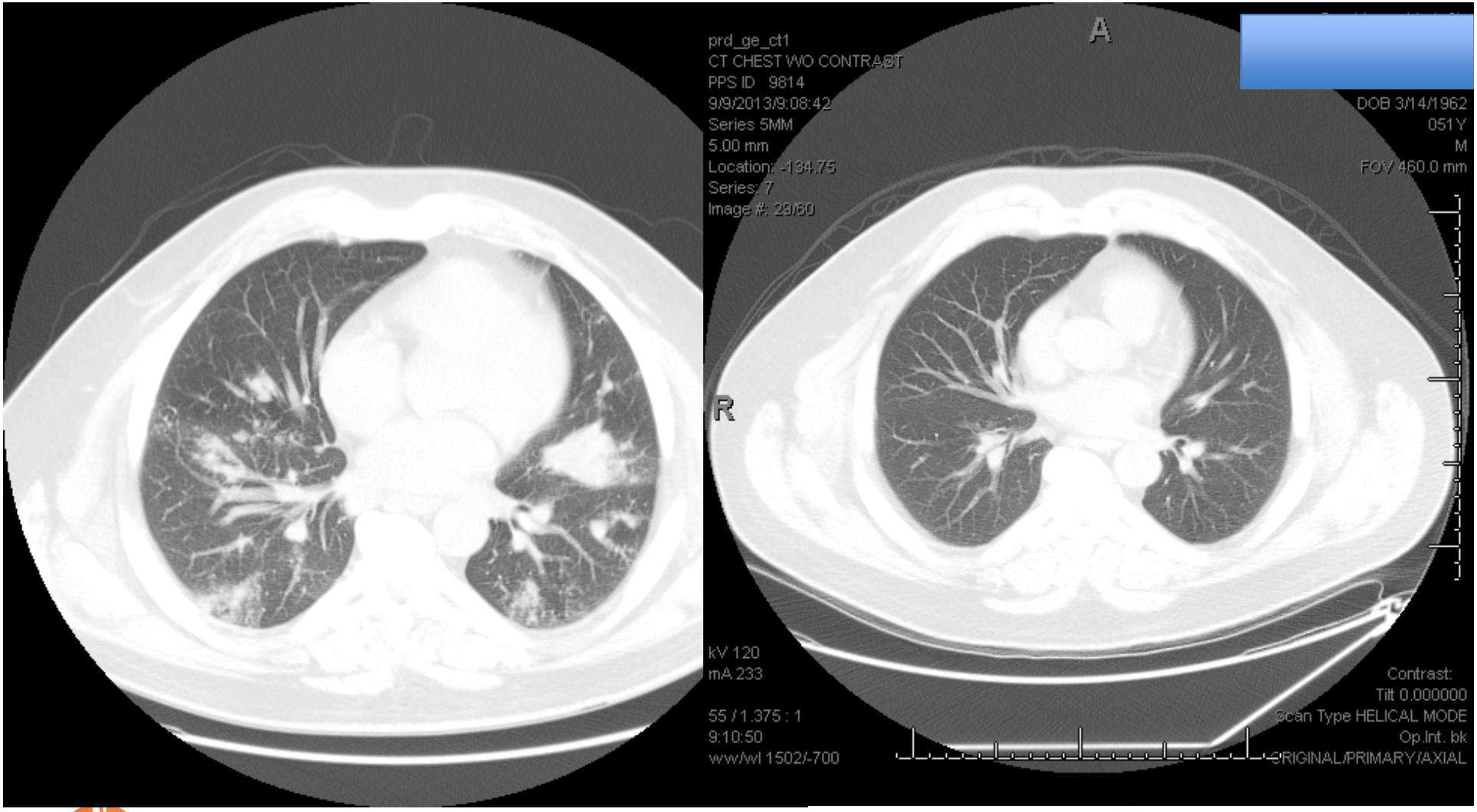

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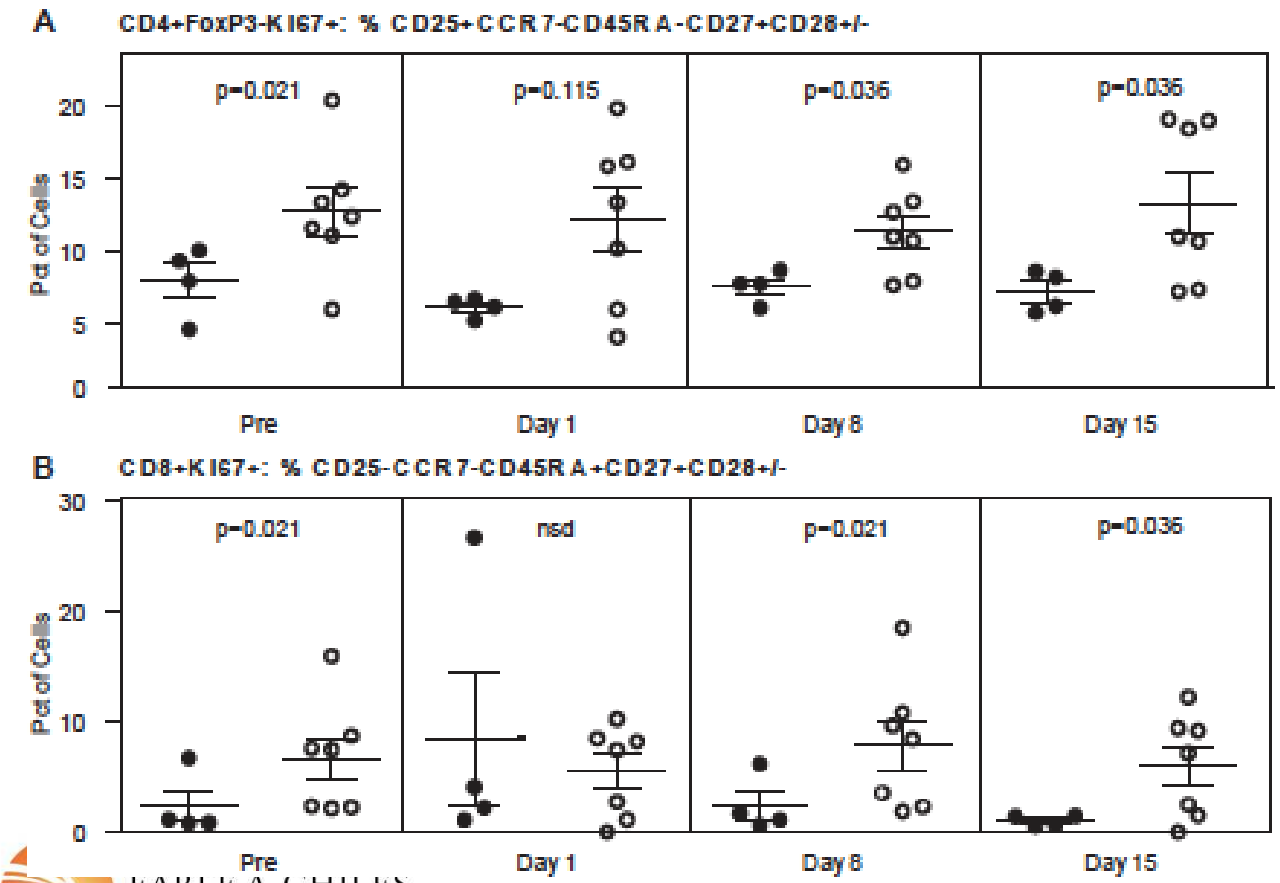
Immune Parameters Associated With Response



Responders-open circle

Progressors-closed circle

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Phase II Study of SBRT + IL-2 in Patients With Metastatic Melanoma

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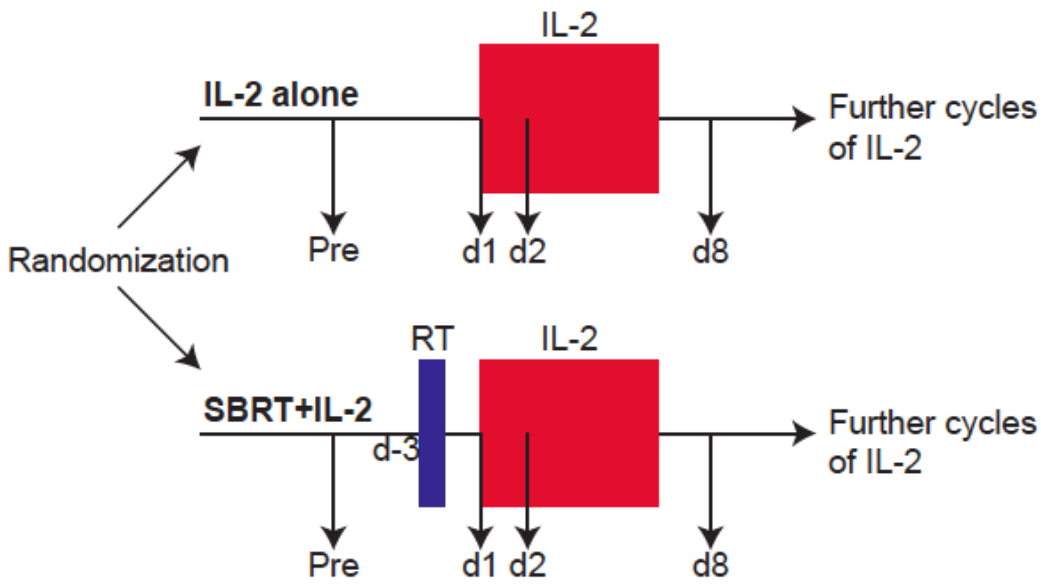
Phase II Clinical Trial Design



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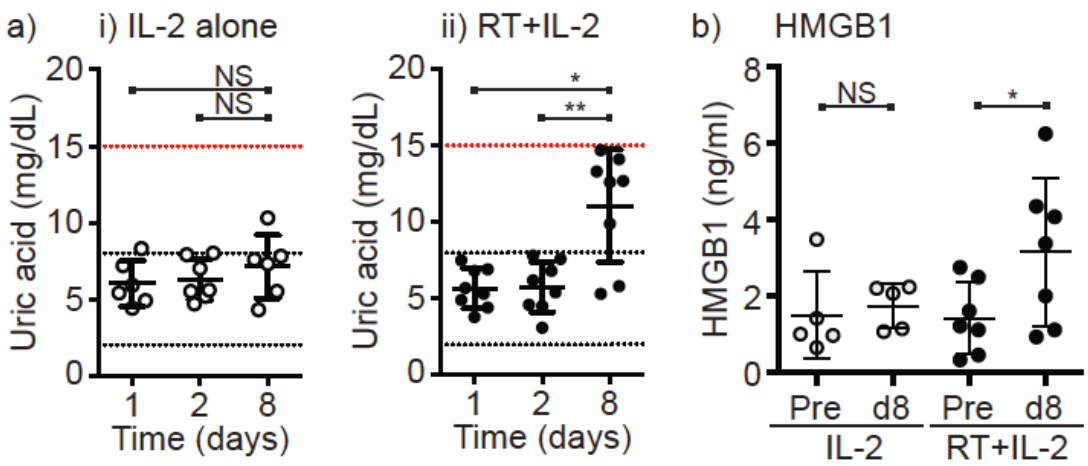
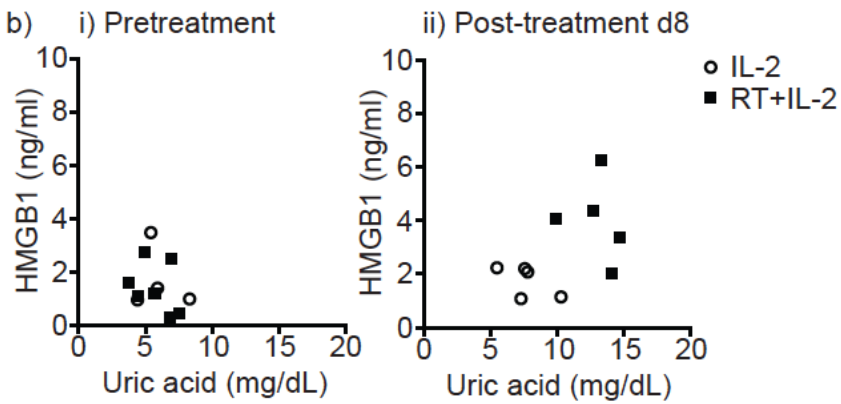
Phase II SBRT IL-2

- Characterize serum parameters including DAMPS, cytokines and chemokines in patients receiving RT+IL-2 versus IL-2 alone.
- Characterize changes in circulating immune cells in patients receiving RT+IL-2 versus IL-2 alone.

DAMP Increase With SBRT and IL-2





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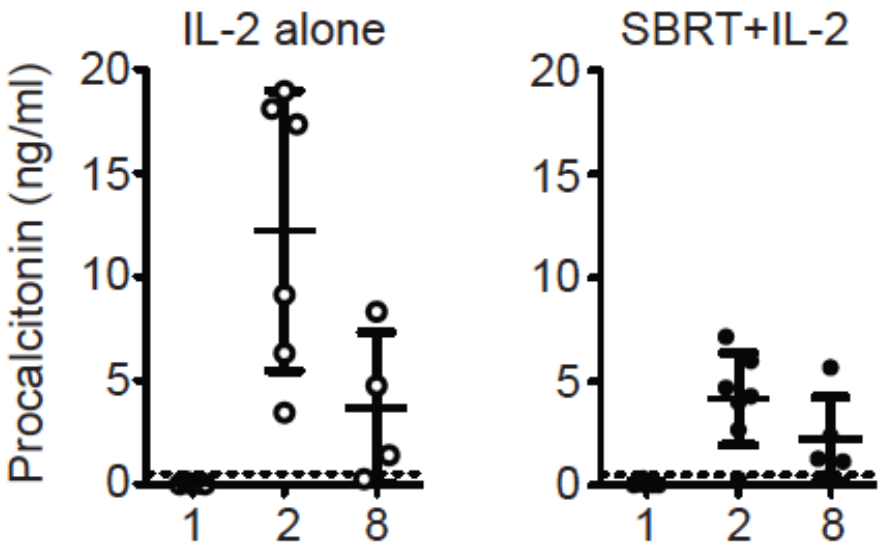
Procalcitonin Attenuated With SBRT + IL-2



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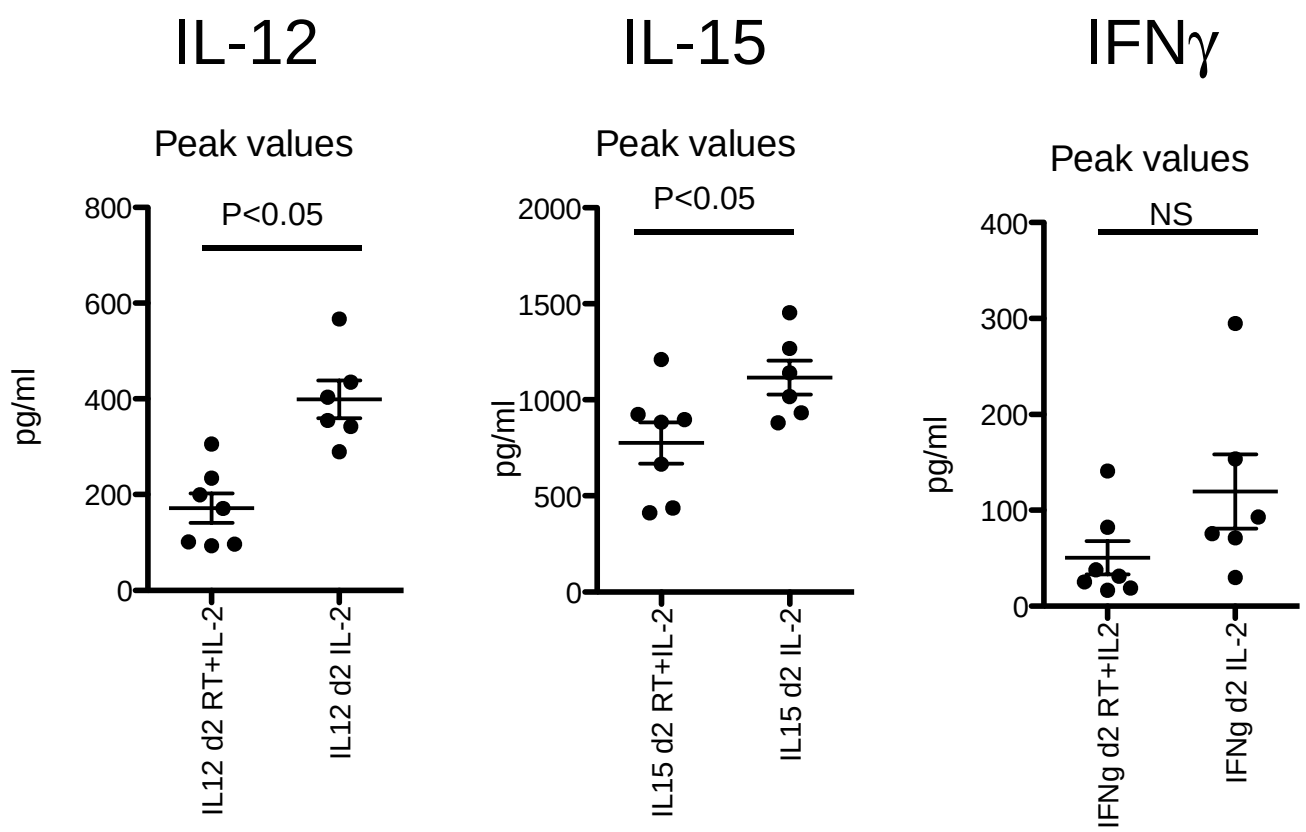
Decreased Inflammatory Cytokine Levels in Irradiated Patients



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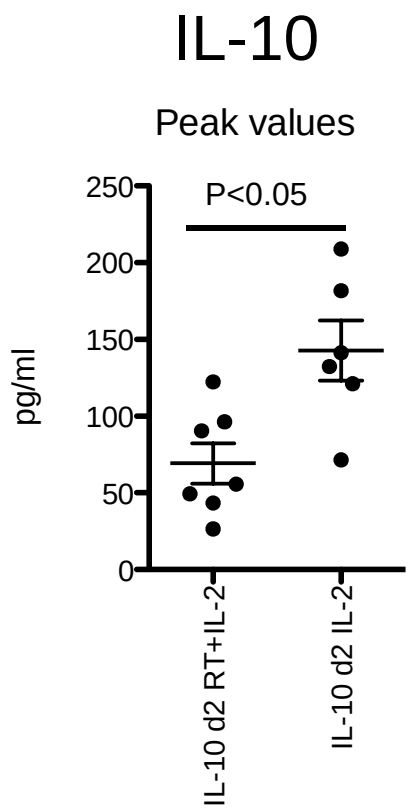
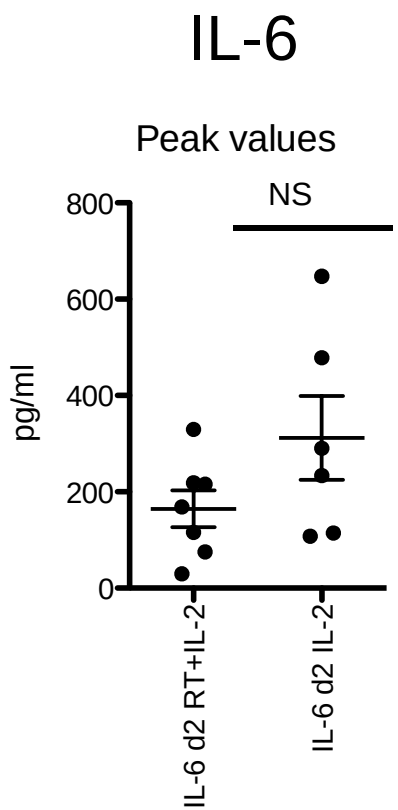
Decreased Anti-Inflammatory Cytokine Levels in Patients Treated With Radiation





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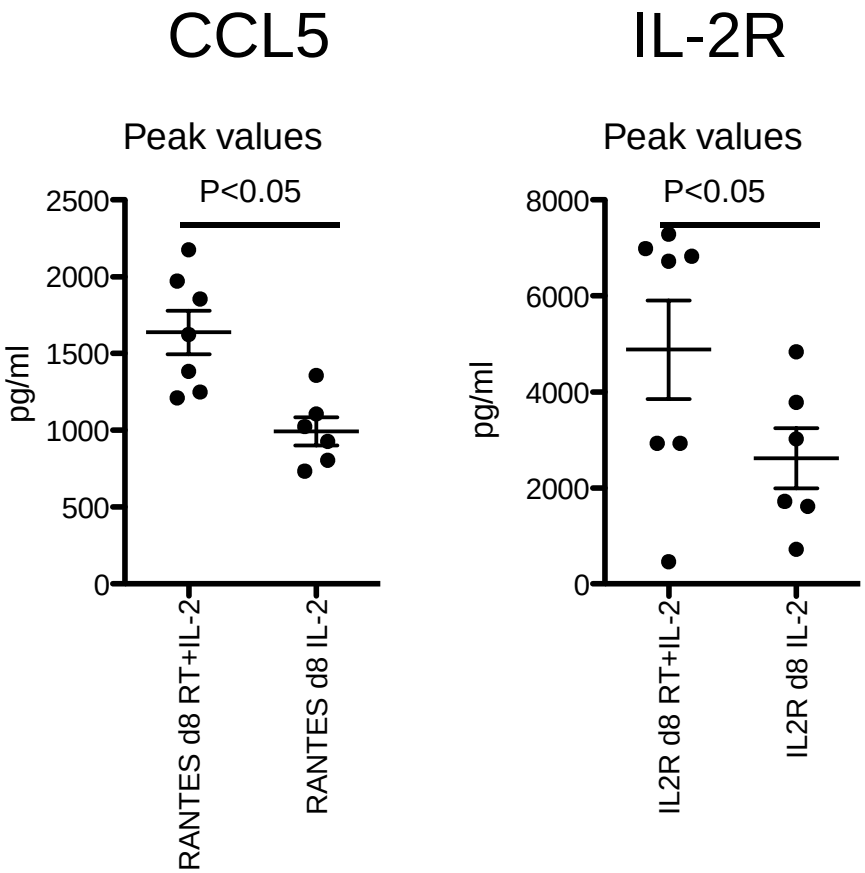
Elevated Levels of Secreted Markers From Activated T Cells in Patients Receiving RT



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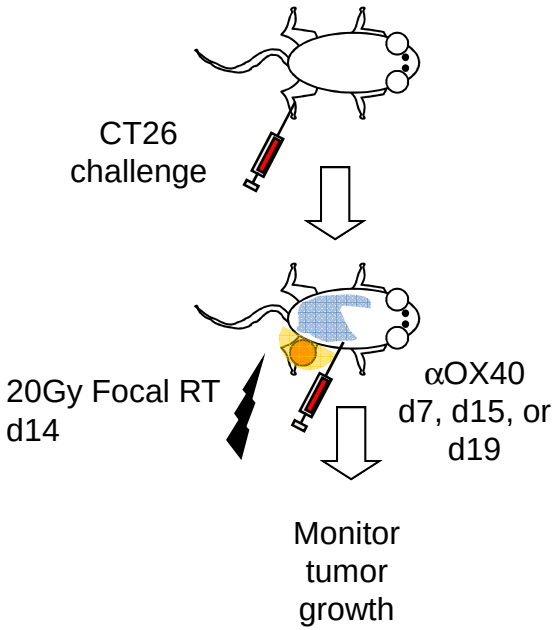
Cytokines, Chemokines and DAMPS

- RT + IL-2 patients showed increased circulating DAMPS compared to IL-2 monotherapy on Day 8.
- RT + IL-2 patients had decreased circulating levels of pro-inflammatory cytokines (IL-12, IL-15) compared to IL-2 monotherapy on day 2.
- RT + IL-2 patients also had decreased levels of anti-inflammatory cytokines (IL-10, IL-6) in the peripheral blood on day 2.

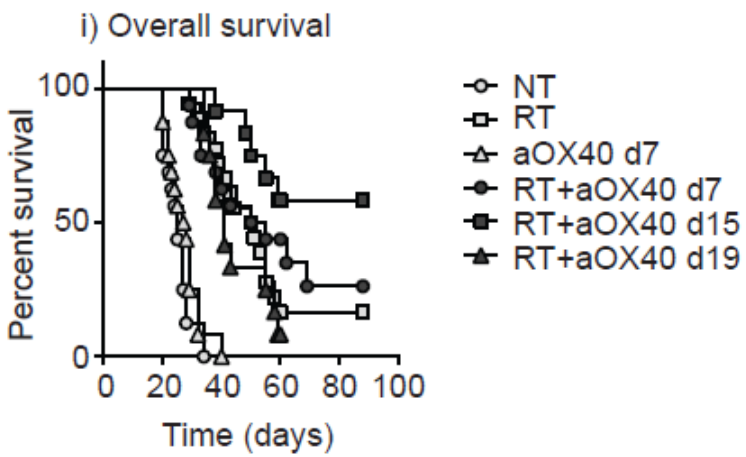
Does radiation enhance other immunomodulators?

Hypofractionated RT Plus Anti-OX40 Agonist Antibody in CT 26

Experimental design



Tumor growth and survival



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Radiation and Ipilimumab

- Wolchok et al. reported on a patient who was progressing on maintenance ipi and was then treated with 2850 cGy in 3 doses over 7 days. One additional Ipi dose was given.
- Abscopal effect noted in non-treated lesions
- Immunological changes after radiation:
  - Increased titers of antibodies against NY-ESO-1
  - Increased CD4+ ICOS+ T cells
  - Increased interferon-gamma production by NY-ESO-1-specific CD4+ T cells (but not CD8s)

Some Questions for Further Study

- What is the mechanism?
  - Is the peripheral blood indicative of events in the tumor?
- Does timing matter as much in humans as in the murine models?
- What happens to the radiated site over time? Is that important to the immune response?
- Is RT + X (where X = IL-2 or Ipi or . . .) more effective than X alone?
- Can RT after X convert non-responders to responders?

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