Presenter Disclosure Information

Simon Dovedi

The following relationships exist related to this presentation:

AstraZeneca, received research funding

MedImmune, received research funding

University of Manchester, employee

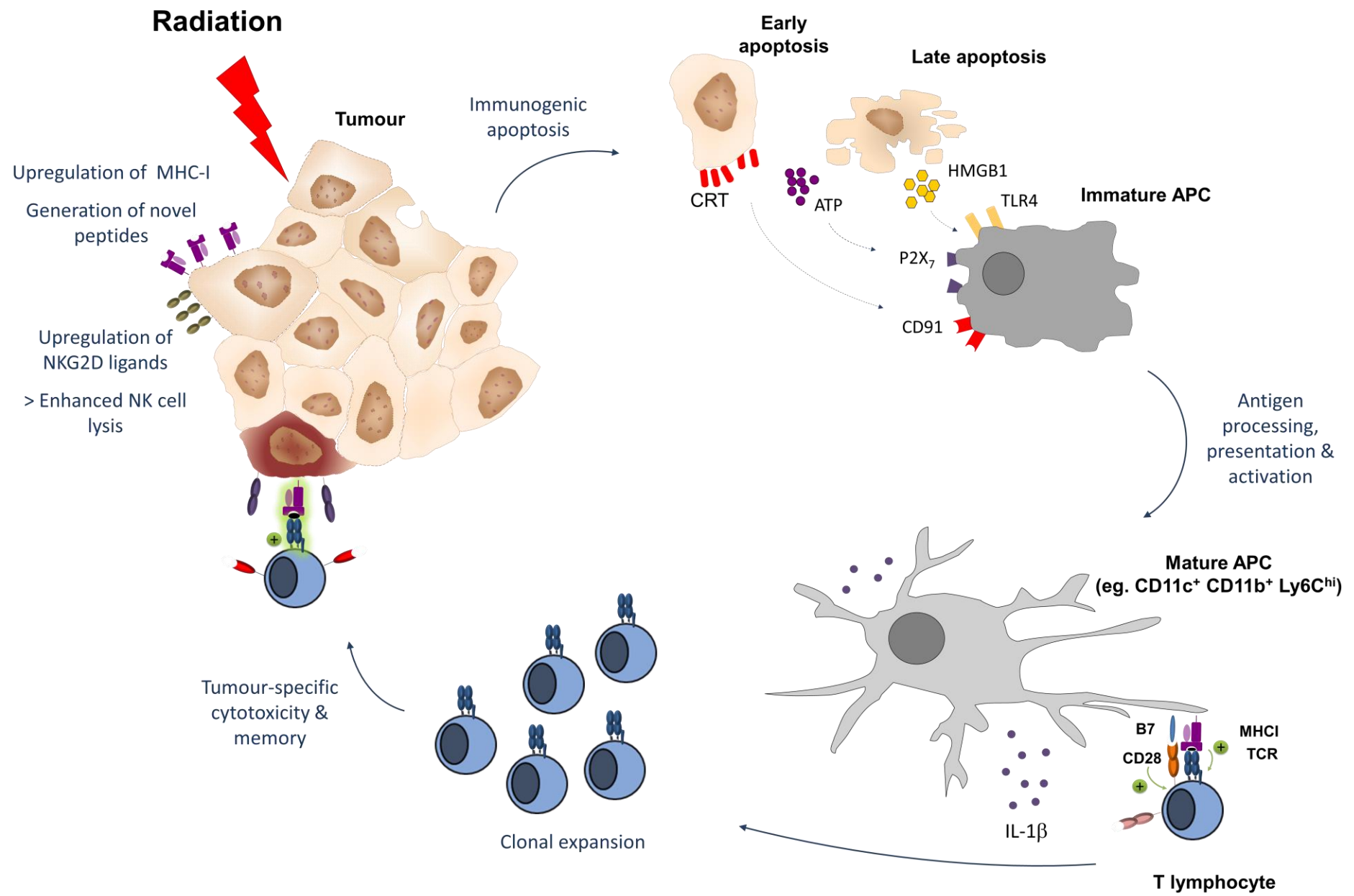
The anti-tumour immune response generated by radiation therapy may be limited by tumour cell adaptive resistance and can be circumvented by PD-L1 blockade

Simon Dovedi

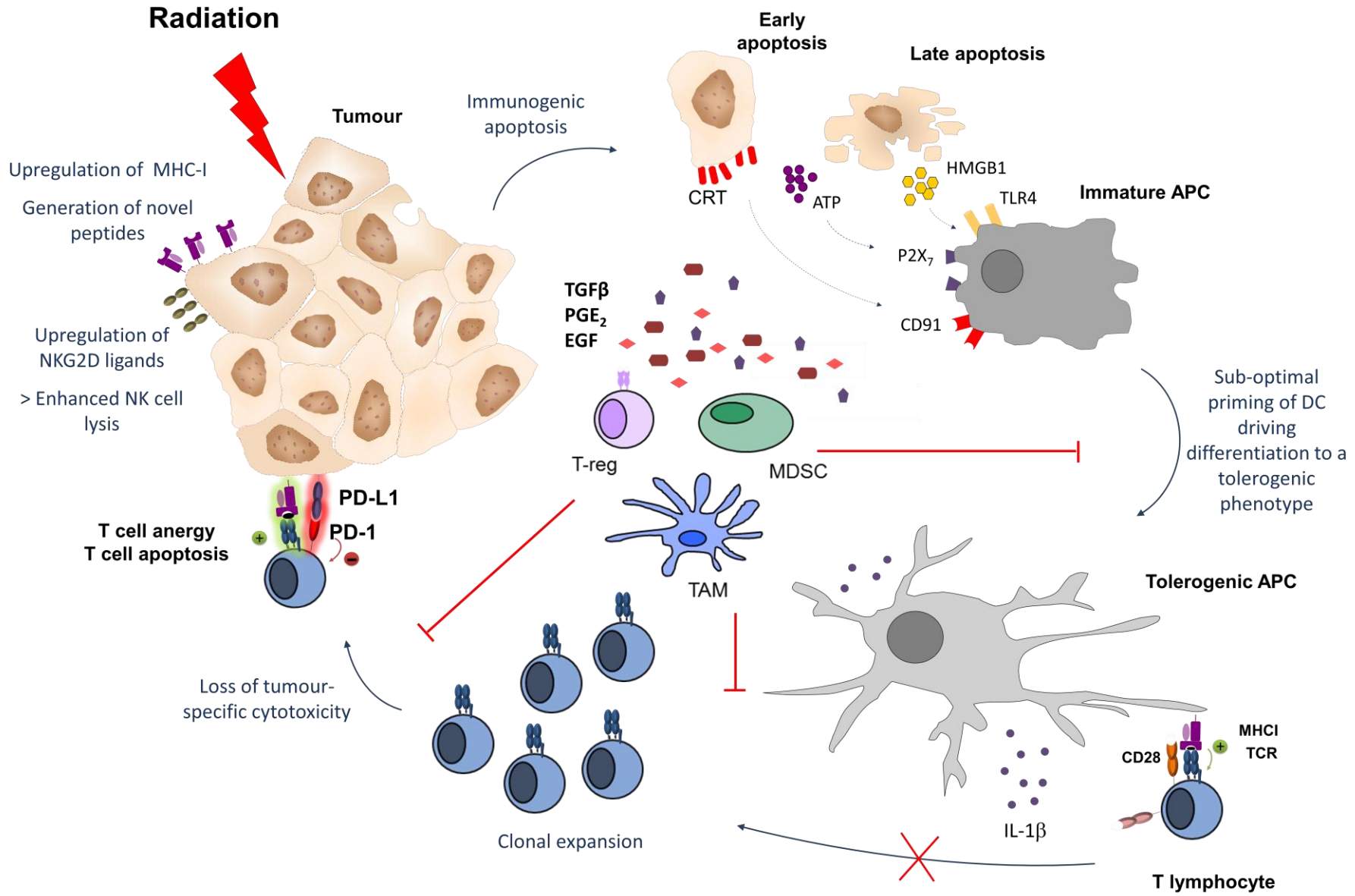
University of Manchester

Manchester Cancer Research Centre

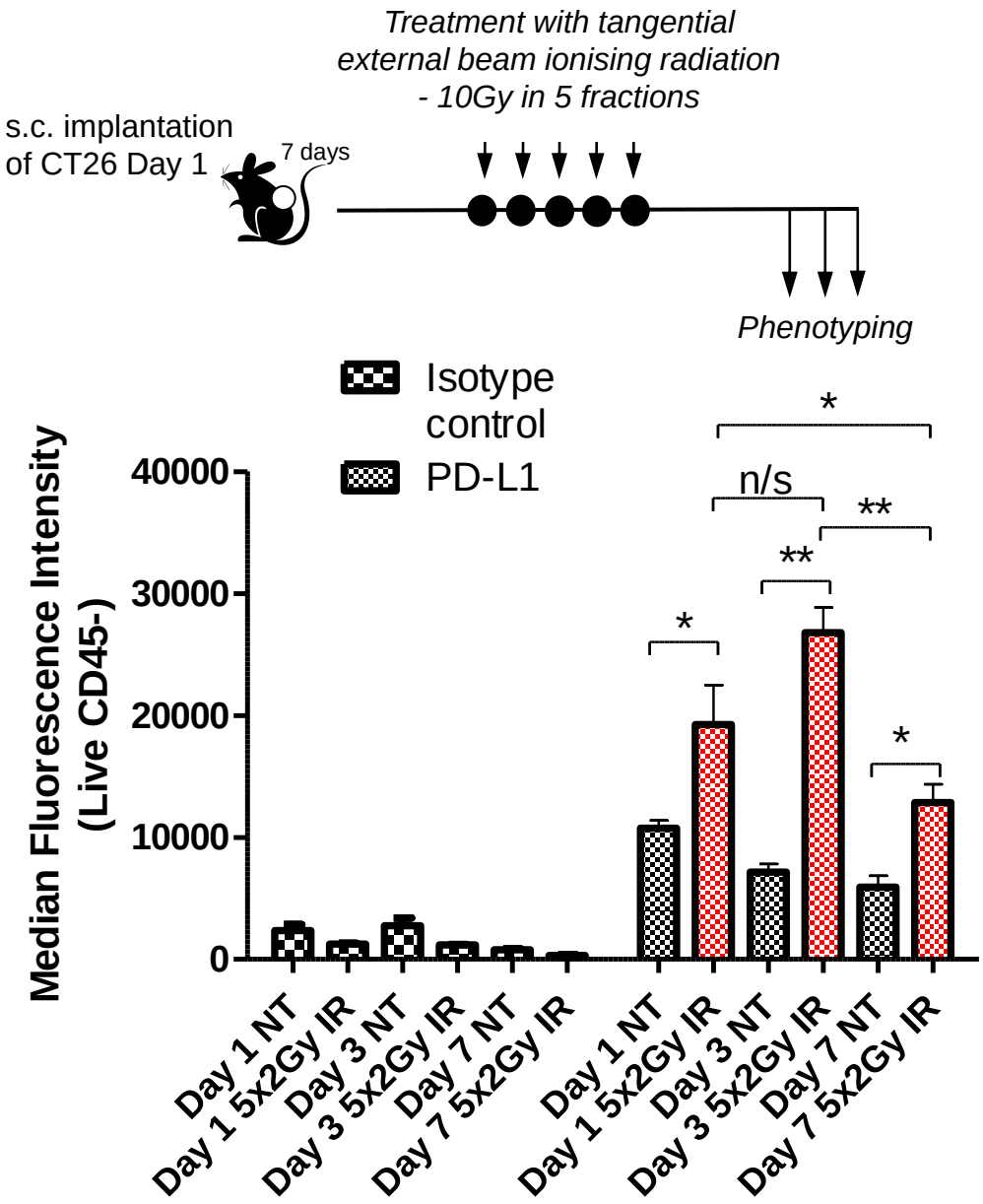
The Immunogenicity of Radiotherapy



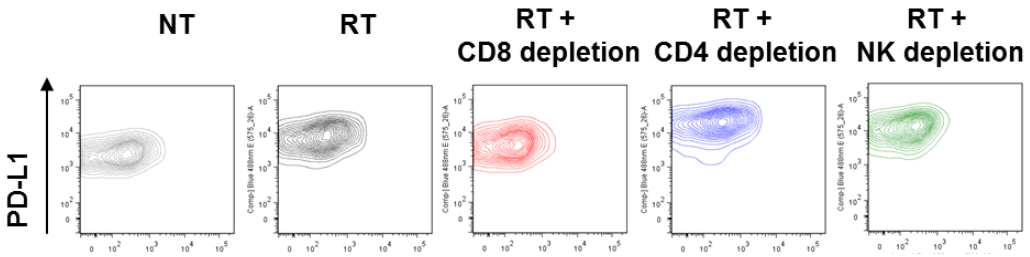
Solid tumours generate an environment that suppresses anti-tumour immune responses

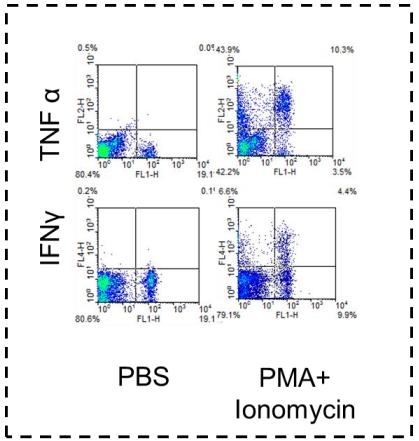


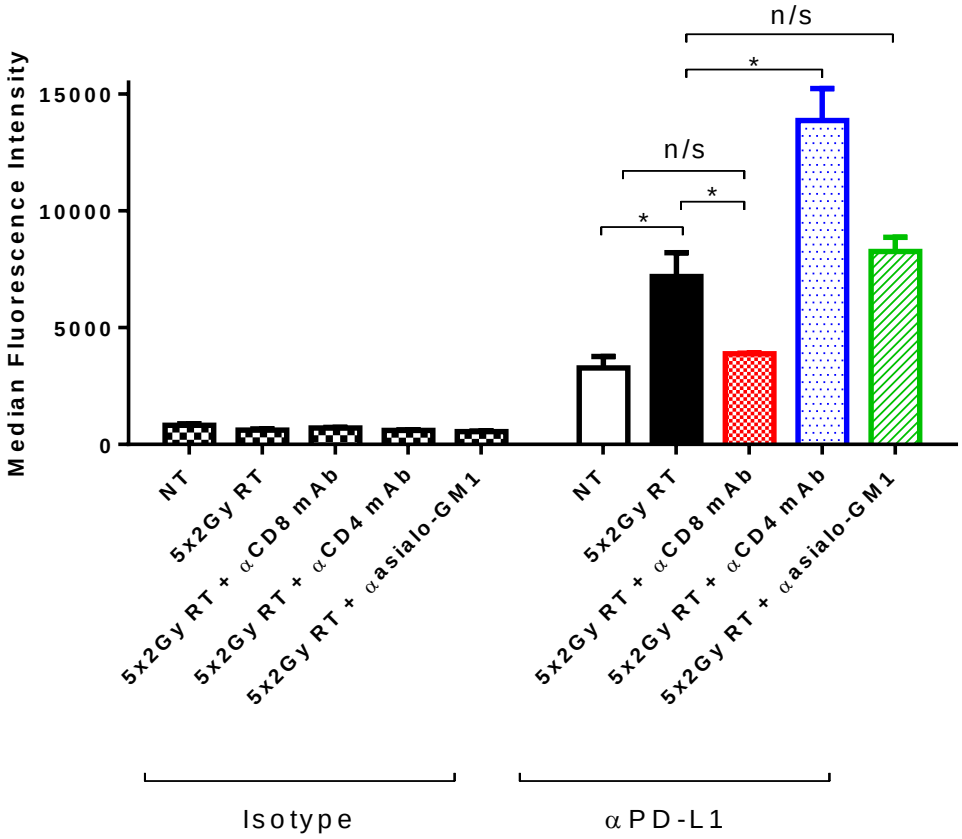
Ionizing radiation leads to increased tumour cell expression of PD-L1 *in vivo*

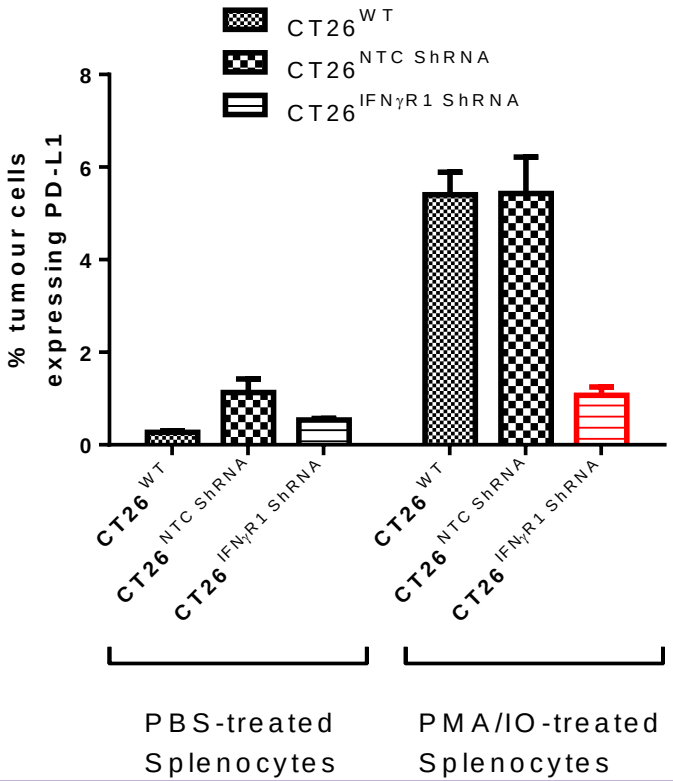


Ionizing radiation leads to increased tumour cell expression of PD-L1 *in vivo* which is dependent on $CD8^+$ T cell production of IFNγ

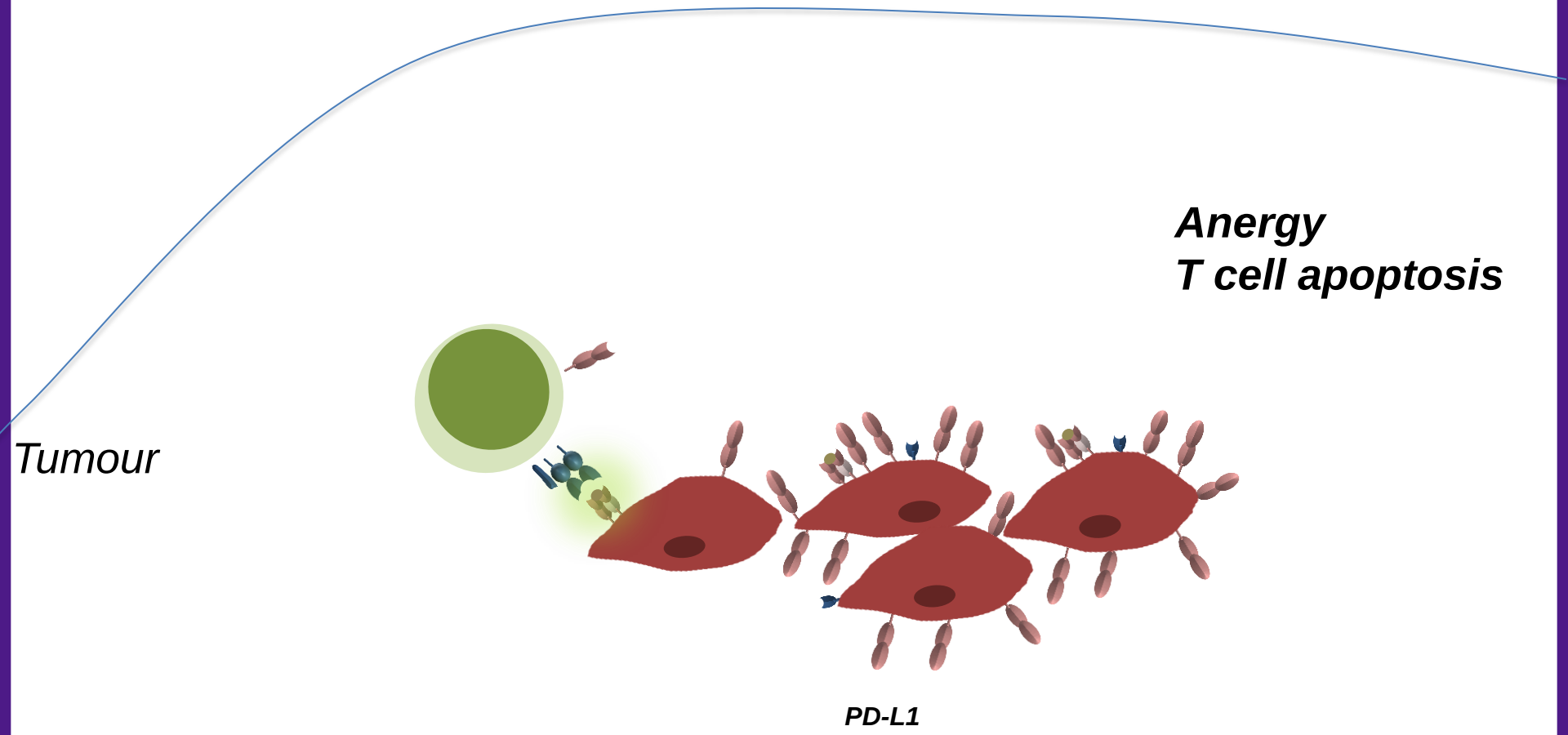




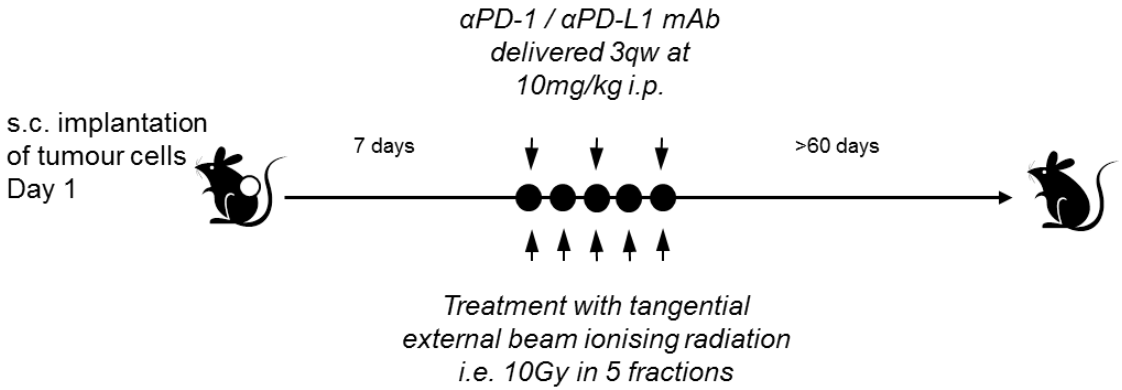


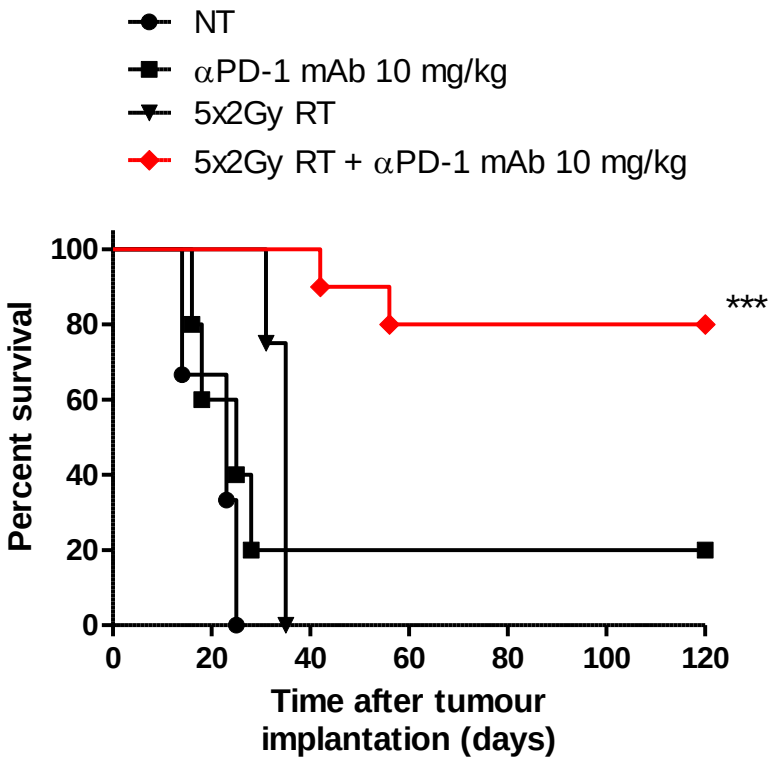


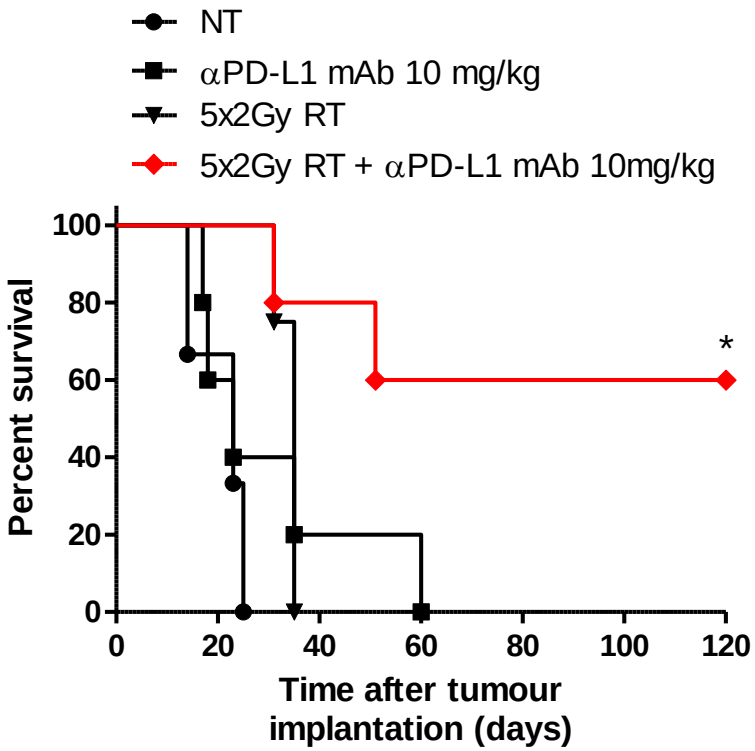
Adaptive resistance hypothesis



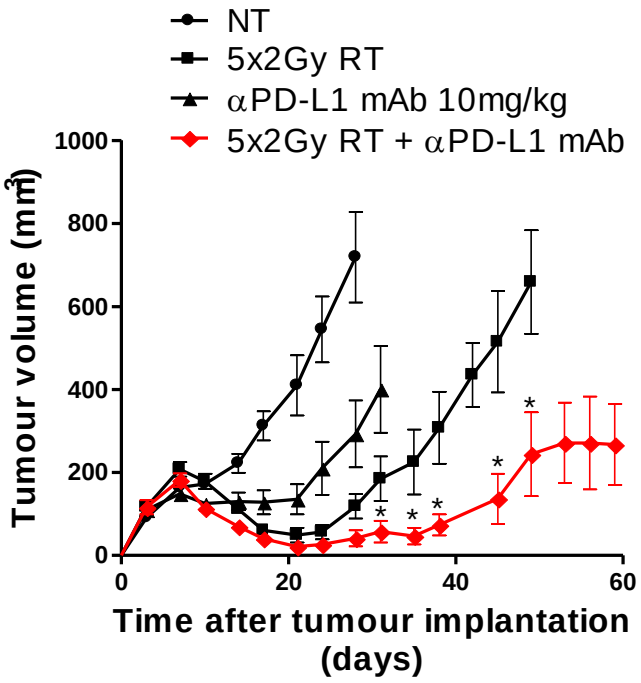
Targeted blockade of PD-1/PD-L1 axis improves survival when combined with radiotherapy



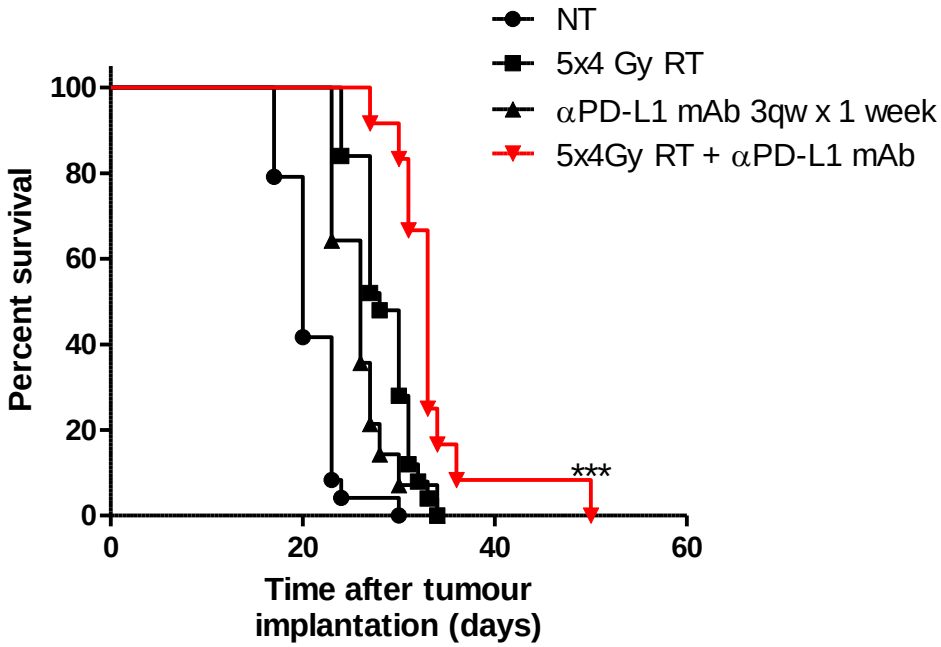




Blockade of PD-1 or PD-L1 improves survival when combined with radiotherapy

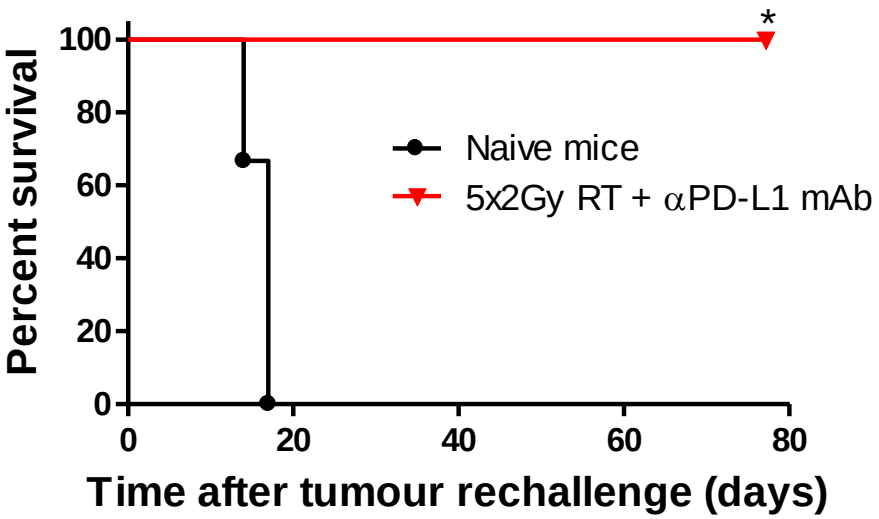


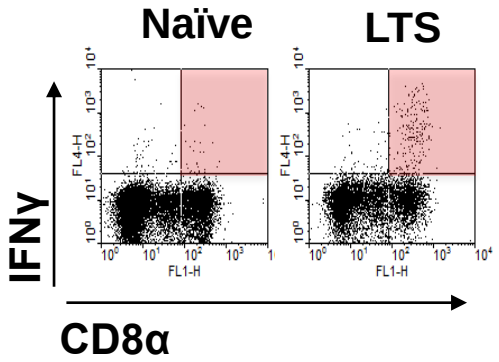
4434 model
Isolated from BRafV600E p16$^{-/-}$ mice

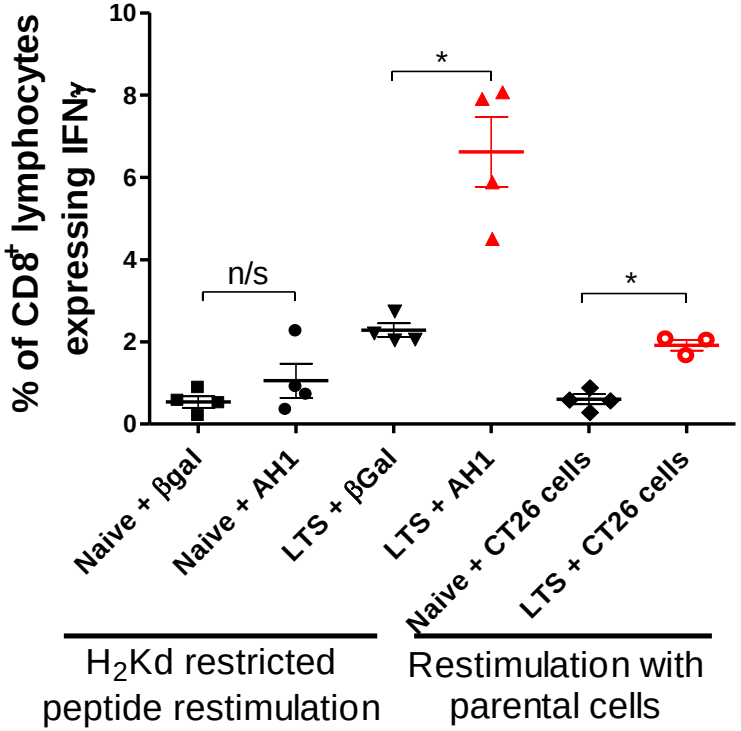


4T1 model
Triple negative breast adenocarcinoma

Complete responders following treatment with RT and αPD-1 / αPD-L1 mAb are protected by a memory immune response which prevents disease recurrence

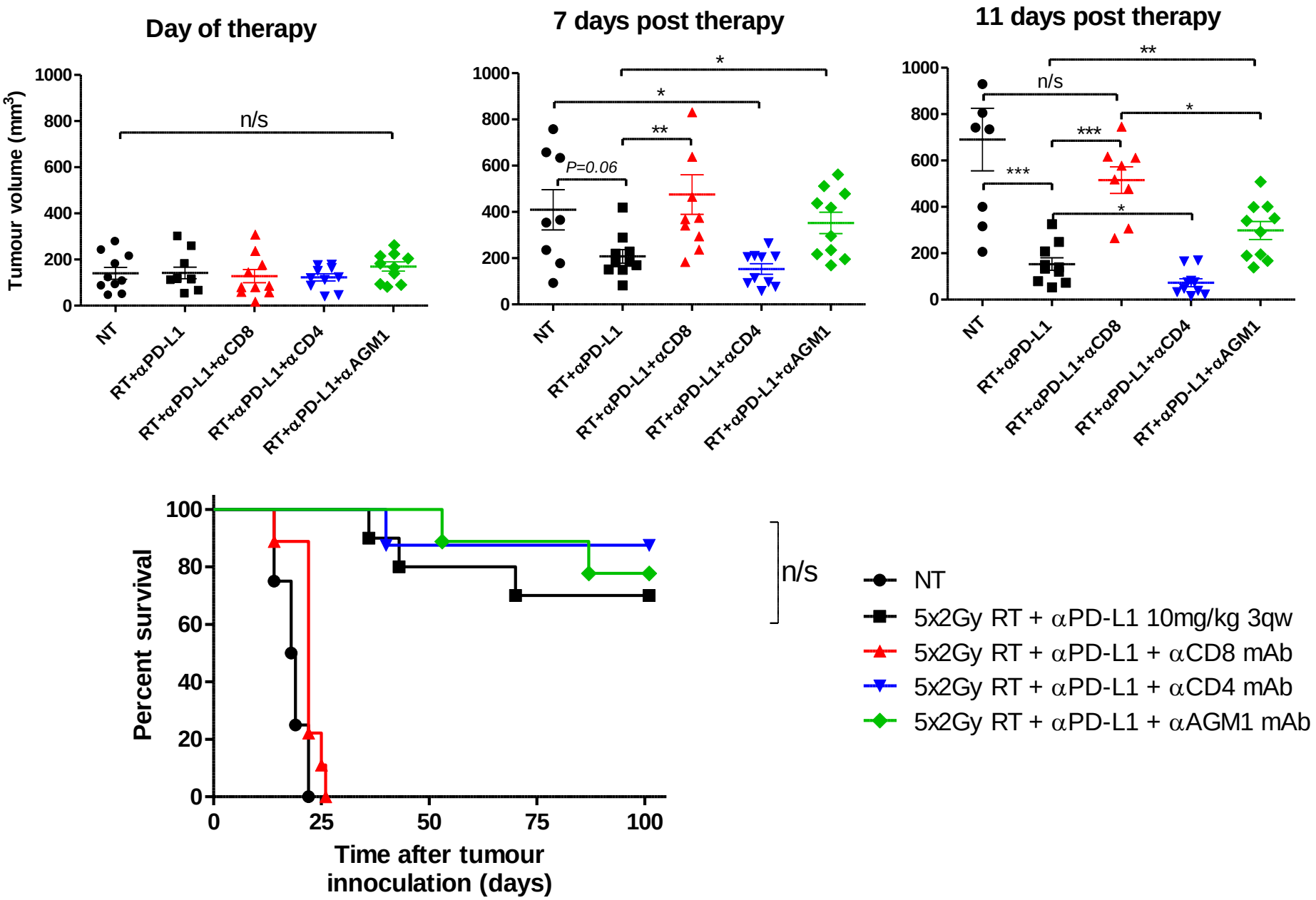




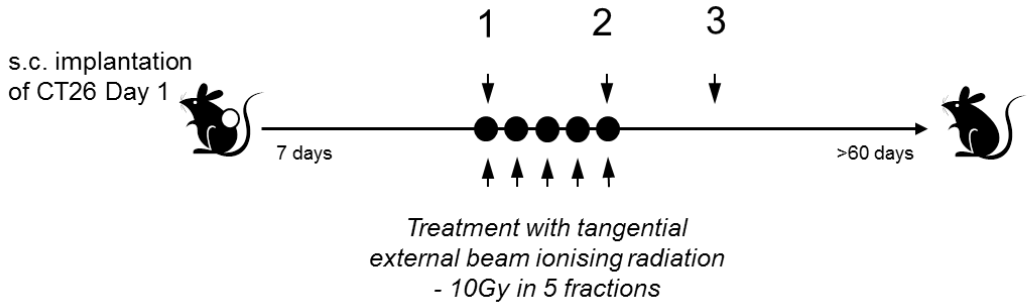


CT26 model

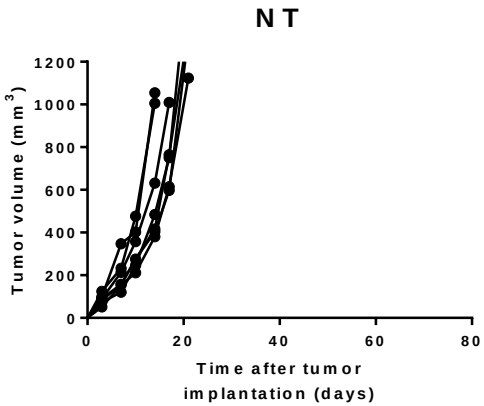
Efficacy of RT / αPD-L1 mAb combination is CD8+ T cell dependent

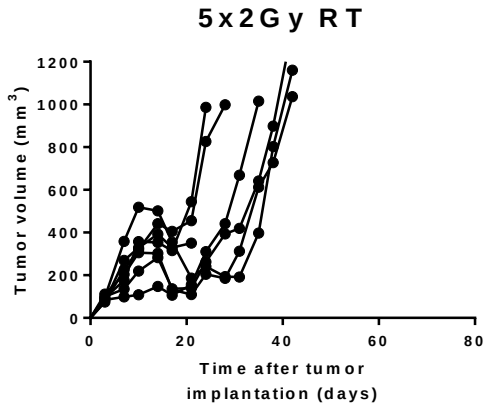


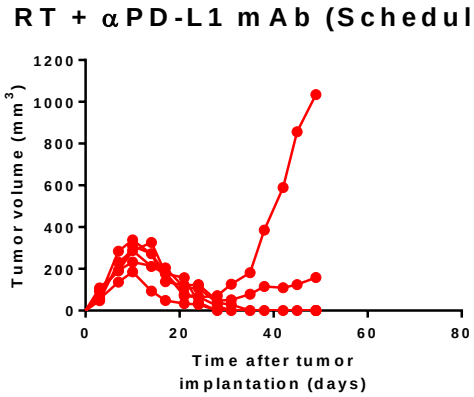
Efficacy of RT and PD-L1 blockade is *dependent on concurrent dosing*

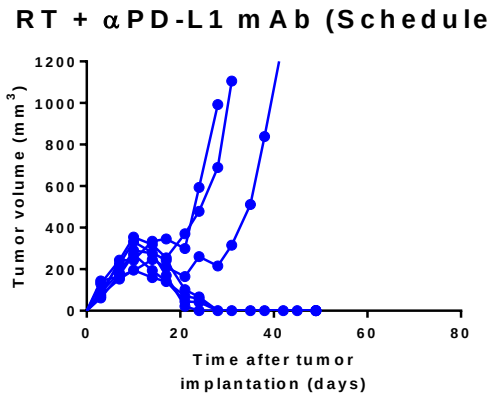


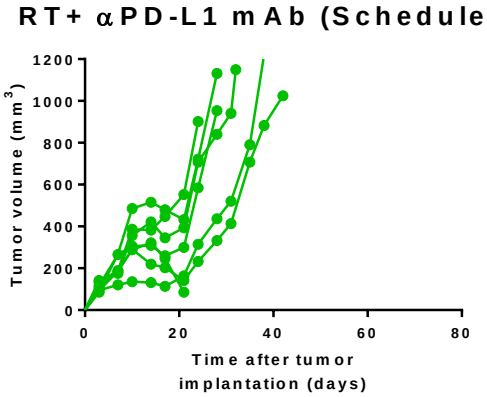
1. *αPD-L1 mAb delivered 3qw at 10mg/kg i.p. starting on day 1 of RT*
2. *αPD-L1 mAb delivered 3qw at 10mg/kg i.p. starting on day 5 of RT*
3. *αPD-L1 mAb delivered 3qw at 10mg/kg i.p. starting 7 days after RT cycle begins*











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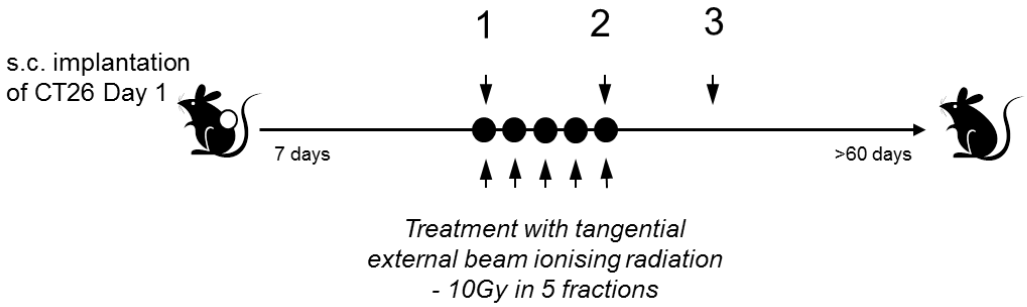

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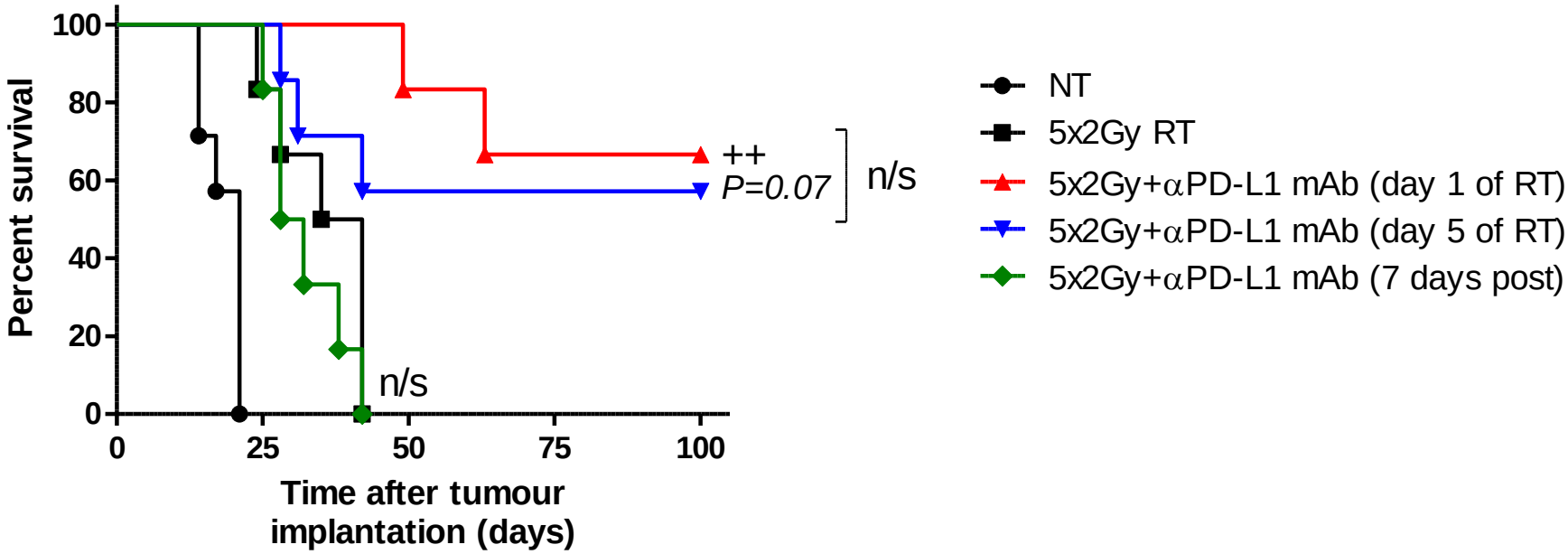
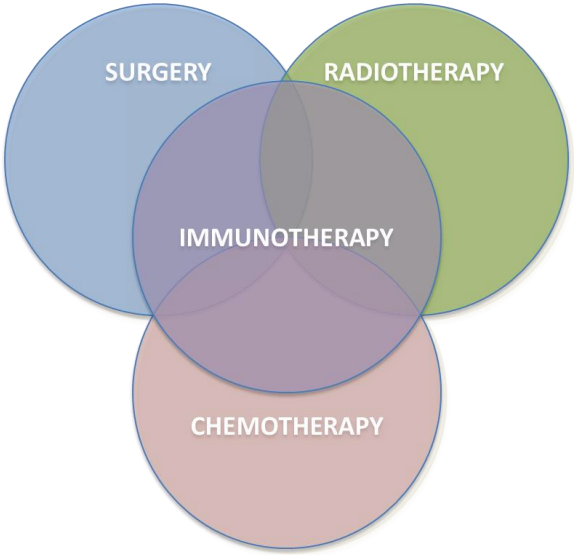


Summary

- Radiotherapy leads to upregulation of PD-L1 expression on cancer cells through $CD8^+$ T cell-issued IFNγ.
  - This represents an adaptive resistance mechanism protecting tumour cells against immune -mediated killing.
  - Blockade of the PD1/PD-L1 axis can enhance the efficacy of radiotherapy.

- The efficacy of *radiotherapy* may be enhanced through combination with *immunotherapy.*

  Also: The efficacy of *immunotherapy* may be enhanced through combination with *radiotherapy.*



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- **Conor McKenna**
- **Sherrie Jones**
- **Charlotte Pollard**
- Eleanor Cheadle
- Jamie Honeychurch
- Grace Lipowska-Bhalla

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