

Non linear mixed effects modelling of tumour interactions with the adaptive immune response during Radiotherapy in combination with Anti-PDL1 or Olaparib.

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Introduction & Aims

- Clinical trials attempting to incorporate radiotherapy (RT) with immune checkpoint inhibitors such as anti-PD-L1 (ICI) or DNA Damage Response agent inhibitors such as olaparib (PARPi) are currently ongoing [1].
- The optimisation of dosage regimen in the clinic, can be aided by preclinical experiments and formulation of predictive mathematical models [2].
- The aims of this research are to develop a robust mathematical model of tumour:immune interactions from preclinical experiments.

Methods

- Syngeneic allograft experiments using the murine colorectal cancer cell line - MC38. These were produced to confirm the effect of RT in combination with ICI or PARPi.
- Mice were randomised 7 days after sub-cutaneous injection of 10^7 MC38 cells. 2Gy of RT was given QD x 5 from day 7 in combination with ICI biweekly x 3 (10mg/kg) and/or PARPi QD x 21 (100mg/kg).
- The Model (Fig 1) was fitted to all datasets simultaneously using FOCE-SAEM. The Inter Individual Variability (IIV) is assumed to be log-normally distributed. Visual Predictive Checks (VPCS) were produced in R version 3.6.3.

Results

- The model was successfully fitted to MC38 syngeneic model experiments (Table 1). Results suggest a 93% reduction in T cell exhaustion with RT/ICI, and little benefit when incorporating PARPi, due to near maximal RT/IO bitherapy effect. VPCs confirmed a successful model validation (Figure 2).

Figure 1) Schematic of the mathematical model fitted to MC38 syngeneic model data. Fitted parameters are in red.

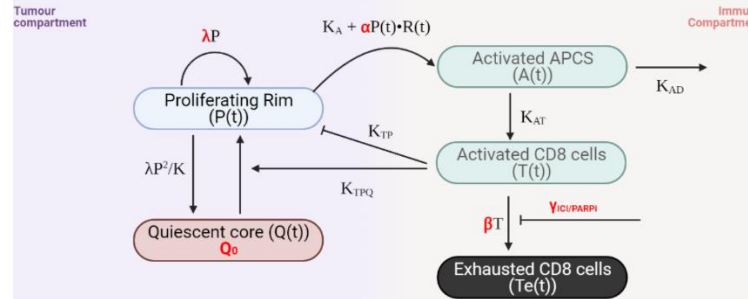
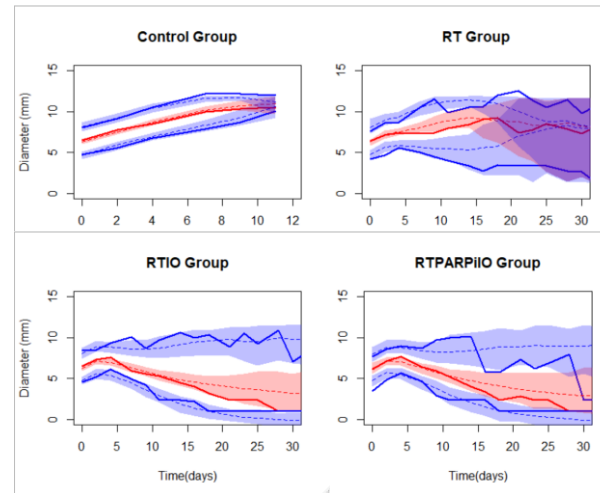


Figure 2) Visual Predictive checks confirm successful model validation and highlight the redundancy of PARPi when combined With RT/ICI.



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Table 1) Model fit output for MC38 syngeneic model data

Parameter	Value (RSE)	IIV (RSE)
Q_0	3.83 (2)	0.429 (18)
λ	0.239 (3)	0.064 (17)
α	3.06 (2)	-
β	0.278 (23)	1.25 (20)
γ_{PARPi}	2.03 (46)	-
γ_{ICI}	11.9 (32)	-
σ	0.506	-

Conclusions and future perspectives

- The model successfully describes T cell infiltration and exhaustion into the tumour during RT/ICI. However, the current model doesn't consist of negative feedback loops which are pivotal to understand relapse in different therapies [2].
- Additional biomarkers from PD studies will now be assessed to see if there are cellular markers which can predict response to RT/ICI/PARPi.
- These biomarkers will be incorporated into the model next.