

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

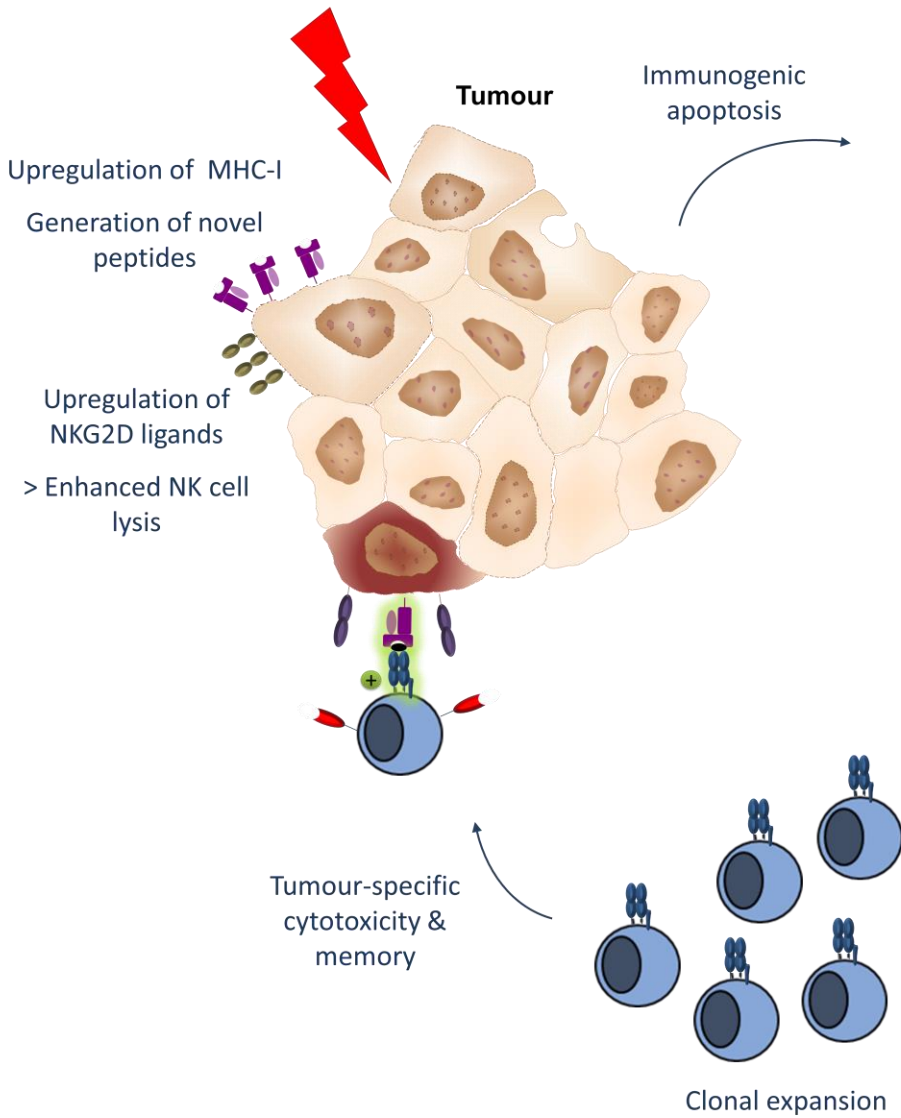
The anti-tumour immune response generated by radiation therapy may be limited by tumour cell adaptive resistance and can be circumvented by PD-L1 blockade

Simon Dovedi

**University of Manchester
Manchester Cancer Research Centre**

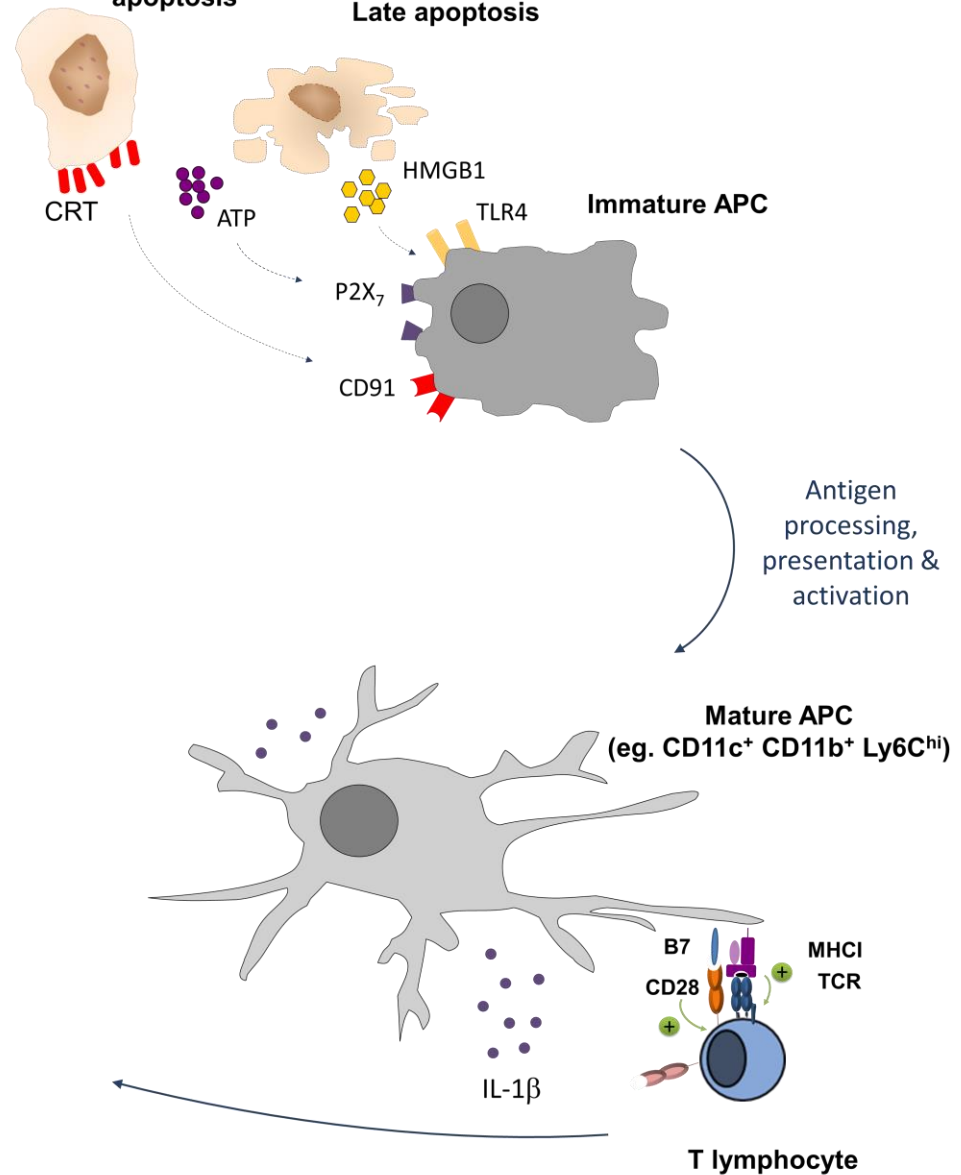
The Immunogenicity of Radiotherapy

Radiation

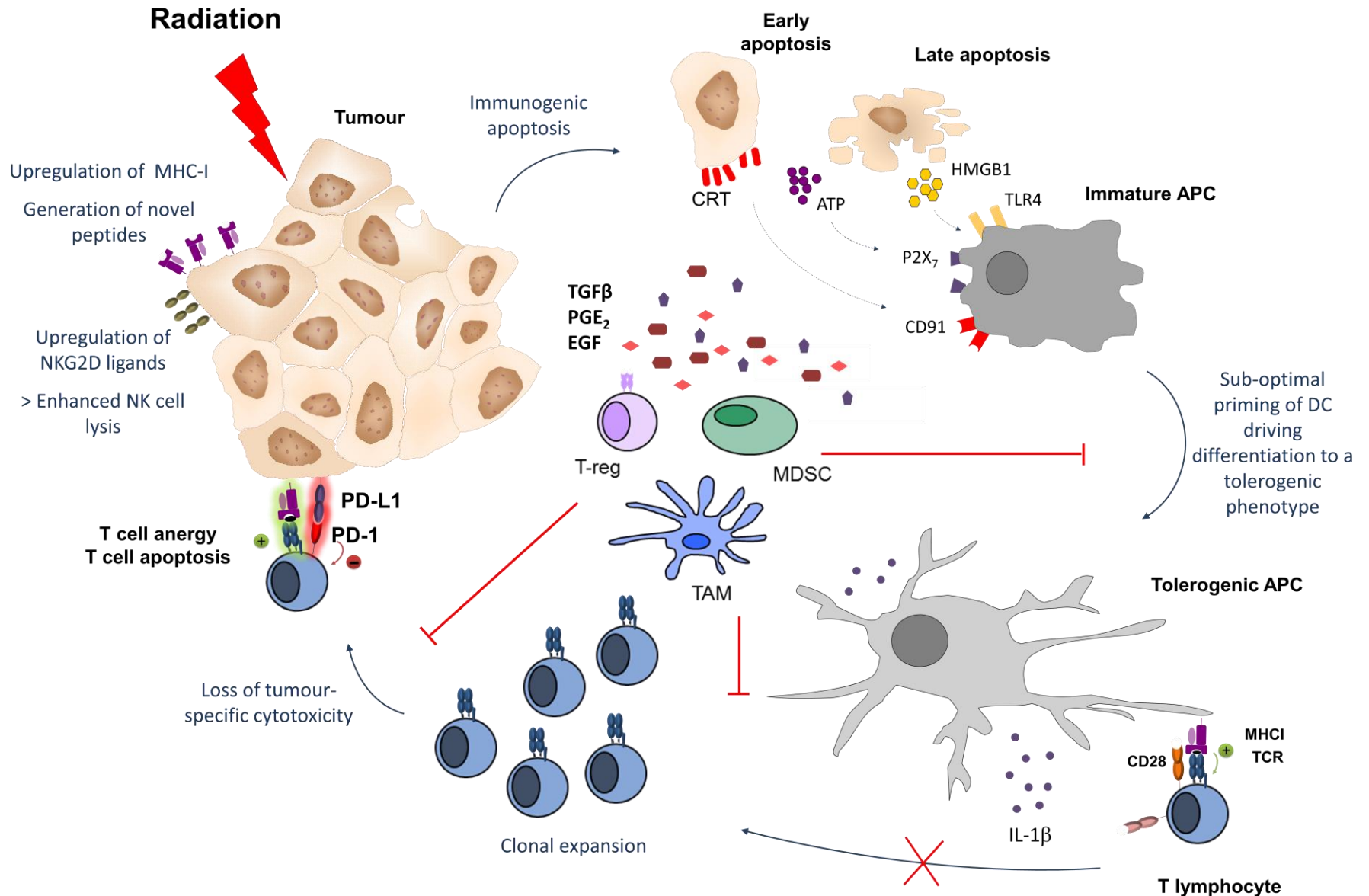


Early apoptosis

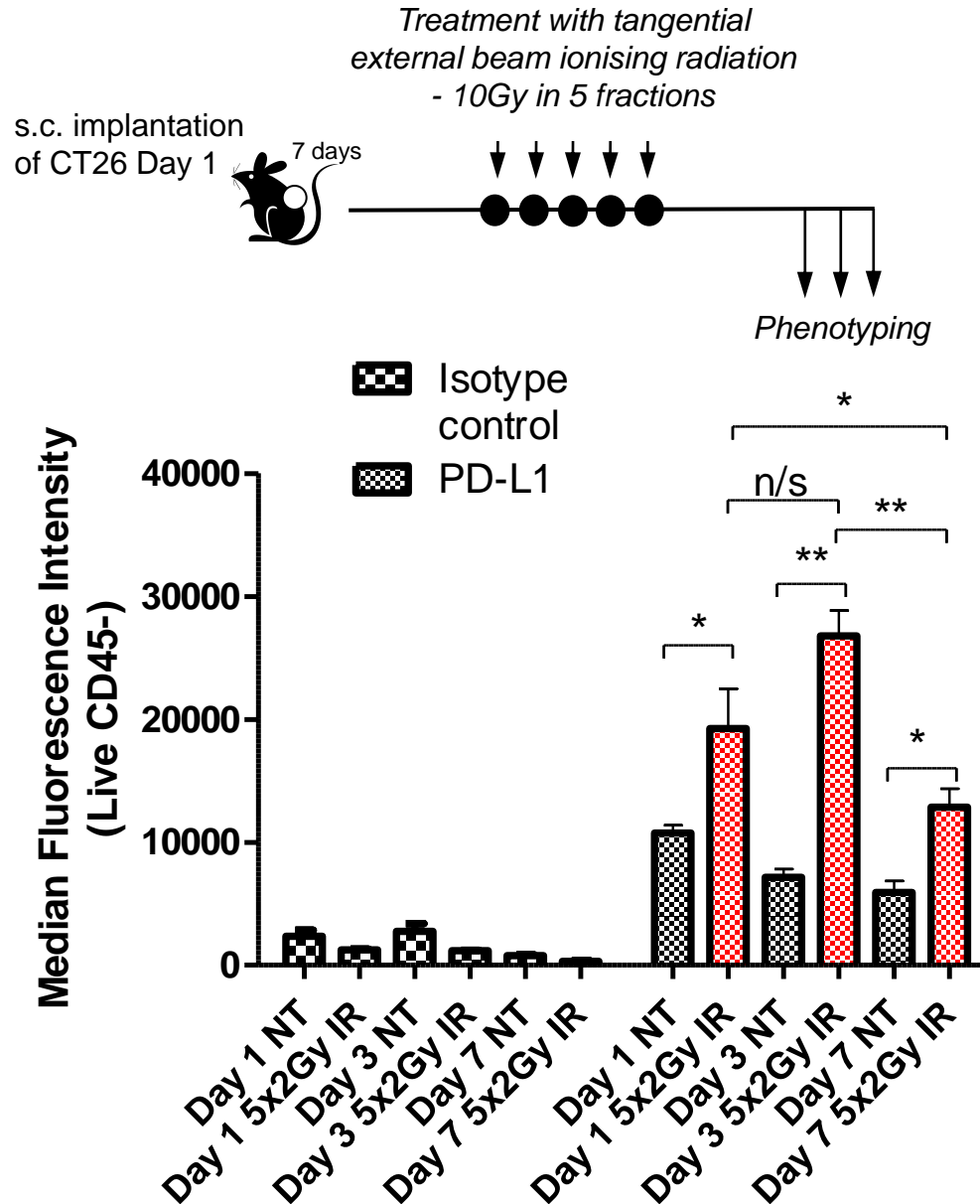
Late apoptosis



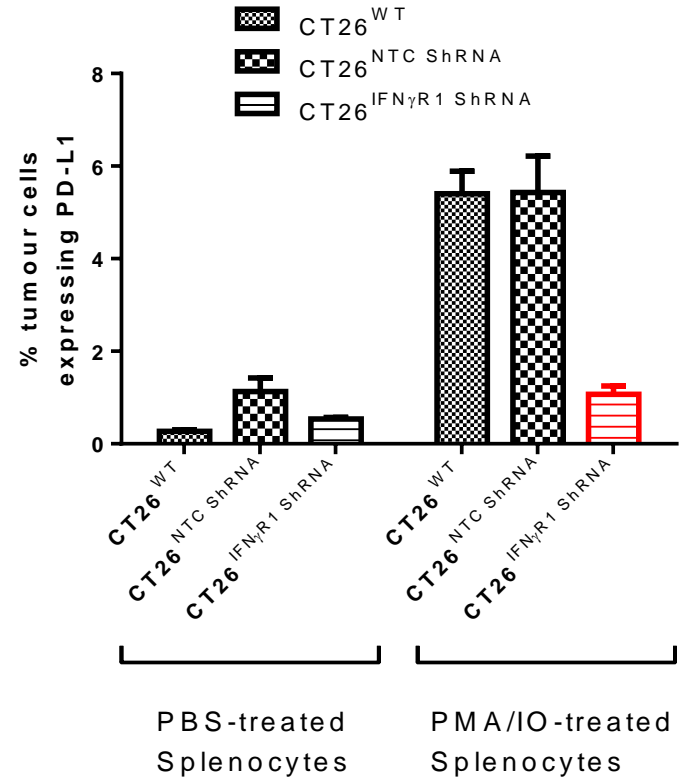
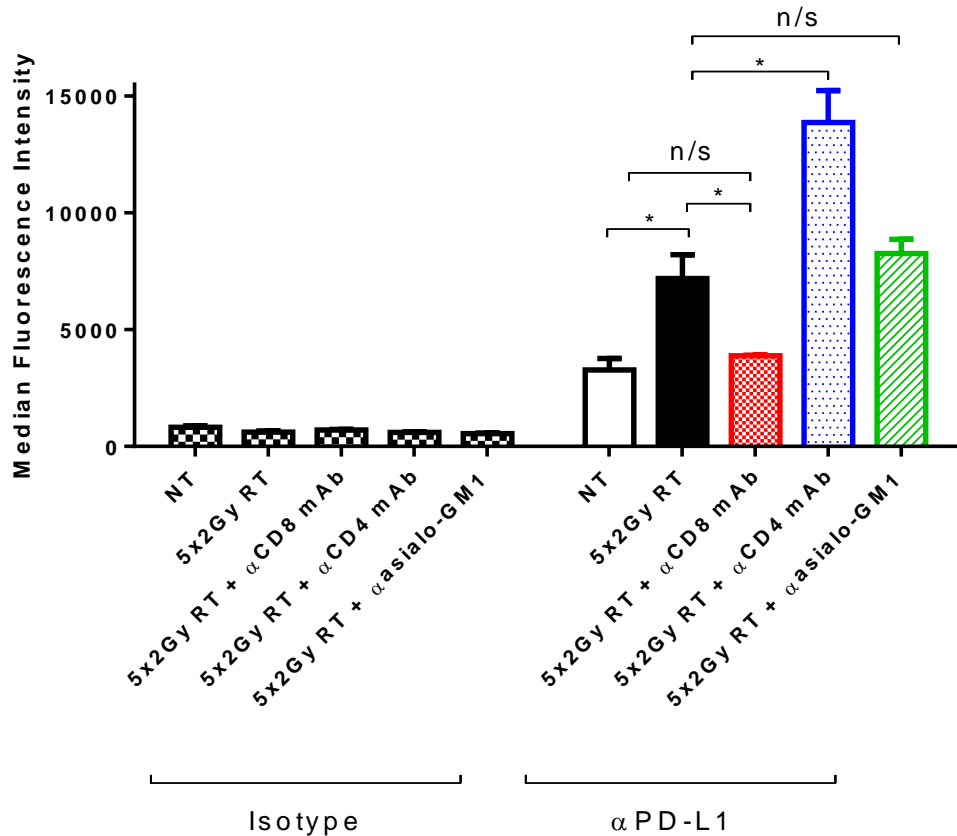
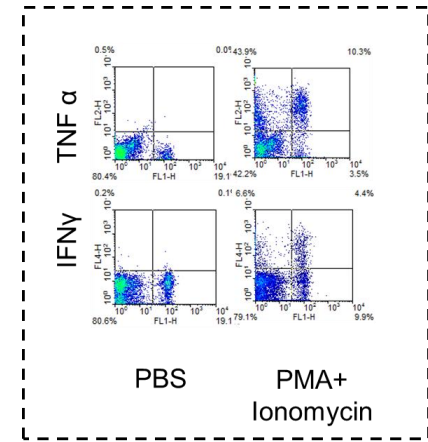
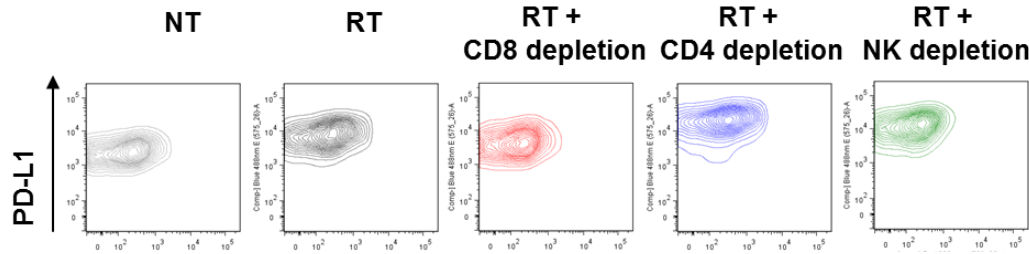
Solid tumours generate an environment that suppresses anti-tumour immune responses



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

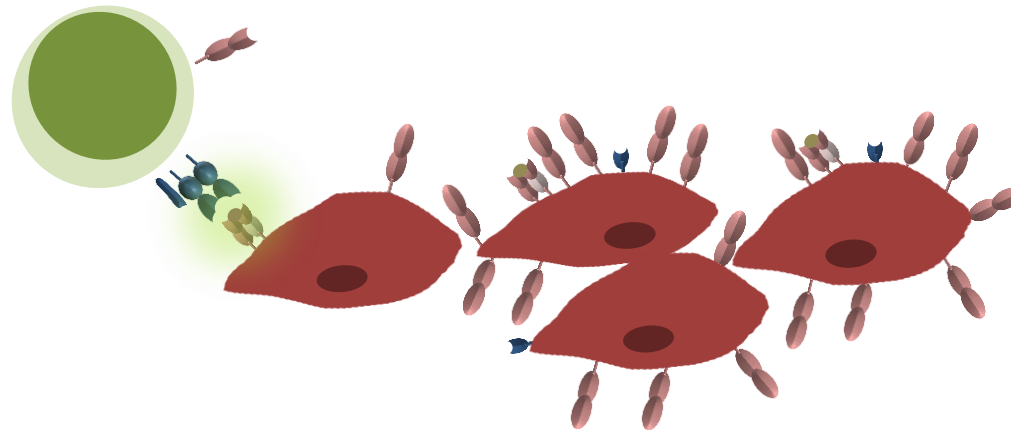


Ionizing radiation leads to increased tumour cell expression of PD-L1 *in vivo* which is dependent on CD8⁺ T cell production of IFN γ



Adaptive resistance hypothesis

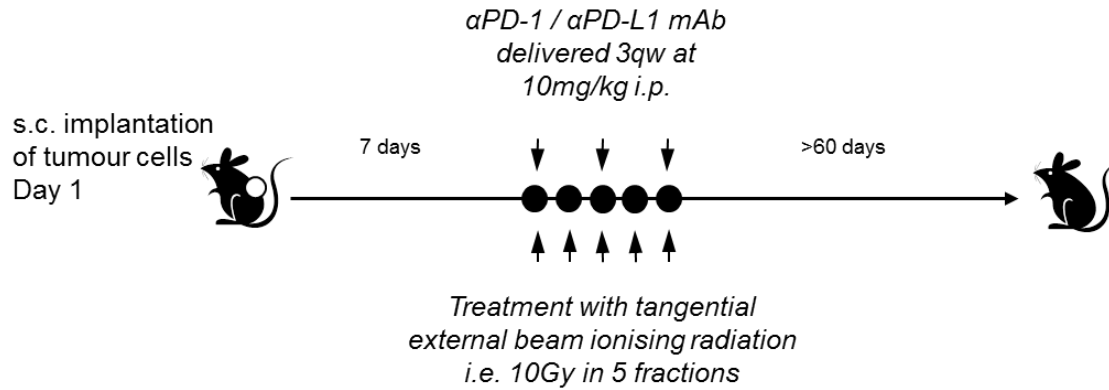
Tumour



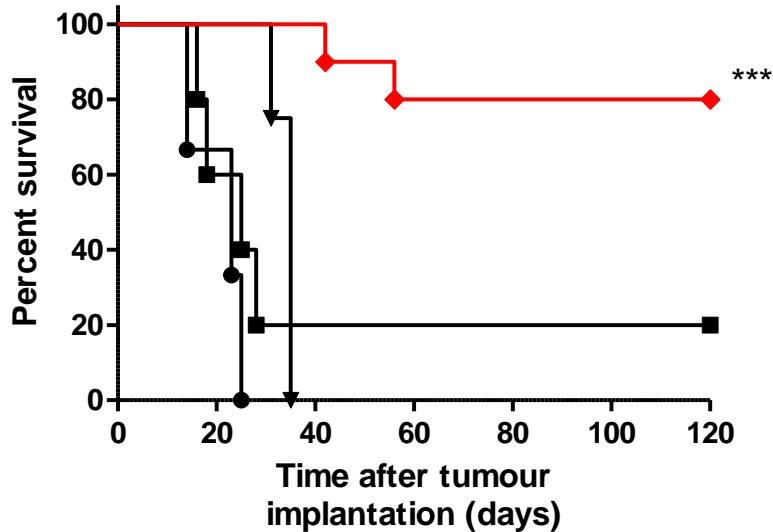
*Anergy
T cell apoptosis*

PD-L1

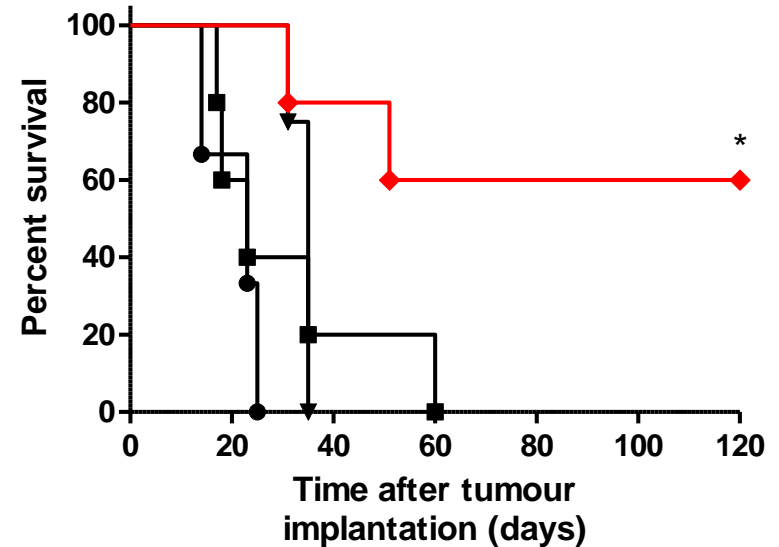
Targeted blockade of PD-1/PD-L1 axis improves survival when combined with radiotherapy



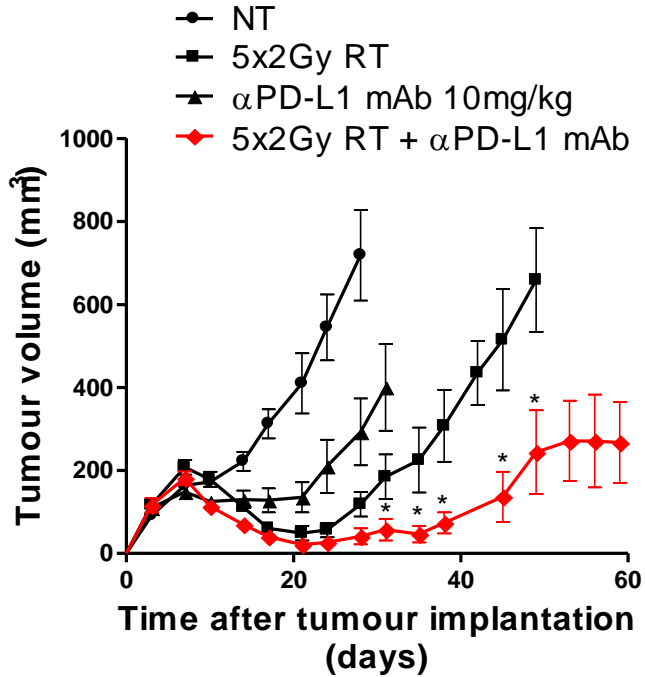
- NT
- α PD-1 mAb 10 mg/kg
- ▼ 5x2Gy RT
- ◆ 5x2Gy RT + α PD-1 mAb 10 mg/kg



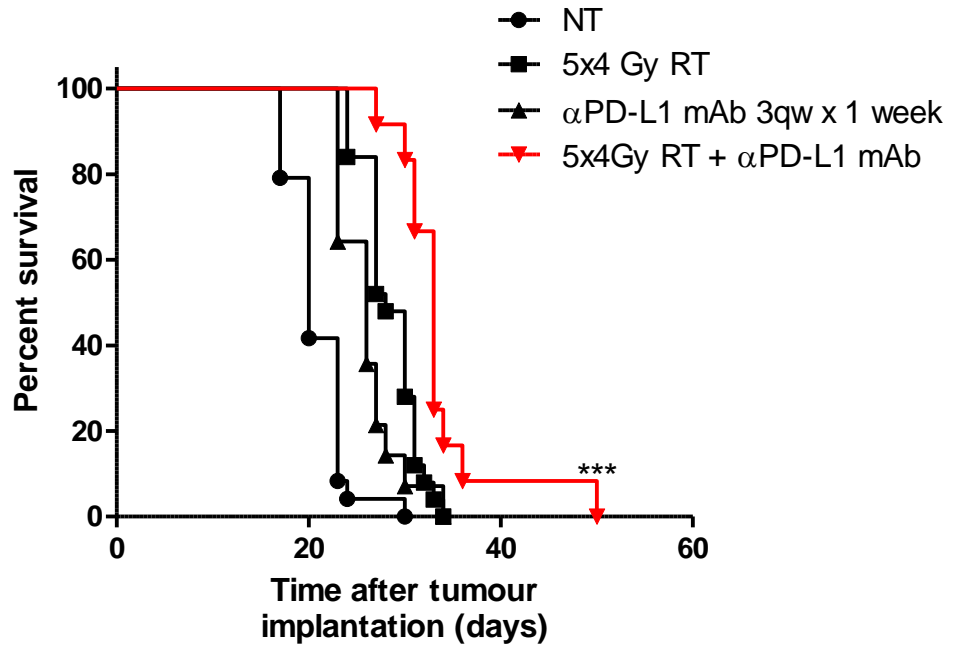
- NT
- α PD-L1 mAb 10 mg/kg
- ▼ 5x2Gy RT
- ◆ 5x2Gy RT + α PD-L1 mAb 10mg/kg



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

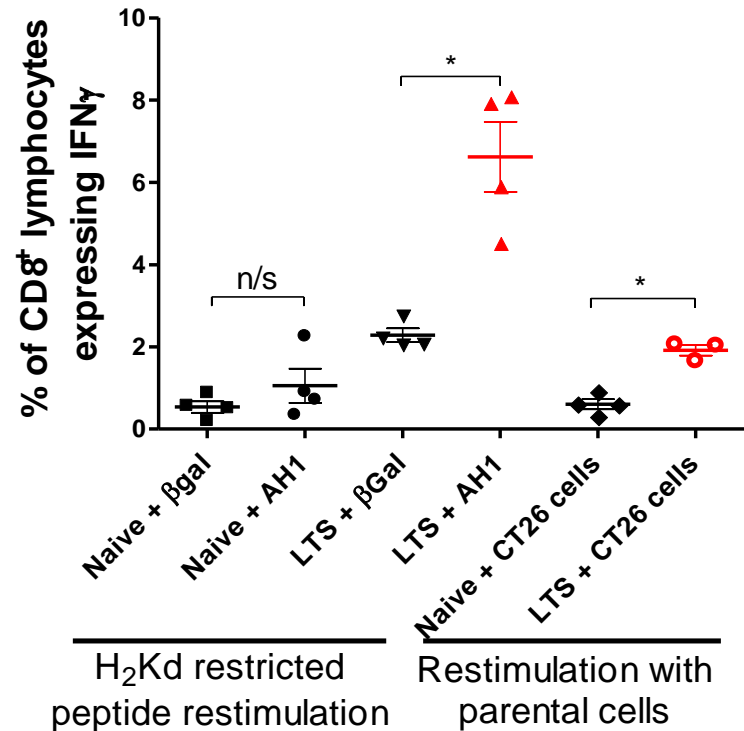
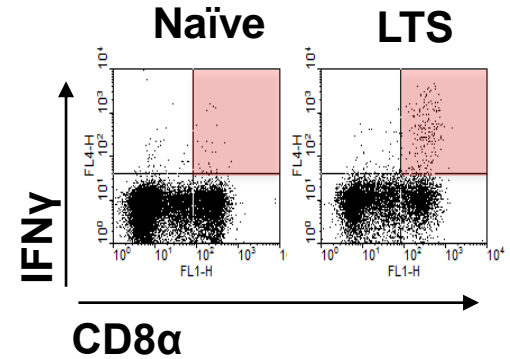
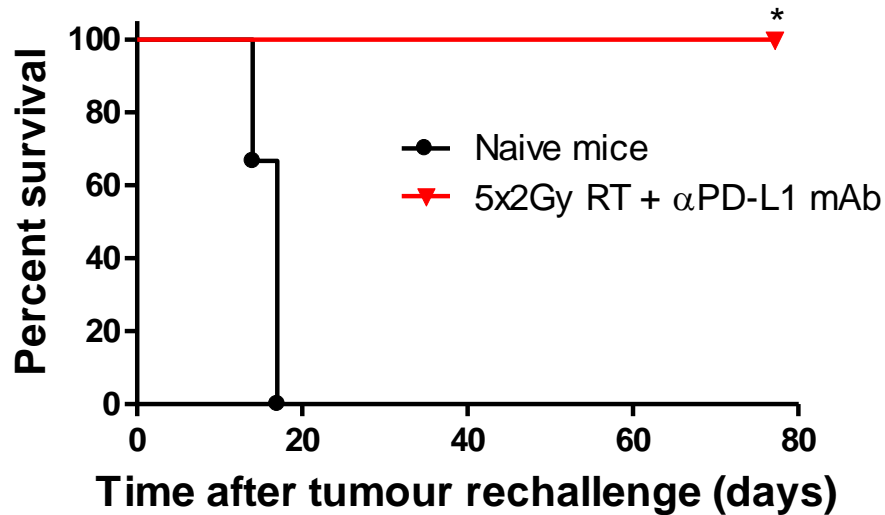


4434 model
Isolated from BRafV600E p16^{-/-} mice



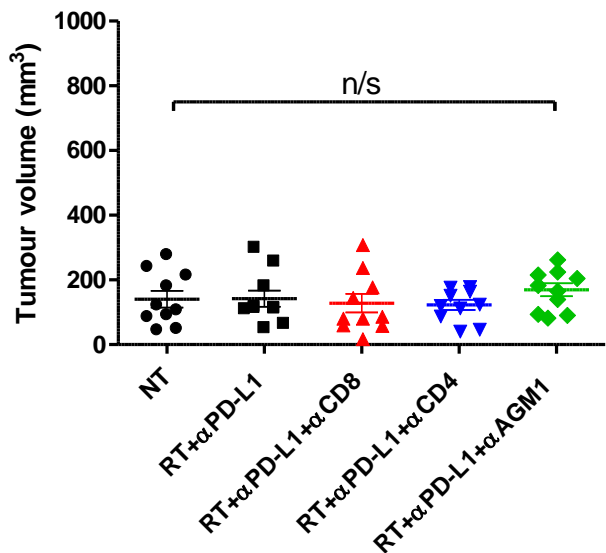
4T1 model
Triple negative breast adenocarcinoma

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

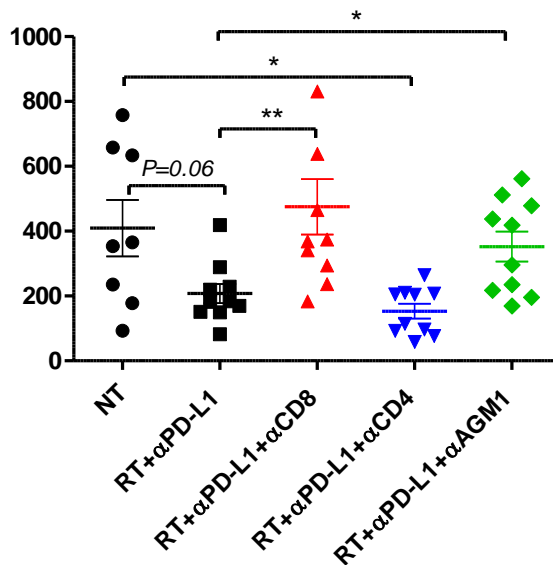


Efficacy of RT / α PD-L1 mAb combination is CD8⁺ T cell dependent

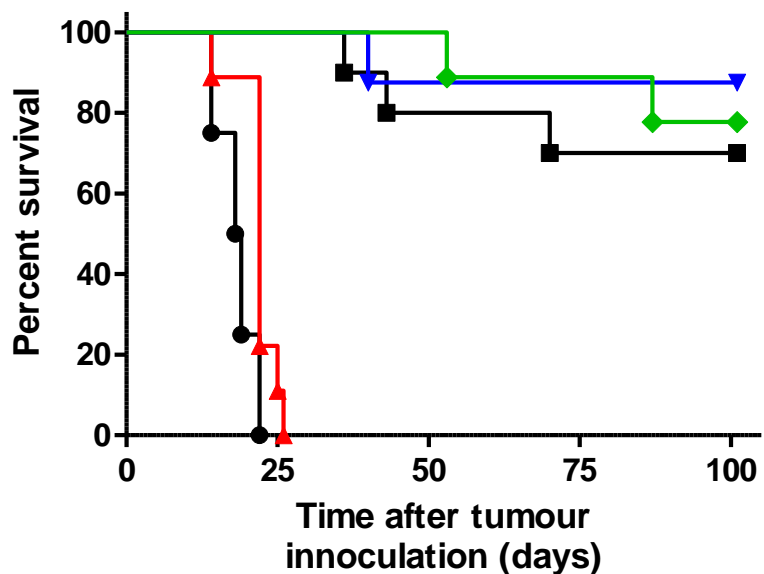
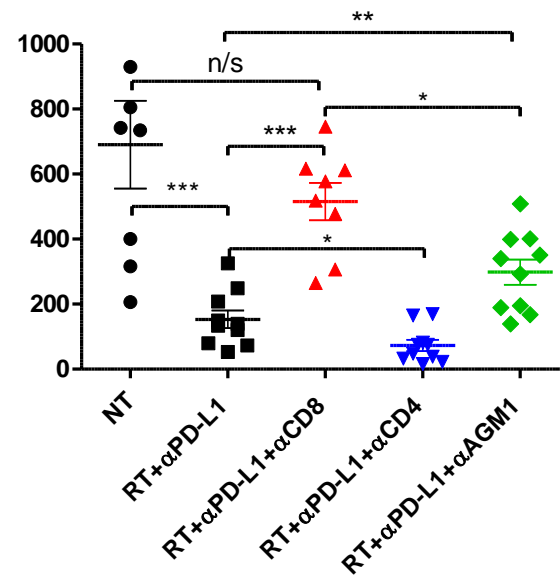
Day of therapy



7 days post therapy



11 days post therapy

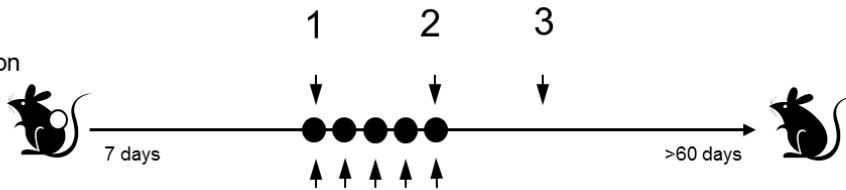


n/s

- NT
- 5x2Gy RT + α PD-L1 10mg/kg 3qw
- ▲ 5x2Gy RT + α PD-L1 + α CD8 mAb
- ▼ 5x2Gy RT + α PD-L1 + α CD4 mAb
- ◆ 5x2Gy RT + α PD-L1 + α AGM1 mAb

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

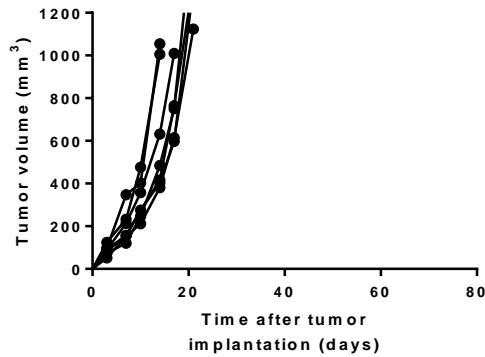
s.c. implantation of CT26 Day 1



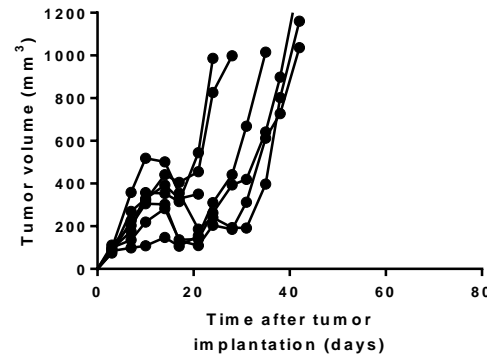
Treatment with tangential external beam ionising radiation - 10Gy in 5 fractions

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

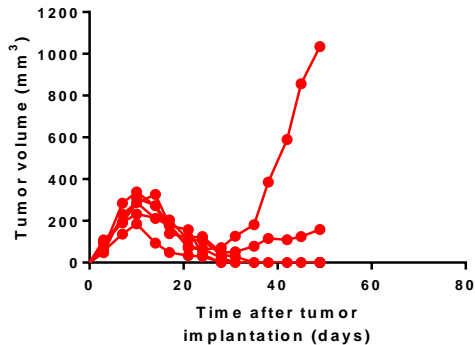
NT



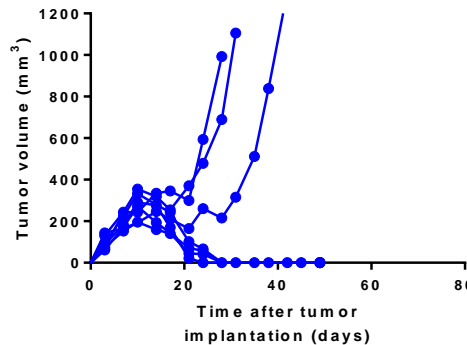
5x2Gy RT



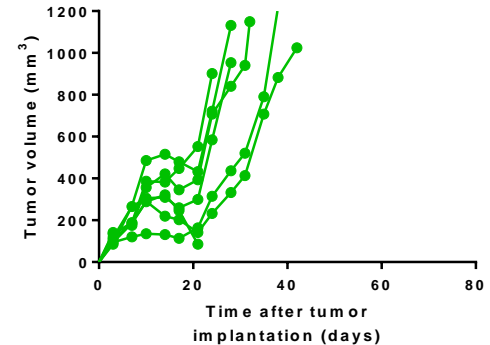
RT + α PD-L1 m Ab (Schedule 1)



RT + α PD-L1 m Ab (Schedule 2)

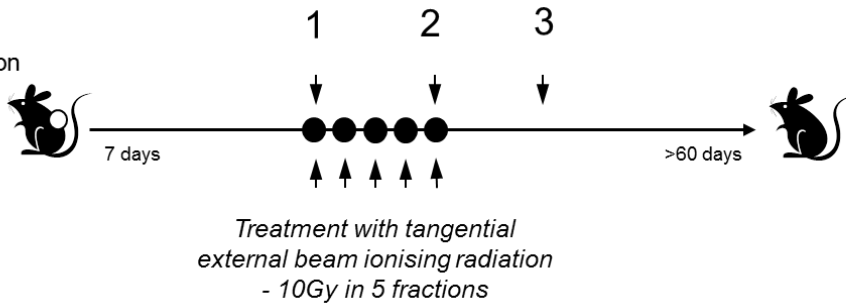


RT + α PD-L1 m Ab (Schedule 3)

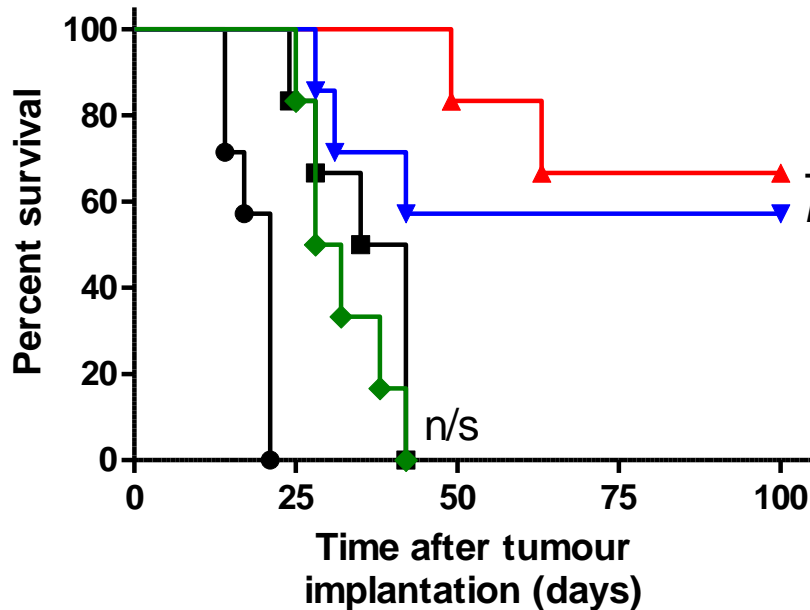


Efficacy of RT and PD-L1 blockade is *dependent on concurrent dosing*

s.c. implantation of CT26 Day 1



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

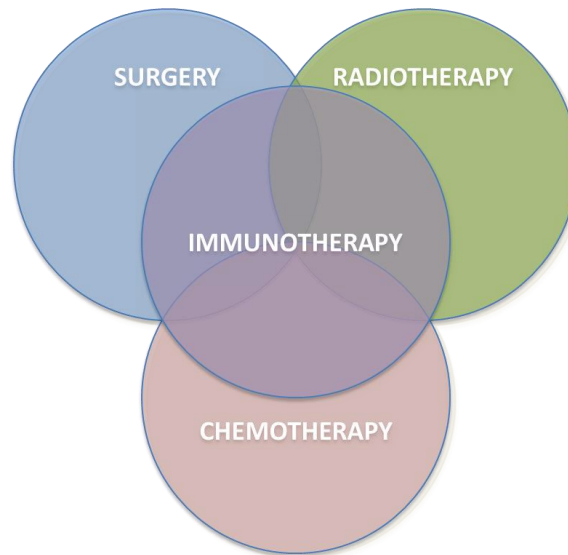


- NT
- 5x2Gy RT
- ▲ 5x2Gy+ α PD-L1 mAb (day 1 of RT)
- ▼ 5x2Gy+ α PD-L1 mAb (day 5 of RT)
- ◆ 5x2Gy+ α PD-L1 mAb (7 days post)

Summary

- ❖ Radiotherapy leads to upregulation of PD-L1 expression on cancer cells through CD8⁺ T cell-issued IFN γ .
 - ❖ 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.



University of Manchester

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- **Sherrie Jones**
- **Charlotte Pollard**
- Eleanor Cheadle
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- Grace Lipowska-Bhalla

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