Targeting mesothelioma with radiation and immunotherapy

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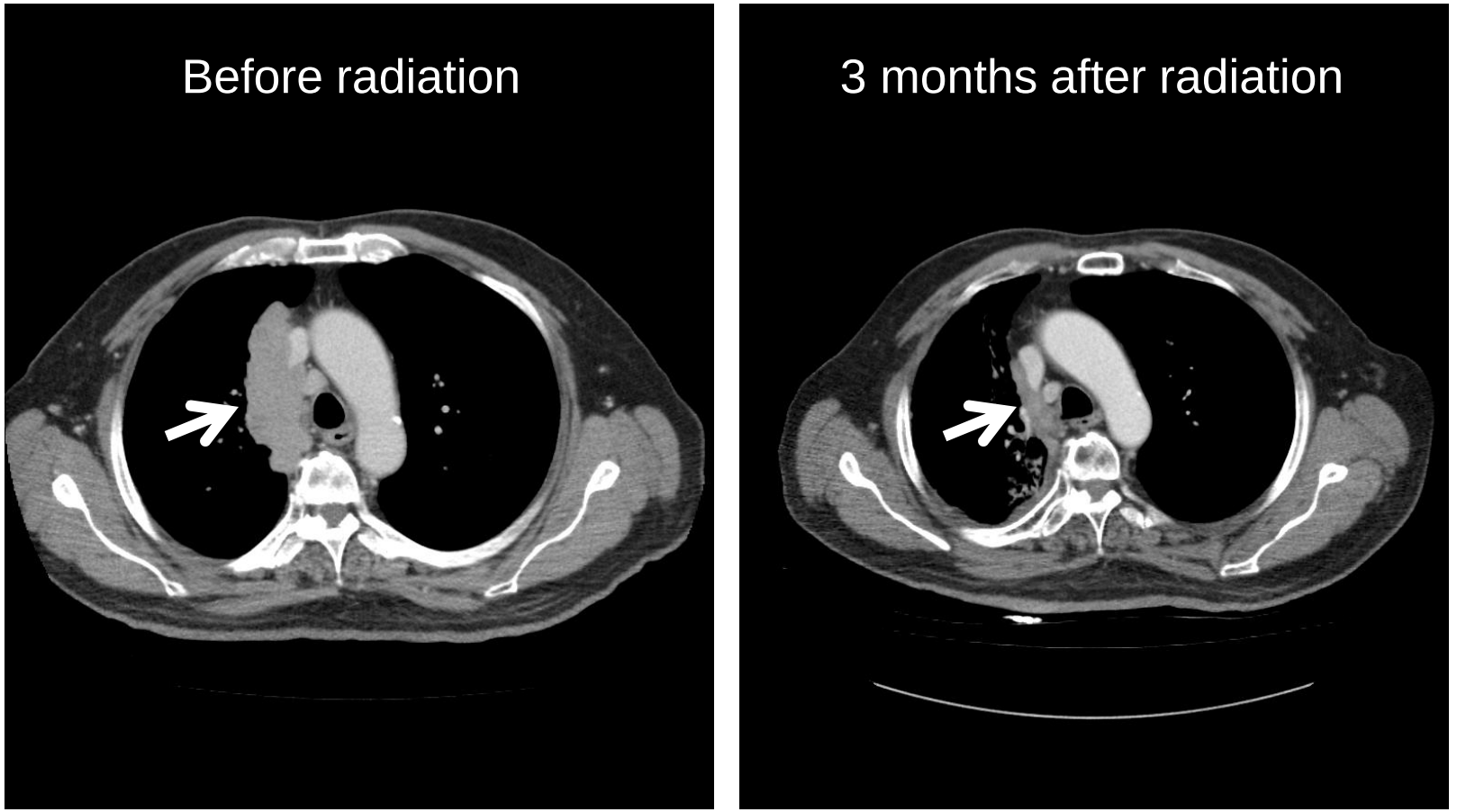
Conflict of interest

- Bayer (speaker fees)
- Astra-Zeneca (Ad board)

Radiation in mesothelioma

- Although mesothelioma had traditionally been considered resistant to radiation, more recent evidence suggests the contrary
  - *In vitro,* epithelial mesothelioma cell lines are more sensitive to radiation than non-small cell lung cancer
  - Radiation can palliate chest pain in up to 60% of patients with mesothelioma
  - Adjuvant high dose hemithoracic radiation after surgery can improve local control
  - Induction accelerated hypofractionated hemithoracic radiation followed by surgery (SMART approach) provides encouraging results in epithelial mesothelioma

Palliative radiation with 20 Gy in 5 fractions



Data from palliative radiation suggests that total dose >40 Gy or doses >4Gy/ fraction provide the best response in mesothelioma

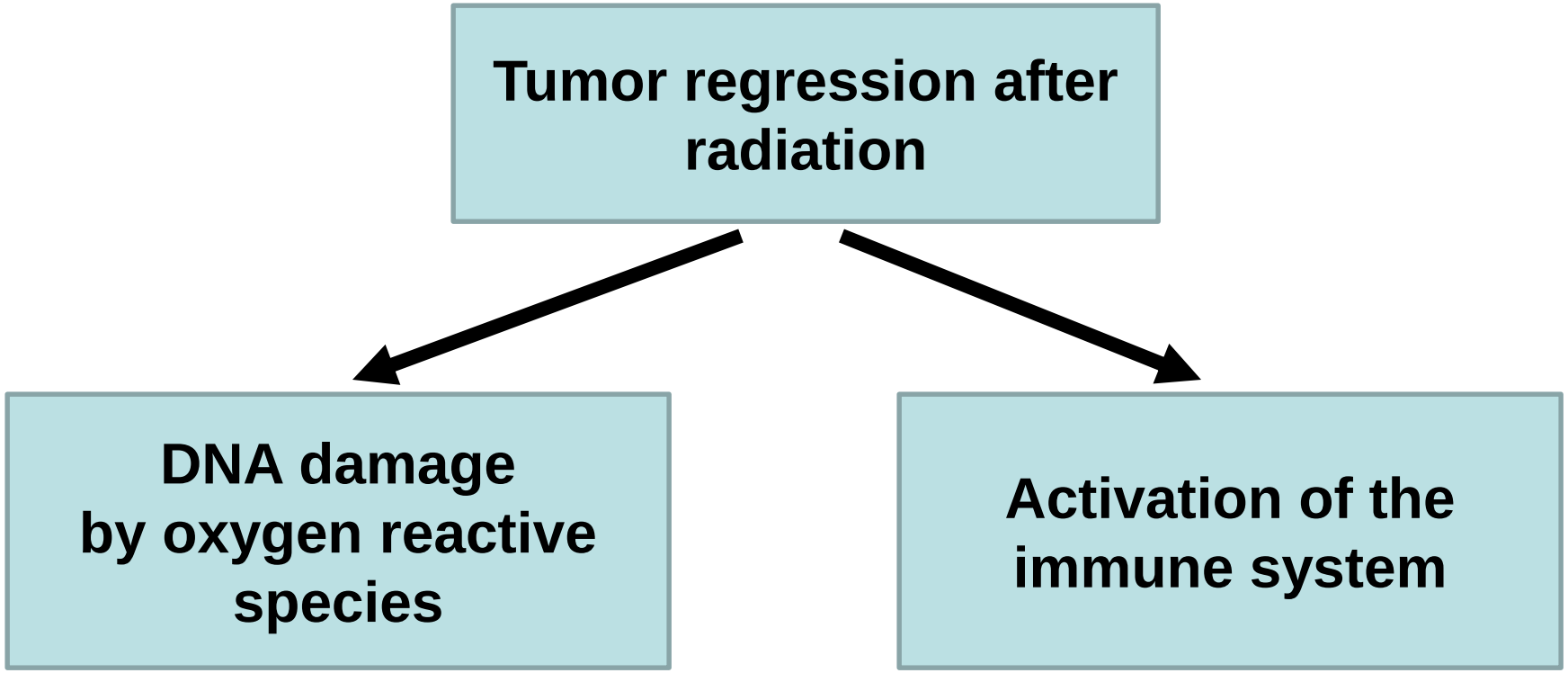
Radiation doses

- Normofractionation ~ 2 Gy per fraction
- Hypofractionation ≥ 3 Gy per fraction
- Ablative radiation ≥ 8 Gy per fraction

} #

These doses of radiation are enabled by technological innovation such intensity modulated radiation (IMRT), image guided techniques, etc

Mechanisms of tumor regression after radiation

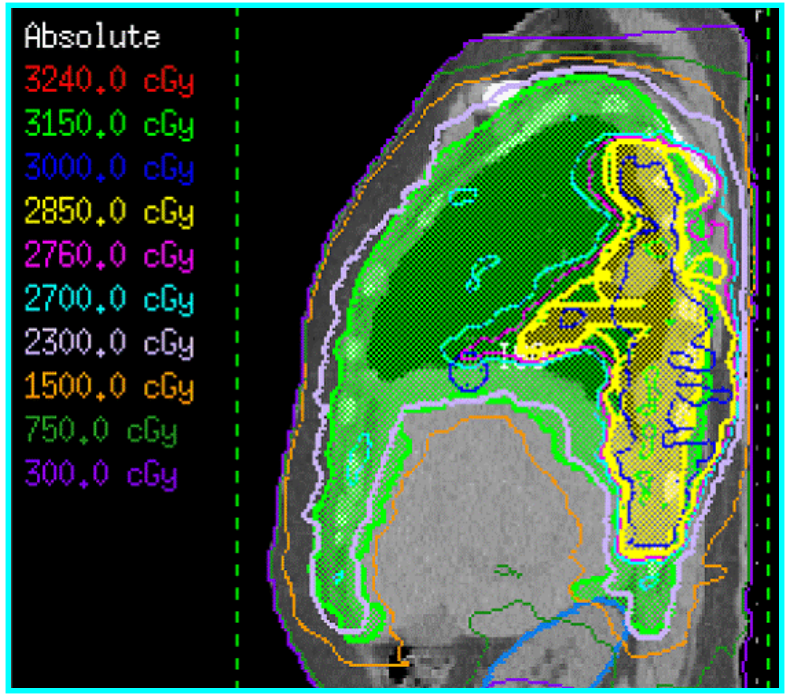


Normofractionated radiation

Hypofractionated radiation (palliative and ablative)

SMART trial

Surgery for Mesothelioma After Radiation Therapy



Study Schema

Histologically Proven, Previously Untreated Malignant Pleural Mesothelioma (cT1-3 N0 M0) Baseline Investigations, Informed Consent

↓

Neoadjuvant Hemithoracic Intensity Modulated Radiotherapy (25 Gy/5 fx +/- concomitant 5 Gy boost over 1 week)

↓

1 week post-RT

↓

Extrapleural Pneumonectomy

↓

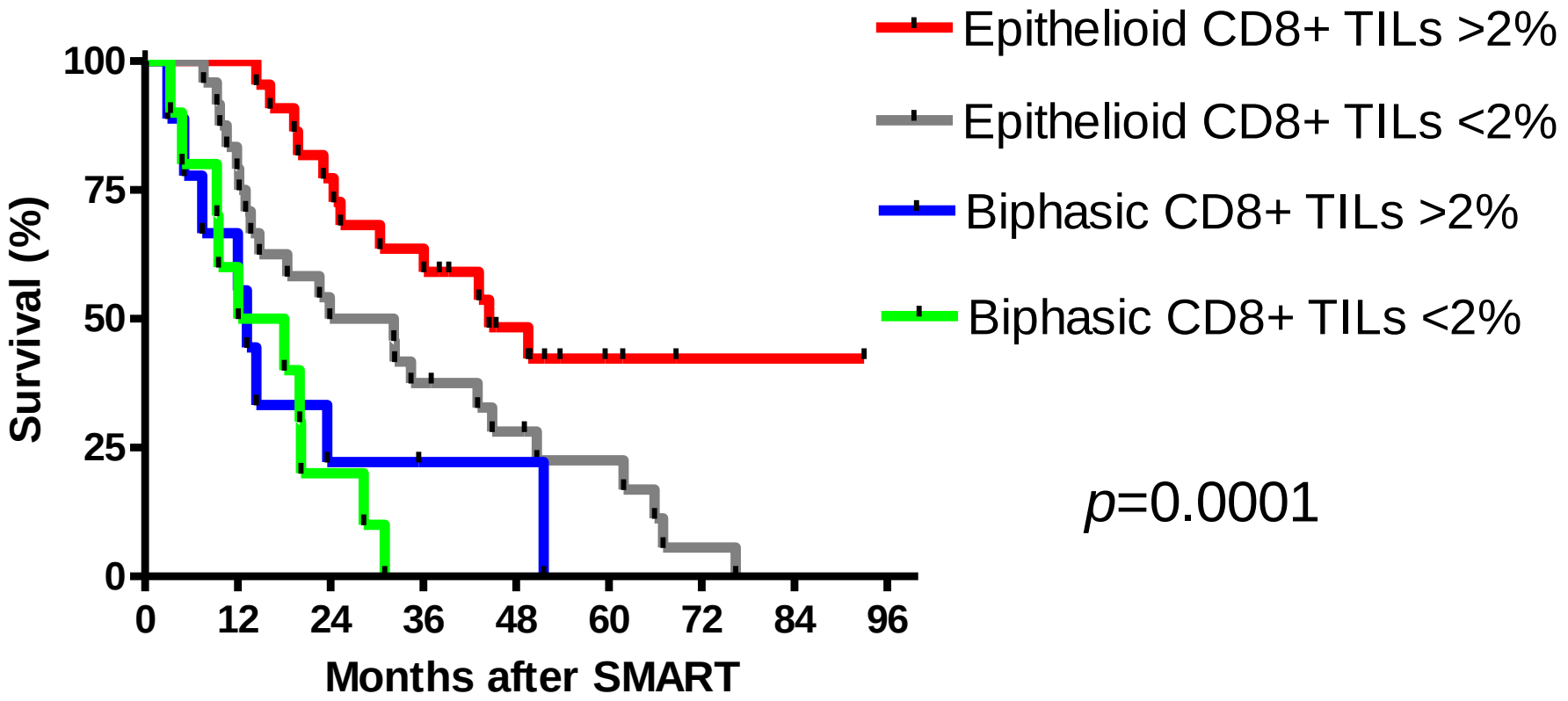
<26 weeks post-op

↓

ypN0-1 → Observation

ypN2 → Adjuvant Chemotherapy

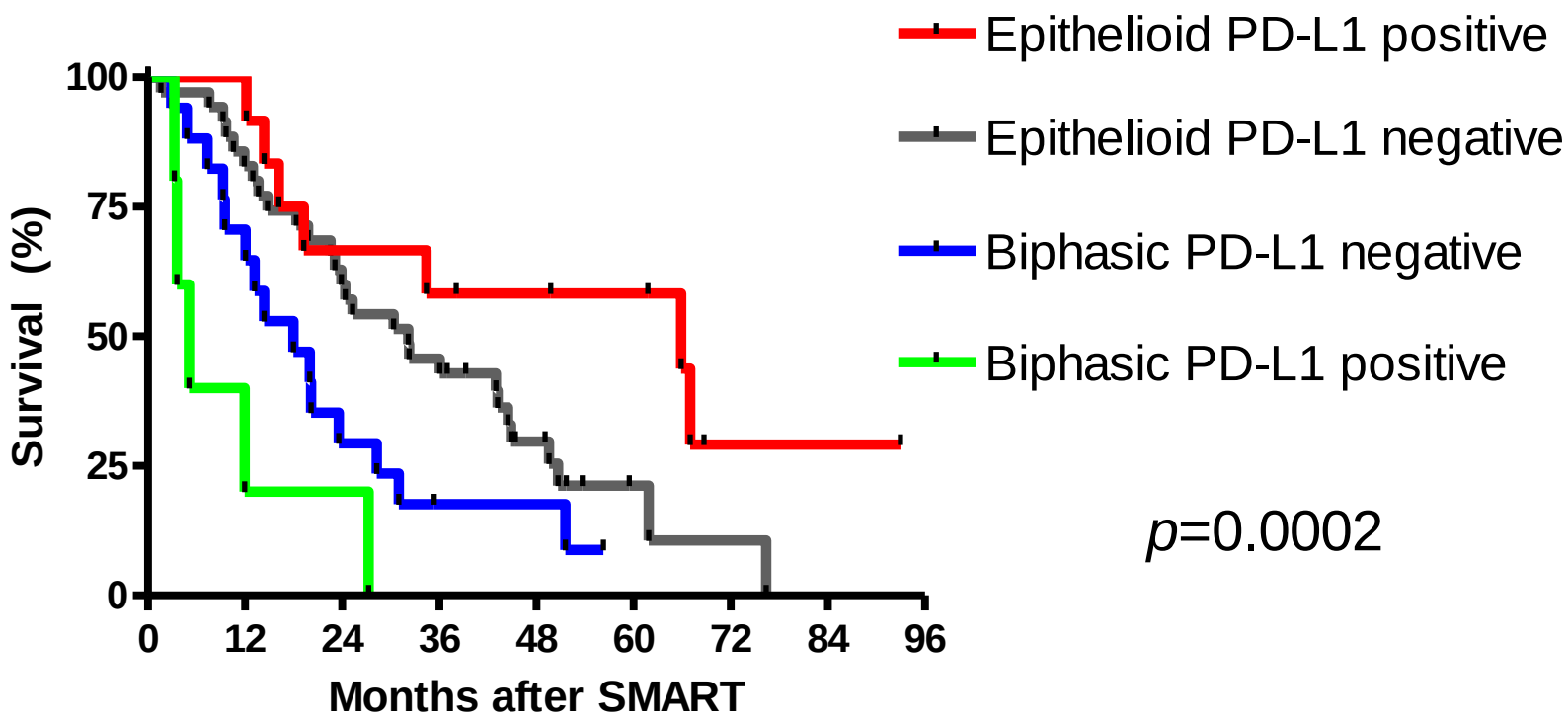
Impact of CD8+ Tumor Infiltrating Lymphocytes (TILs) on survival after SMART



p=0.0001

de Perrot et al. *J Thorac Cardiovasc Surg* (in press)

Impact of PD-L1 expression on tumor cells (≥1%) on survival after SMART



p=0.0002

de Perrot et al. *J Thorac Cardiovasc Surg* (in press)

Multivariate analysis of factors predicting survival after SMART

Continuous variable	Patients # (total n=68)	P-value	Hazard ratio	Lower 95% CI	Upper 95% CI
CD8+ TILs >2%	33	0.02	0.47	0.25	0.89
Positive lymph nodes (N+)	42	0.03	1.92	1.05	3.51
Epithelioid histology	34	0.0004	0.3	0.16	0.59
PD-L1 positive cancer cells (>1%)	17	0.9	0.94	0.43	2.06
PD-1 cells >0.3%	32	0.8	0.96	0.71	1.32
Male gender	55	0.2	1.79	0.79	4.06

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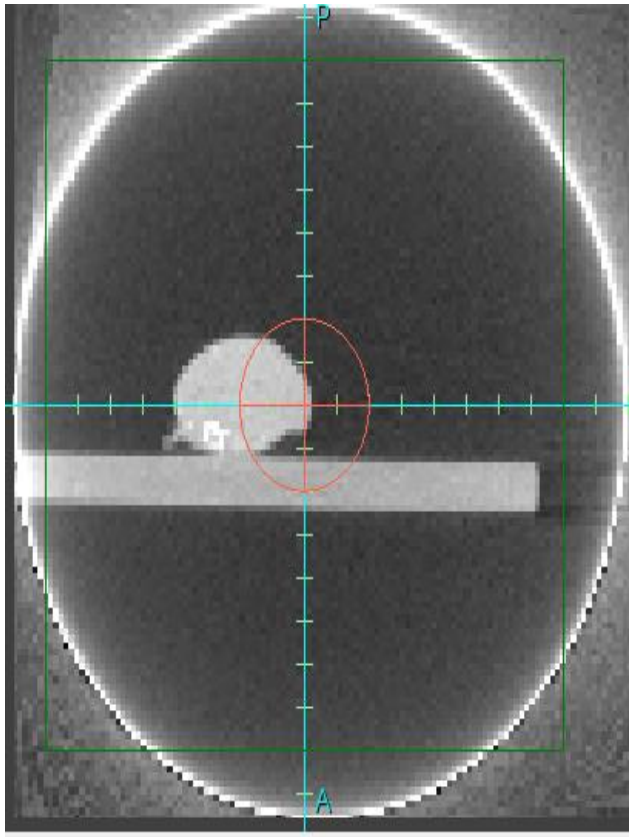
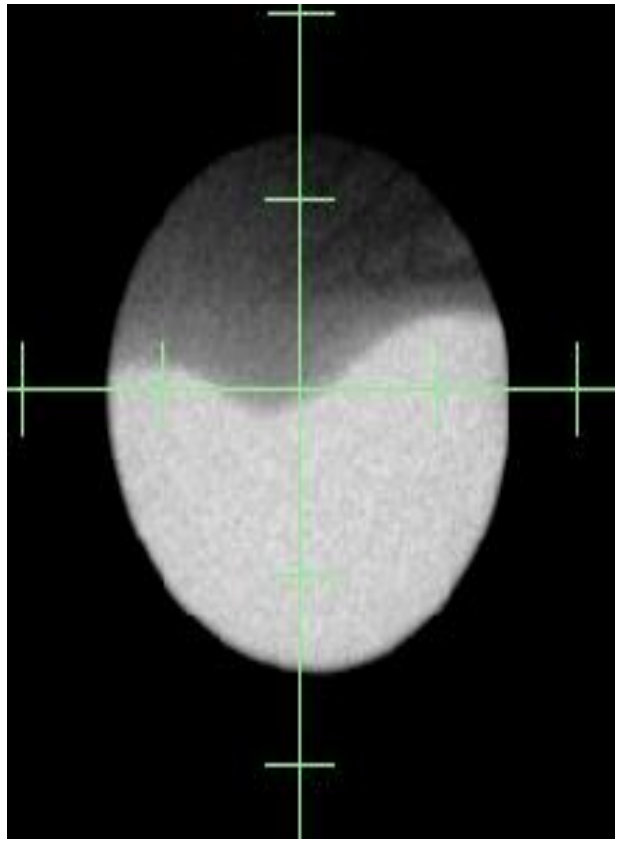
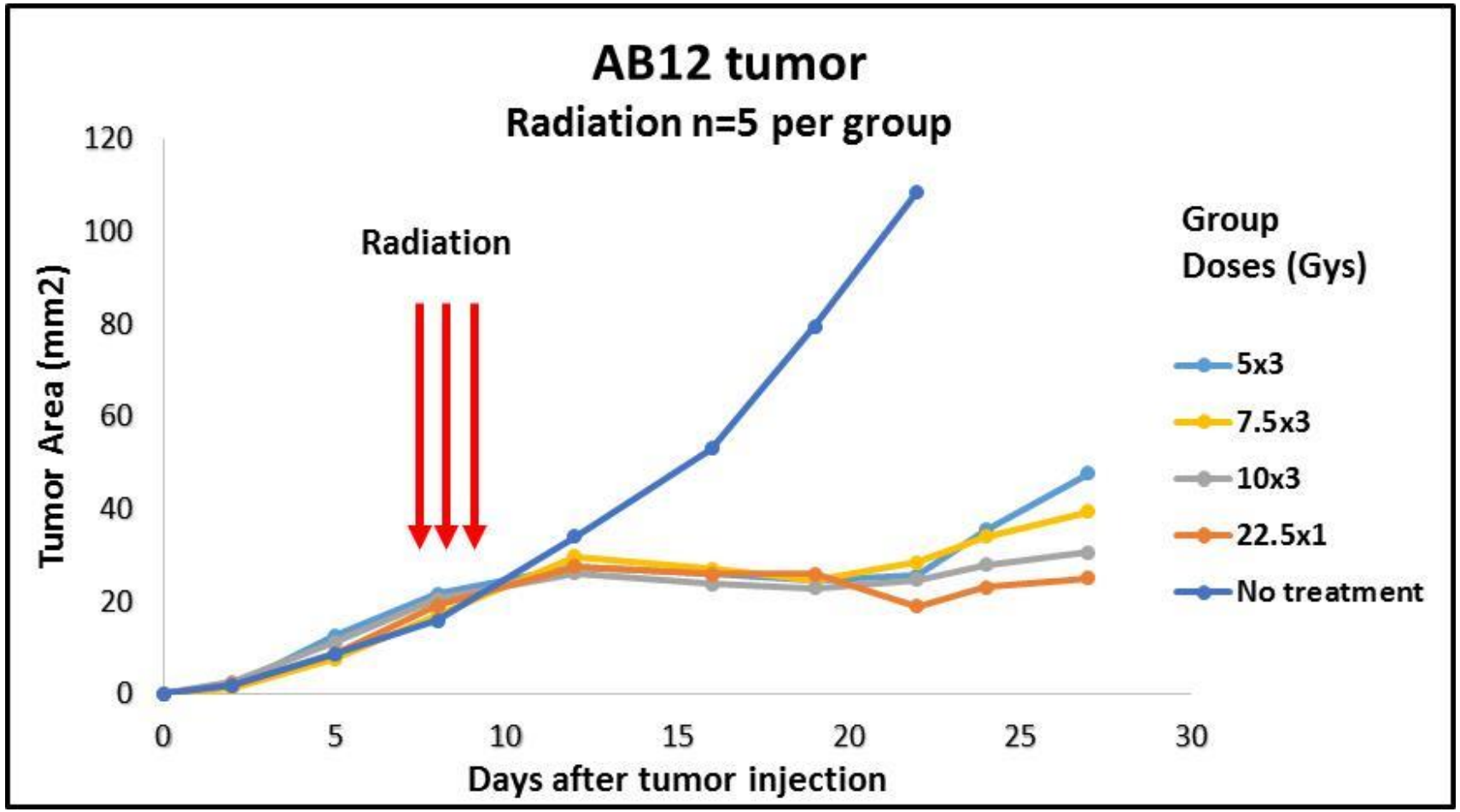
Mice model of local accelerated hypofractionated radiation

Local Radiotherapy (LRT)

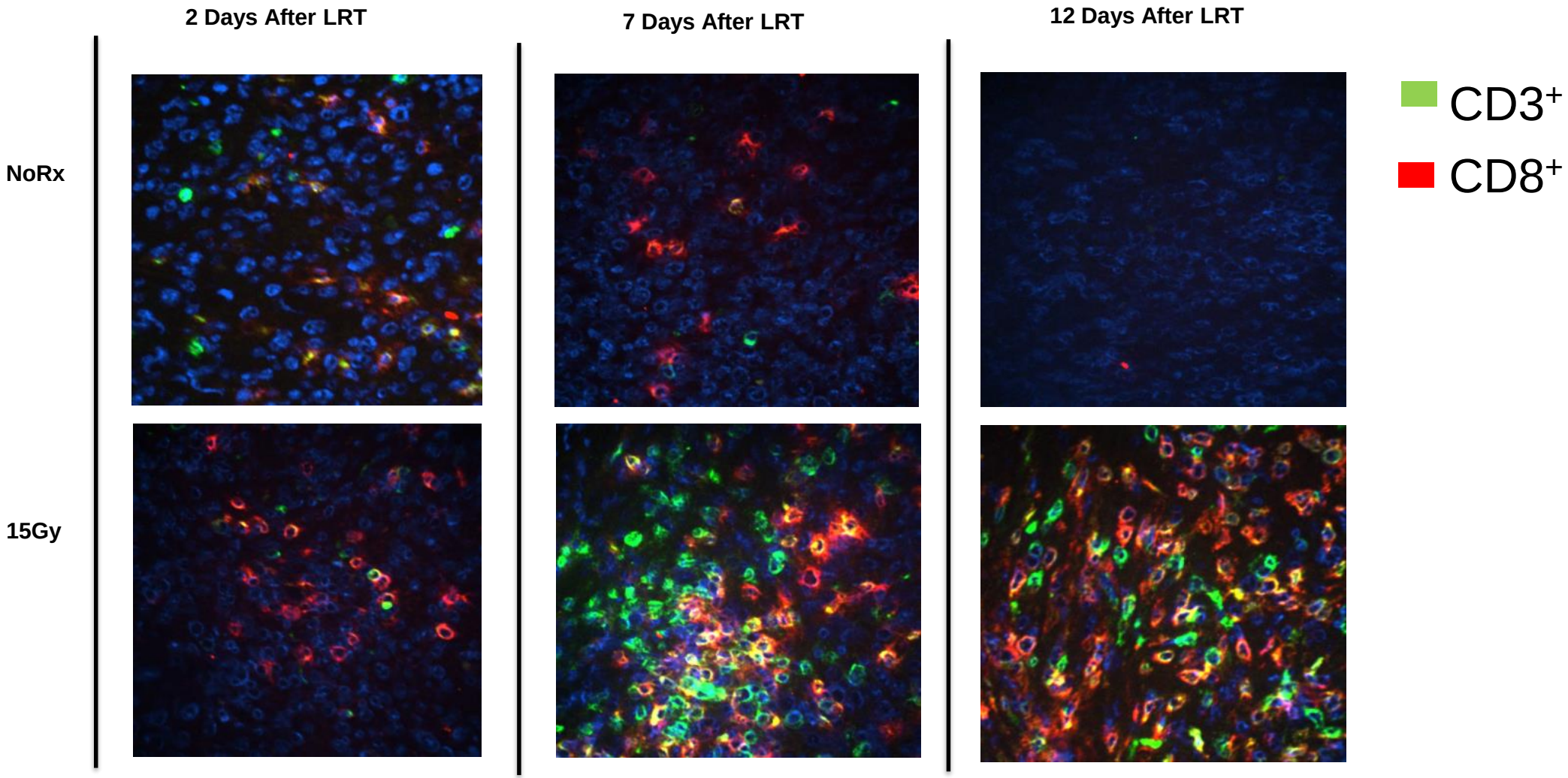




Accelerated hypofractionated non-ablative radiation in a mice model of mesothelioma



Local RT induces upregulation of tumor infiltrating T cells



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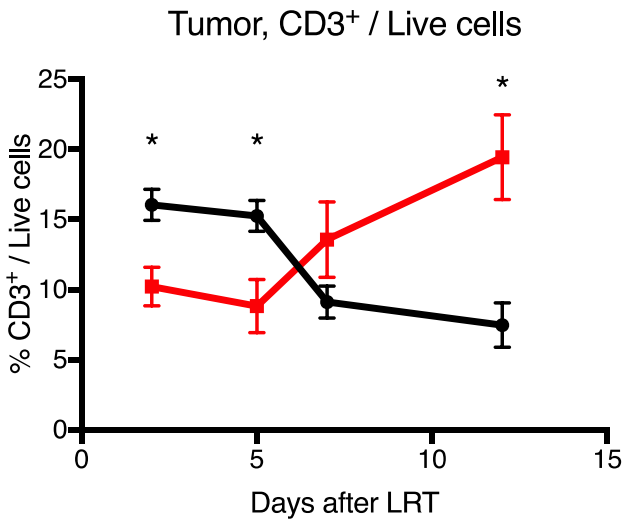
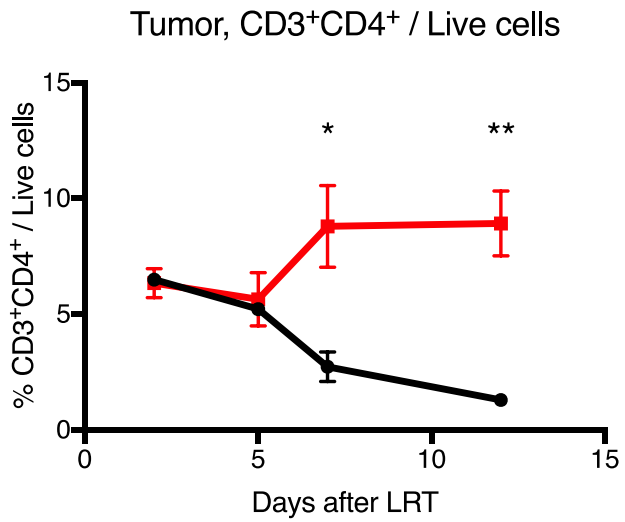
Kinetics of T cell recruitment after LRT

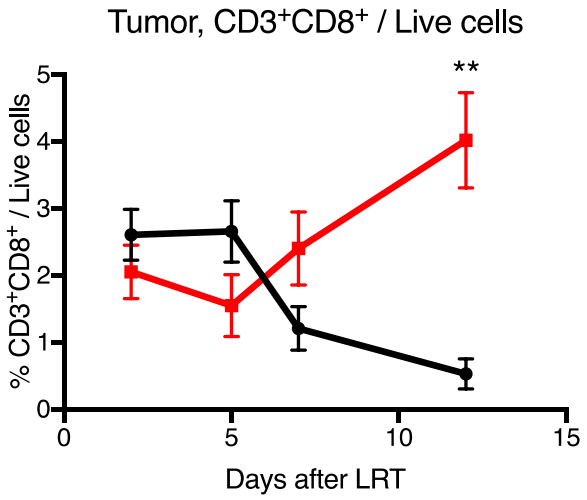
CD3⁺ T cells

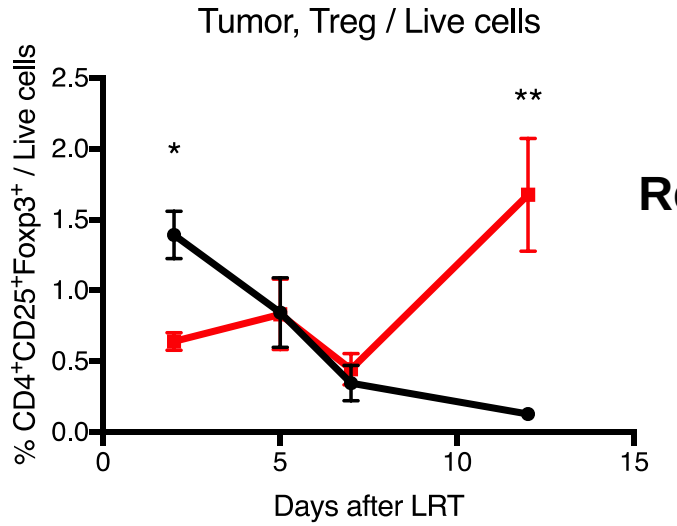




CD4⁺ T cells

CD8⁺ T cells

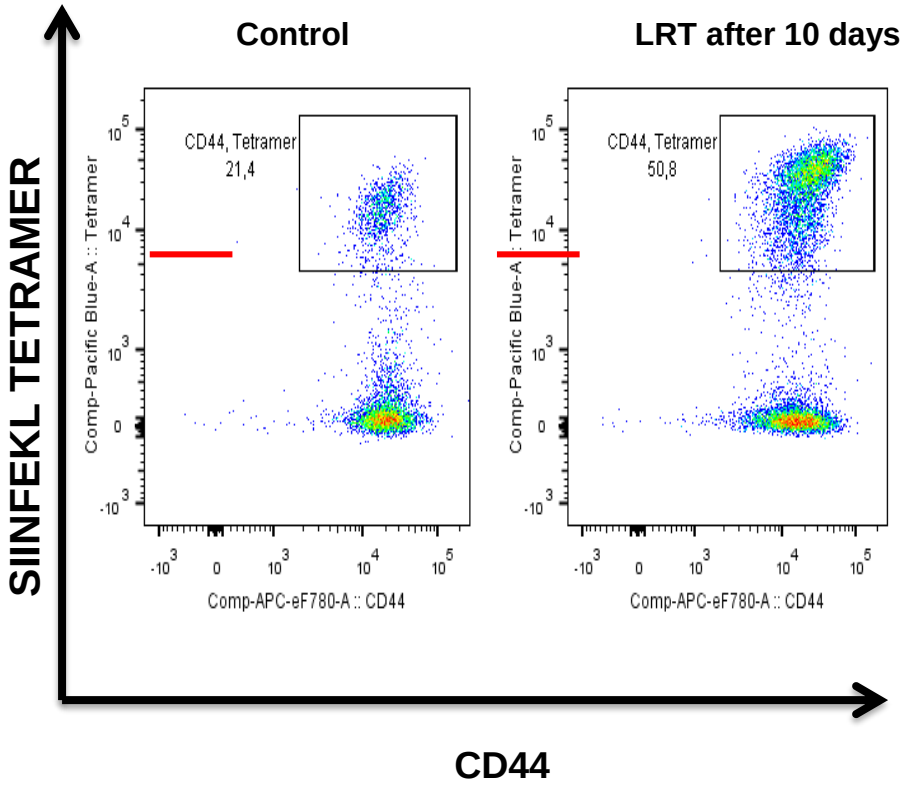


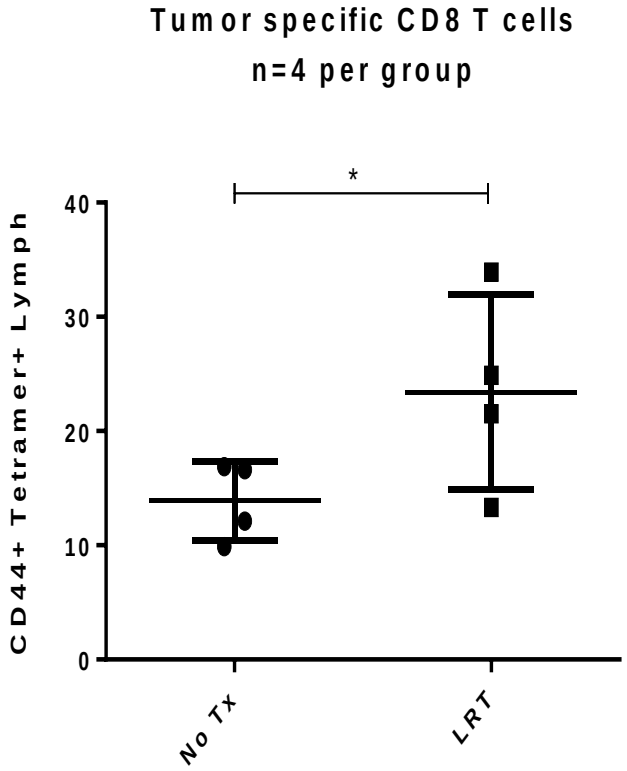


Regulatory T cells

Mikihiro Kohno (manuscript in preparation)

CD8+ lymphocytes infiltrating AE17-OVA tumor are OVA specific





Tumor specific CD8+ T cells in AE17-OVA tumor. Radiation vs no treatment

* p=0.07

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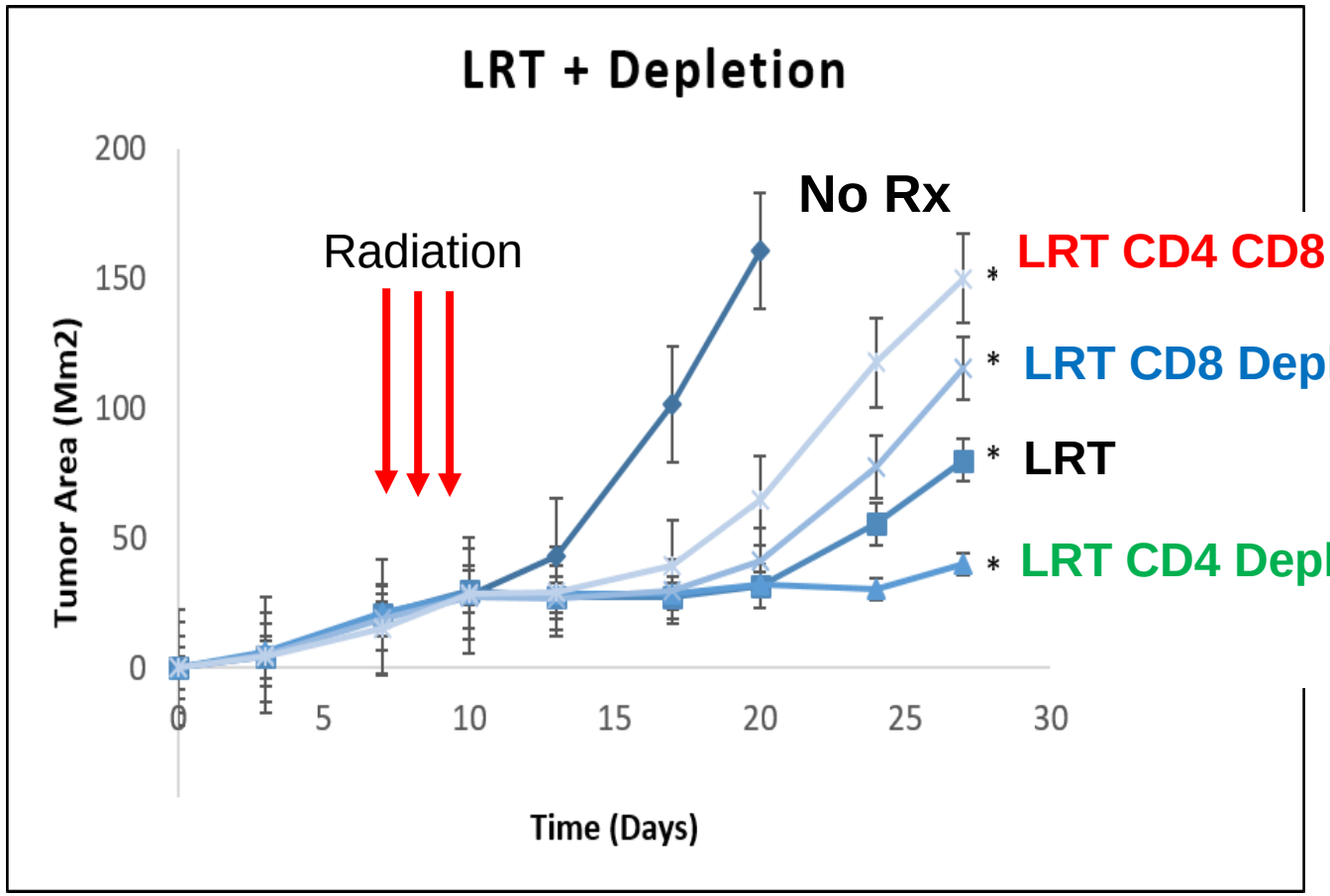
Benefit of radiation (3x 5Gy) is reduced after T cells depletion



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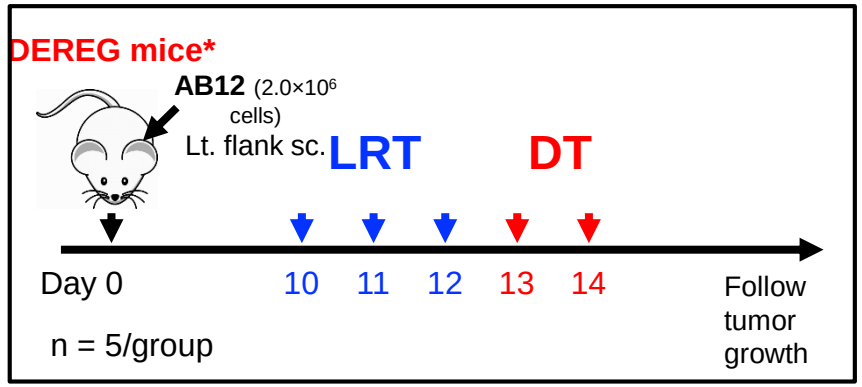
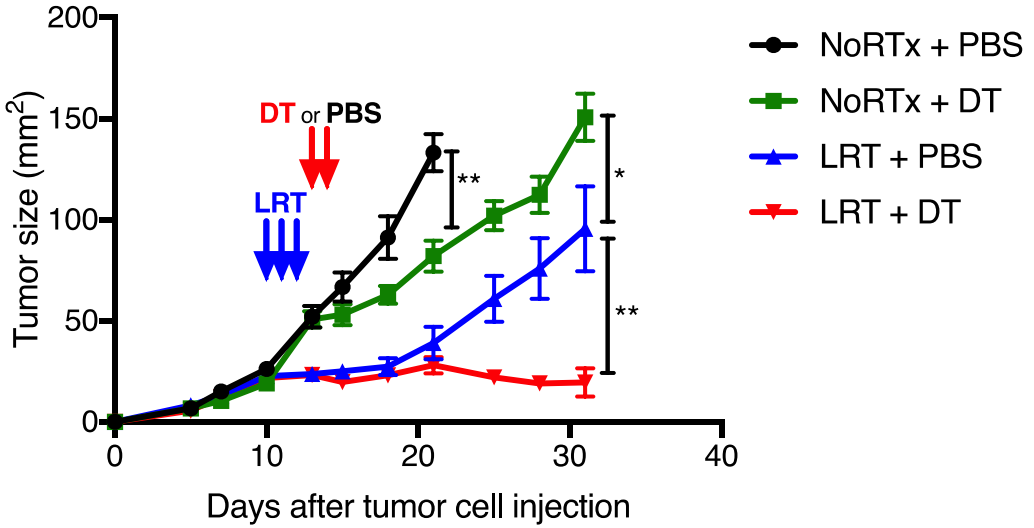
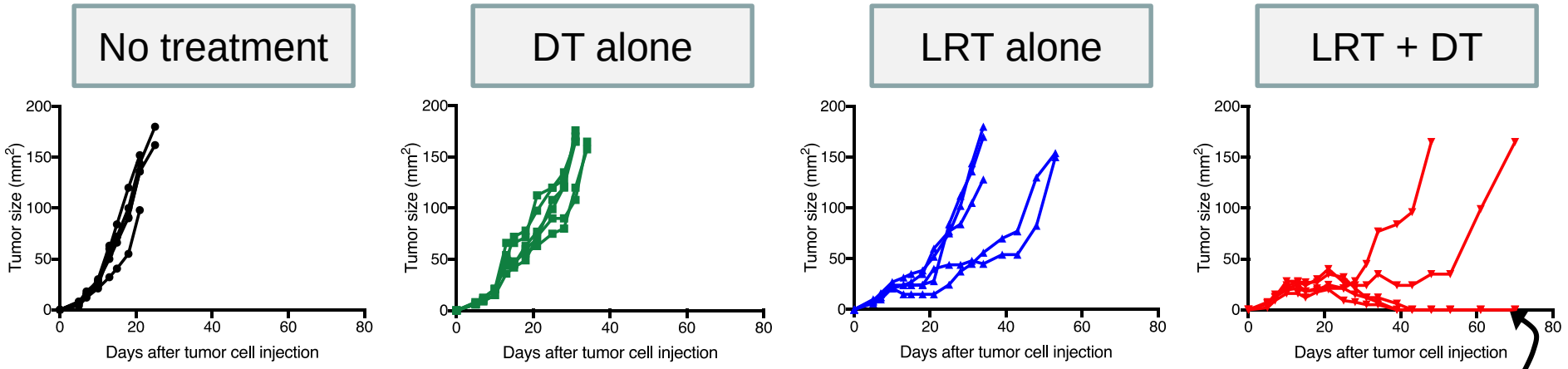
Selective depletion of Foxp3^{+} Tregs with LRT demonstrated synergistic antitumor effects

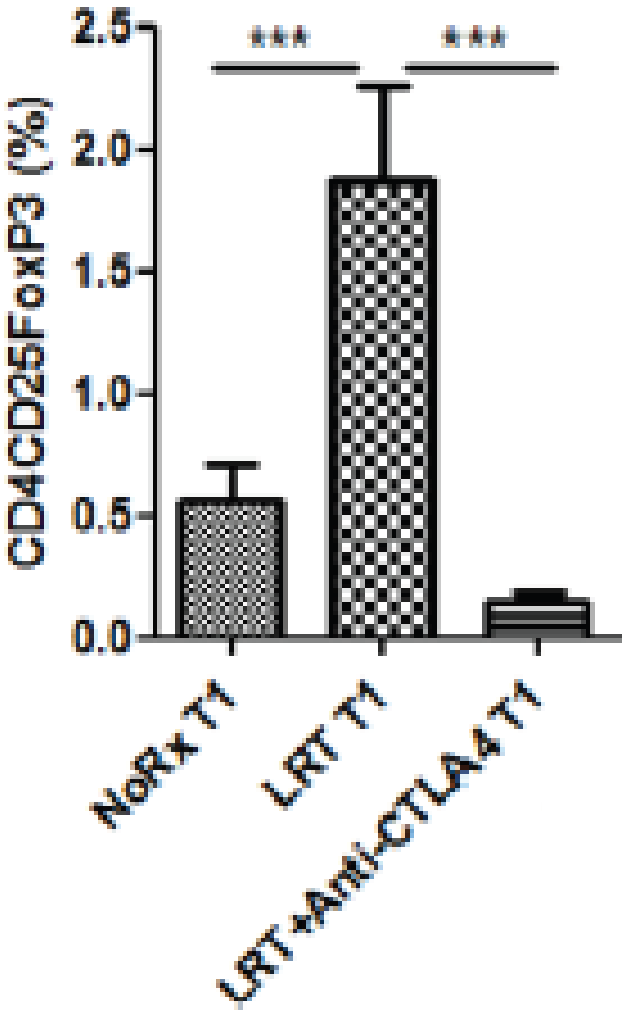






*DTR-eGFP transgene under the control of the Foxp3 locus
Mikihiro Kohno (unpublished data)

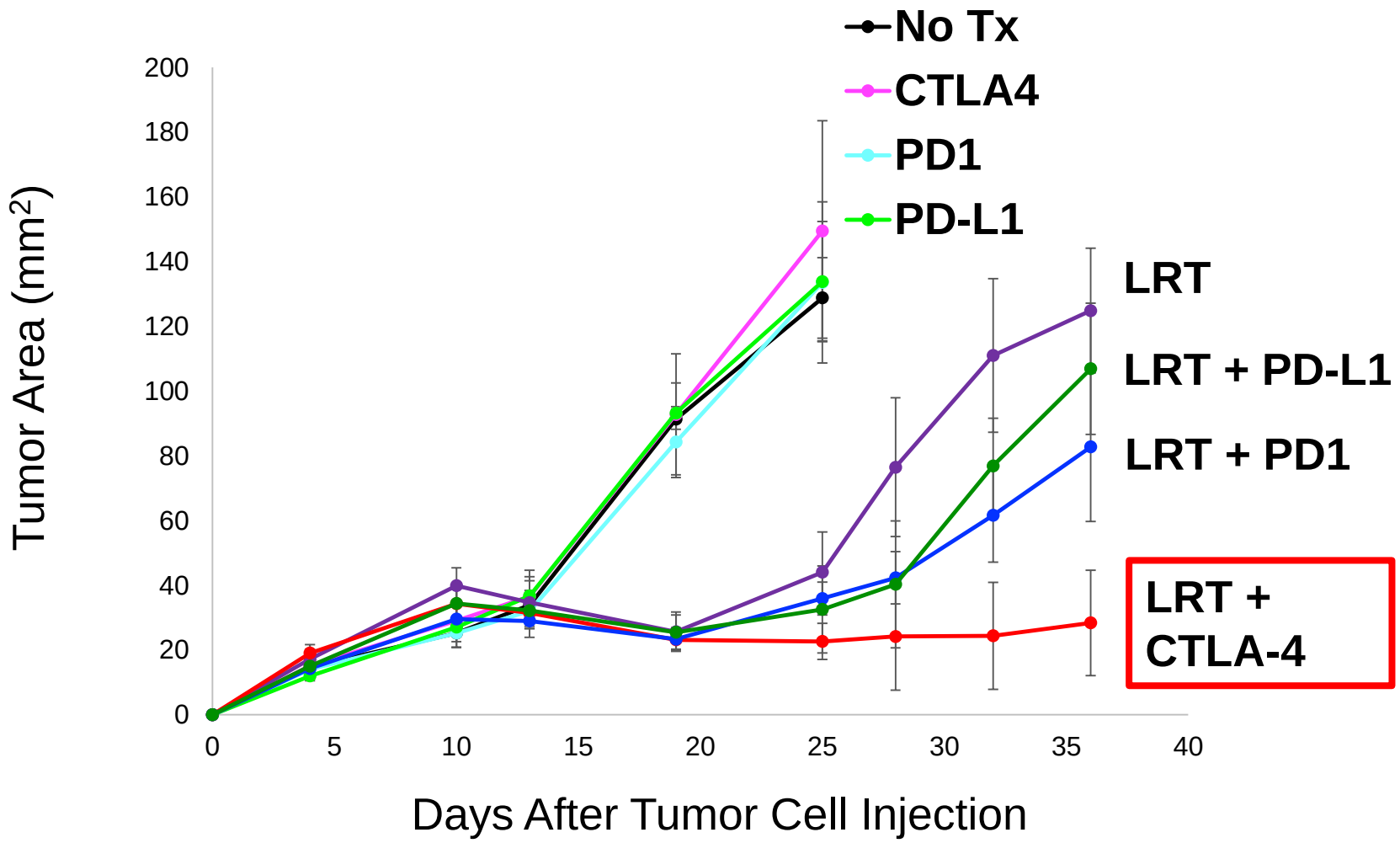
Upregulation of regulatory T cells after LRT



- Treg characterized by CD4+CD25+FoxP3+
- Combination of LRT with CTLA4 inhibitor prevent the upregulation of Treg after radiation

Wu/ de Perrot et al *Oncotarget* 2015 March 8

Combining CTLA-4 blockade with LRT improves local control



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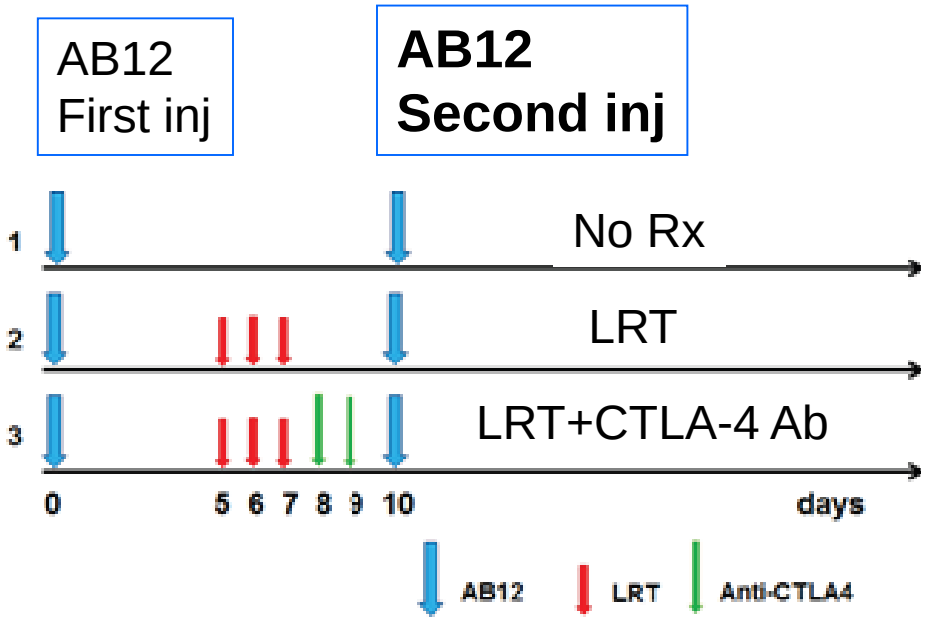
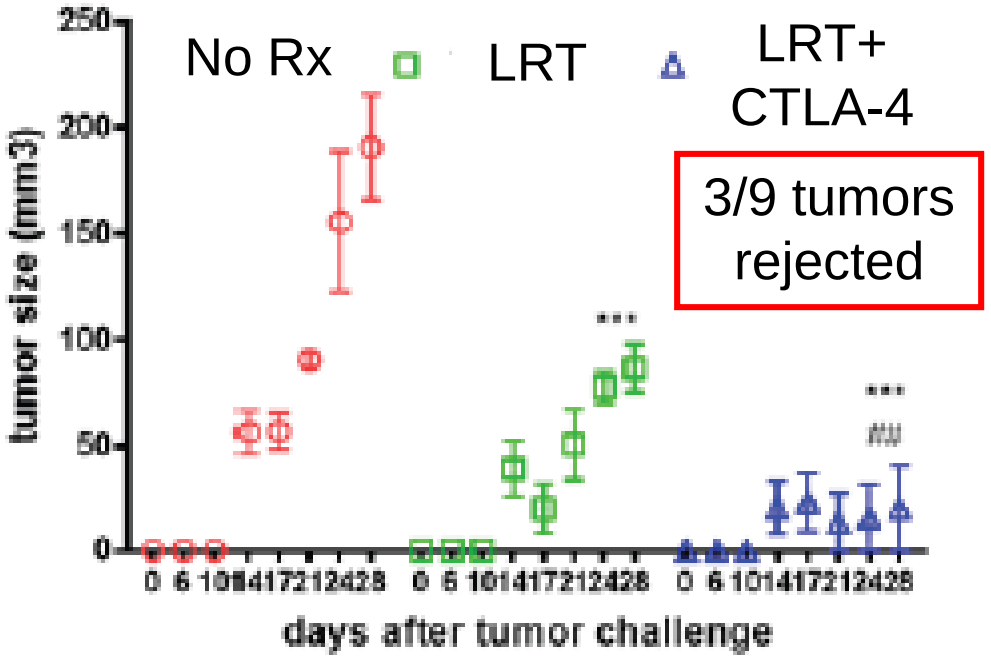
Impact CTLA-4 blockade with accelerated hypofractionated radiation (3x5Gy) Abscopal effect



Secondary tumor growth



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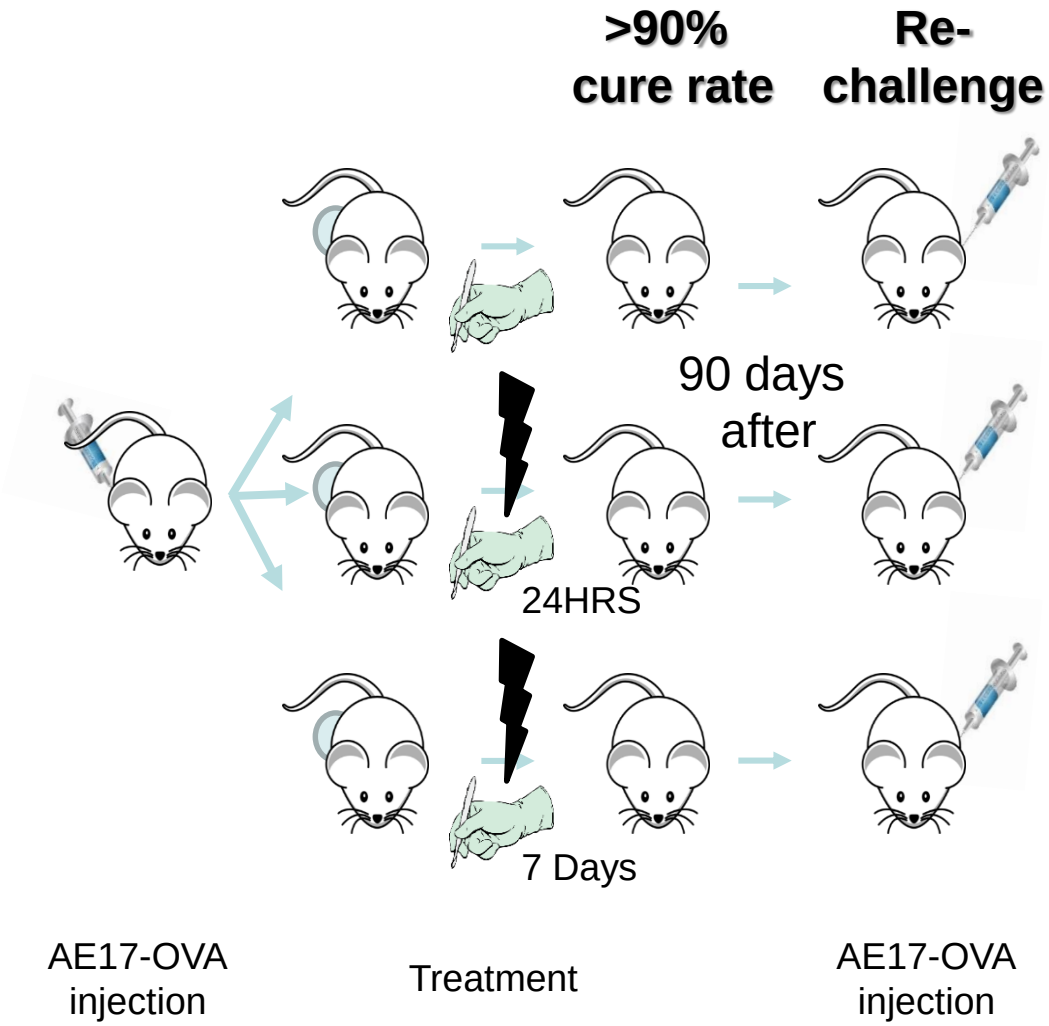
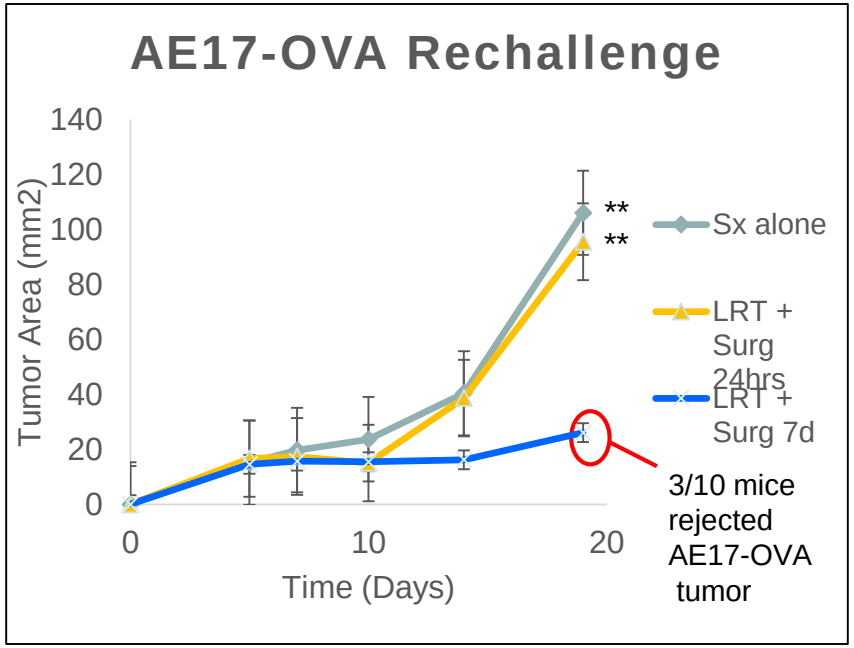
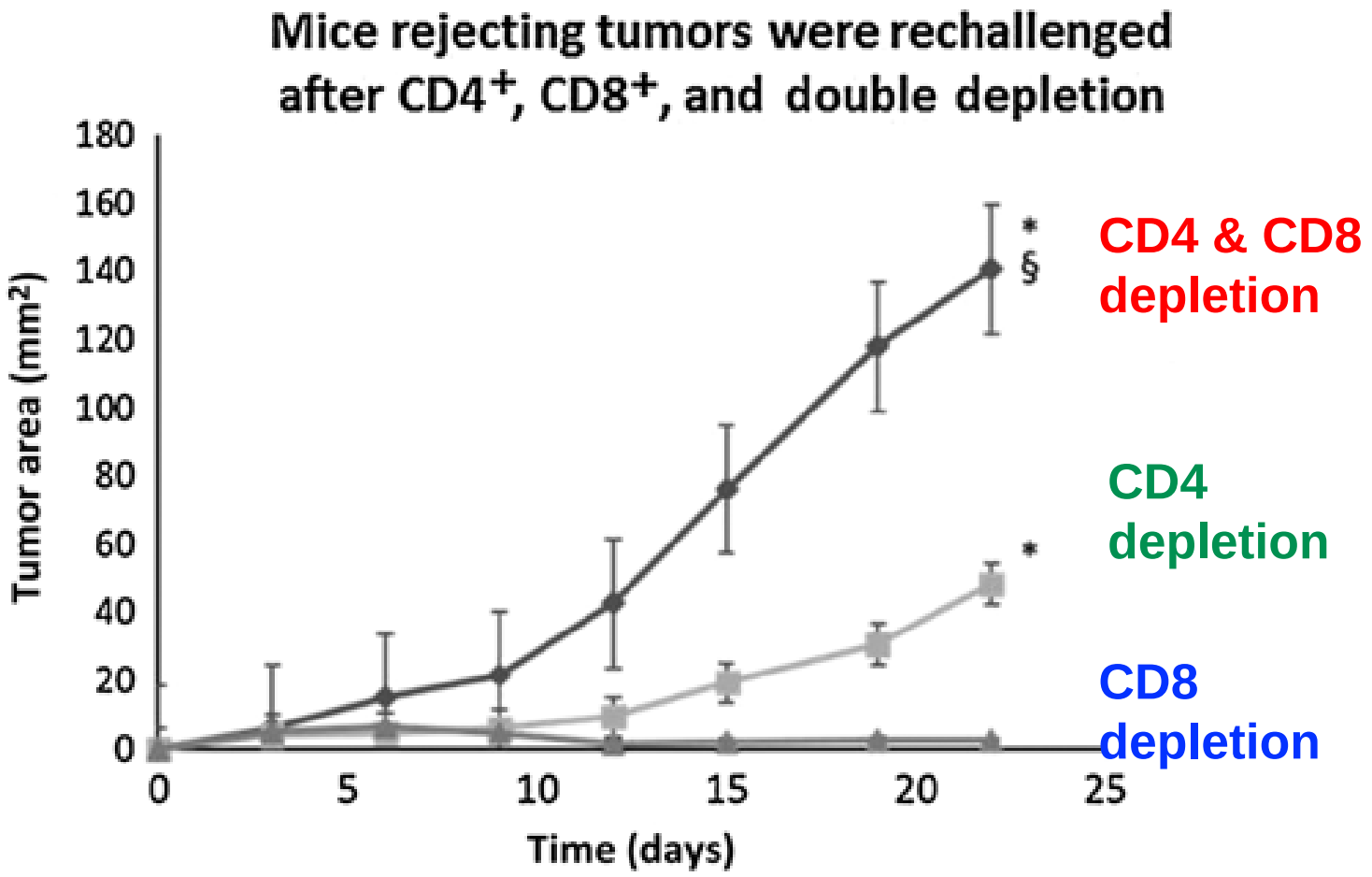
Tumor growth was significantly reduced in mice treated with LRT and radical surgery





CD4 and CD8 lymphocyte depletion completely abrogates tumor protection



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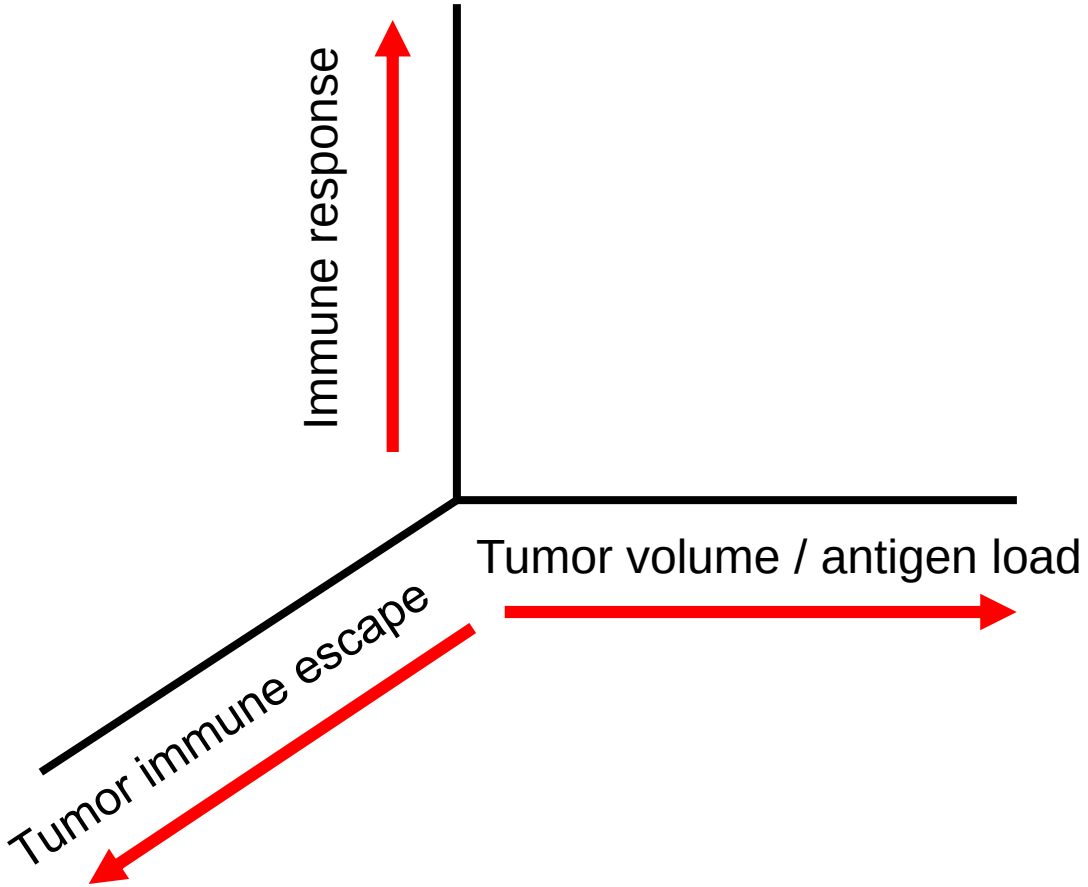
Key steps to a successful immune response after non-ablative hypofractionated radiation and immunotherapy



1. **Generate an immune response with new T cell clones**
   - Adequate mutational burden, functional dendritic cells
2. **Overcome the immunosuppressive tumor microenvironment**
   - Tumor volume and Treg are major limiting factors
3. **Overcome the mechanism of resistance from tumor cells**
   - Tumor cells can upregulate of PD-L1, SerpinB9, GITRL as mechanisms of resistance to the radiation induced immune

Adapted from Huang et al. *Nature* 2017; 545: 60-65

Conclusions

- Mesothelioma are sensitive to radiation, particularly the epithelial subtypes
- Accelerated hypofractionated radiation can activate the immune system with upregulation T cells in the tumor
- The immediate benefit of accelerated radiation is related to CD8+ T cells, while the long term benefit is predominantly driven by CD4+ T cells
- Surgery can optimize the benefit of radiation and immune activation by reducing the tumor antigen load
- Non-ablative hypofractionated radiation combined with surgery can provide an excellent platform for immunotherapy in mesothelioma

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CMF Canadian Mesothelioma Foundation

Mesothelioma Applied® Research Foundation research - education - support - advocacy

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FNSNF Swiss National Science Foundation

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Thank you