

Optimising Radiotherapy–Immunotherapy Combinations to Improve Glioblastoma Treatment via Mathematical Modelling

Daniel Golshmid | Supervised by: Dr. David Morselli and Dr. Carina Dunlop

Department of Mathematics, University College London, London, UK

Introduction

Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumour, with a dismal median survival of 12–15 months. It remains resistant to practically all current therapies, due to its dynamic tumour microenvironment (TME) and, particularly, the relapse-driving capacity of glioma stem cells (GSCs).

Radiotherapy (RT), the main treatment method of GBM, involves the fractionated administration of ionizing radiation (IR) aimed precisely at the tumour. However, due to GSCs' radioresistance, tumours almost inevitably recur.

Immunotherapies (IT), such as anti-PD-L1, are an emerging cornerstone of GBM treatment. Anti-PD-L1 prevents the suppression of cytotoxic T-cell antitumour activity by the PD-L1 protein. Since PD-L1 is upregulated following RT, there's a strong rationale for combining RT and anti-PD-L1 in GBM treatment.

The aim of this work is to develop a comprehensive mathematical model of the GBM TME to understand how radiotherapy–immunotherapy combinations could be optimised to maximise synergistic benefit and improve patient outcomes.

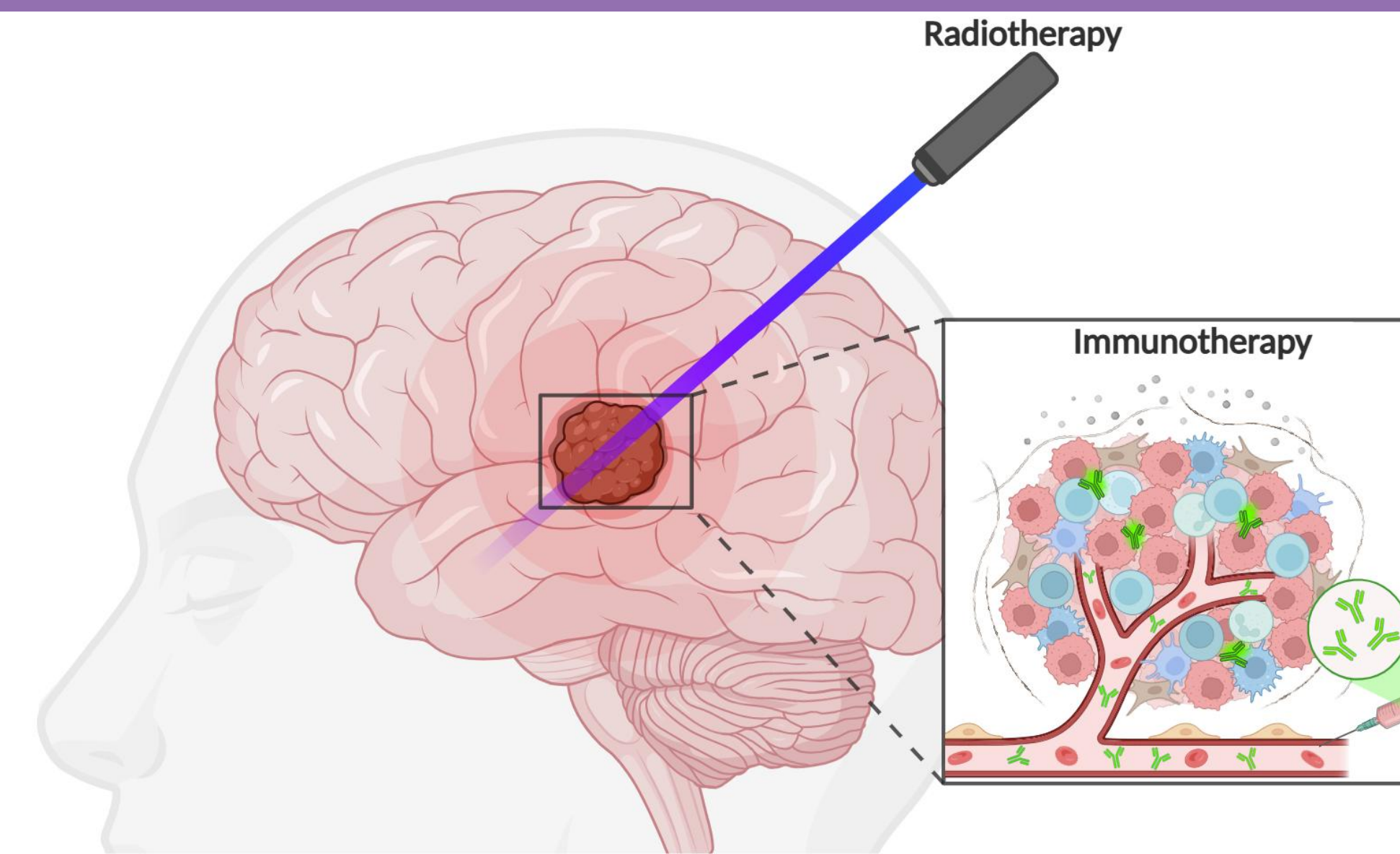


Figure 1: Combined RT-IT for GBM targeting. RT activates antitumour immunity while IT (anti-PD-L1) prevents immune evasion of cancer cells.

Mathematical Model

The developed model is a non-spatial ODE model describing the dynamic interplay among tumour cells, immune cells, and cytokines within the GBM TME. Equation for differentiated tumour cells is given as an example.

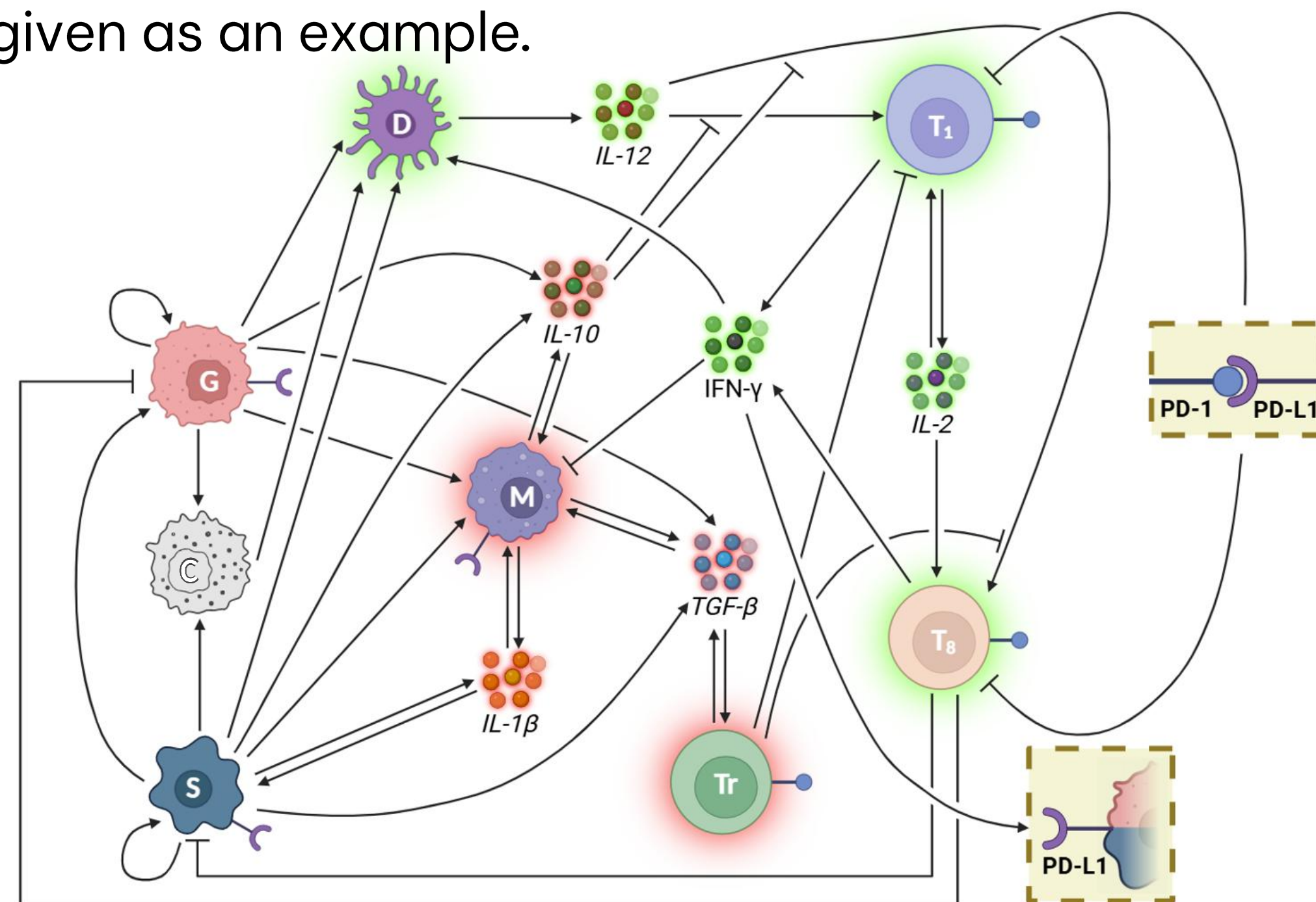


Figure 2: Tumour immune microenvironment interactions.

G: differentiated cancer cells; S: glioma stem cells; C: radiation-damaged cancer cells; D: dendritic cells; M: myeloid-derived suppressor cells and M2 macrophages; T1: CD4+ Th1 cells; T8: CD8+ T cells; Tr: T regulatory cells. Green/red halo indicates tumour-suppressive/promoting components.

$$\frac{dG}{dt} = \underbrace{\lambda_G G \left(1 - \frac{S+G}{K_{SG}}\right)}_{\text{Proliferation of G}} + \underbrace{\lambda_S S (1 - p_{S0} - \varepsilon_p R(I, t)) \left(1 - \frac{S+G}{K_{SG}}\right)}_{\text{Asymmetric differentiation from S}} - \underbrace{\eta_{GT_8} T_8 \frac{G}{K_G + G}}_{\text{Cytotoxic T-cell killing}} - \underbrace{\mu_G(I, t) G}_{\text{Radiation damage}} - \underbrace{d_G G}_{\text{Natural death}}$$

Model Simulation

As a proof of concept, tumour growth was simulated under RT and IT alone and in combination, using a representative schedule, to assess whether the two therapies act synergistically.

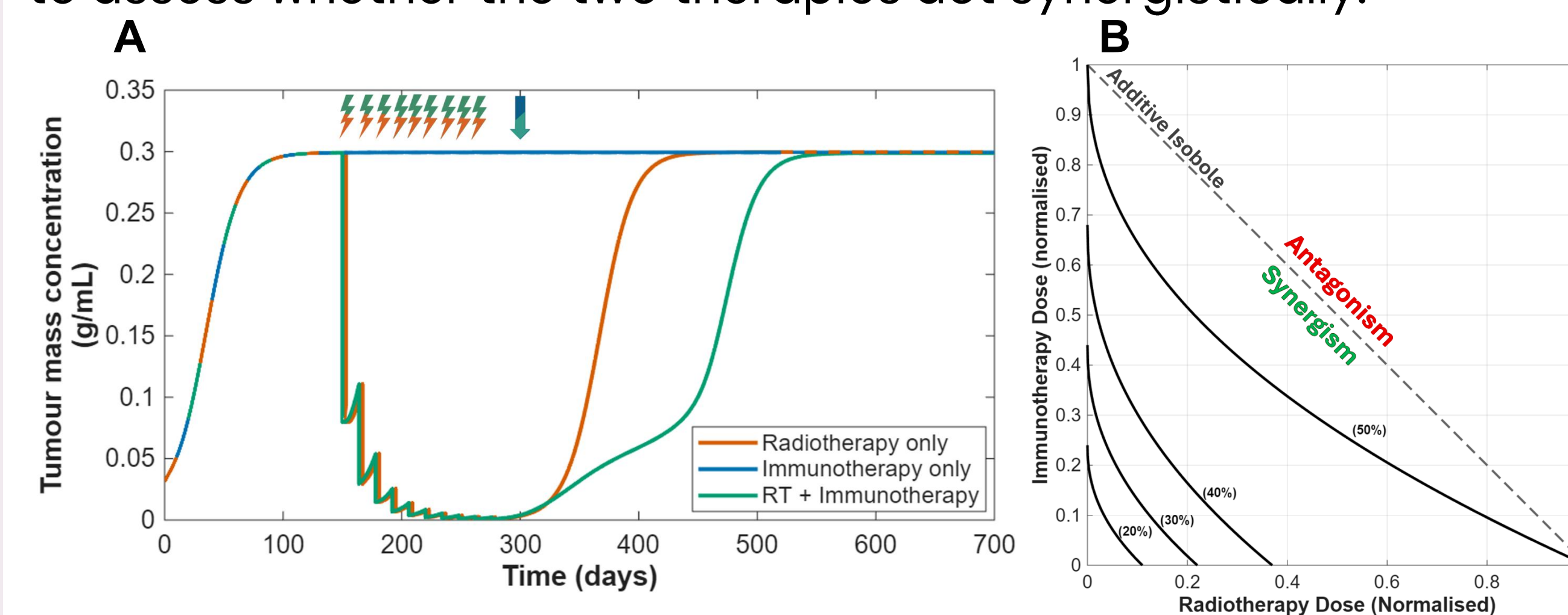


Figure 3: RT and anti-PD-L1 act synergistically against GBM. A: Tumour mass concentration over time under RT alone, IT alone, and combined RT-IT (10 fractions of 5 Gy, 14 days apart; anti-PD-L1 at 300 ng/mL). B: Isobologram showing RT-IT combinations required to achieve 20–50% tumour reduction; curves below the additive isobole indicate synergism.

Conclusions

Some scheduling strategies show the potential to **significantly improve outcomes** over current GBM treatment, offering candidate regimens for prioritisation in future clinical trial design. This model can be applied in clinical and research settings to **accommodate patient-specific cases** and scenarios and provide information to support treatment-planning decisions.

RT-IT Optimisation

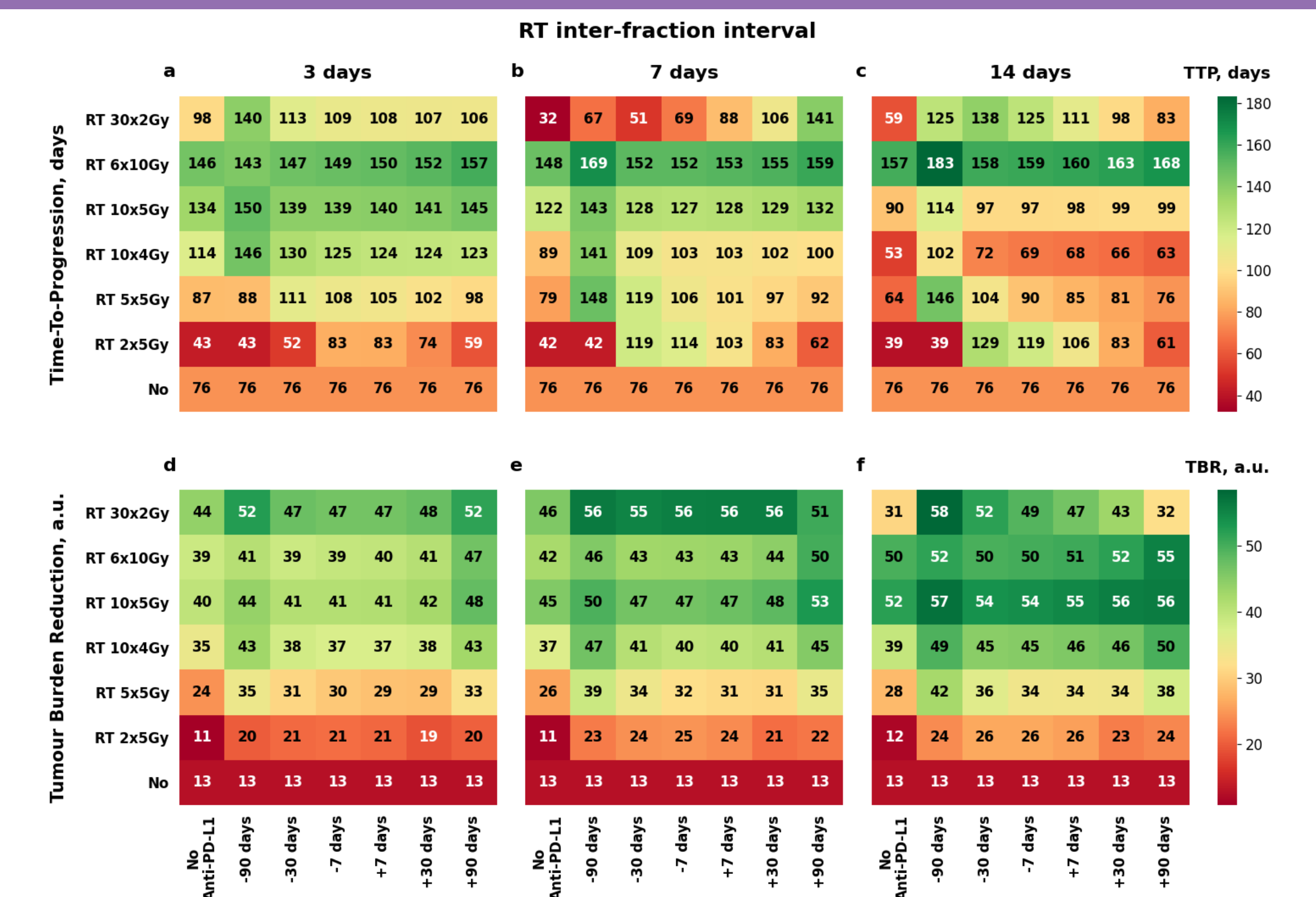


Figure 4: time to progression (TTP) and tumour burden reduction (TBR) across RT-anti-PD-L1 schemes. a–c: TTP (time until tumour relapse) for different RT schedules (rows) and anti-PD-L1 timing relative to last RT fraction (columns), across three RT inter-fraction intervals. Negative values indicate RT before anti-PD-L1 administration. d–f: Corresponding TBR (area between treatment and no treatment curves) for the same combinations.

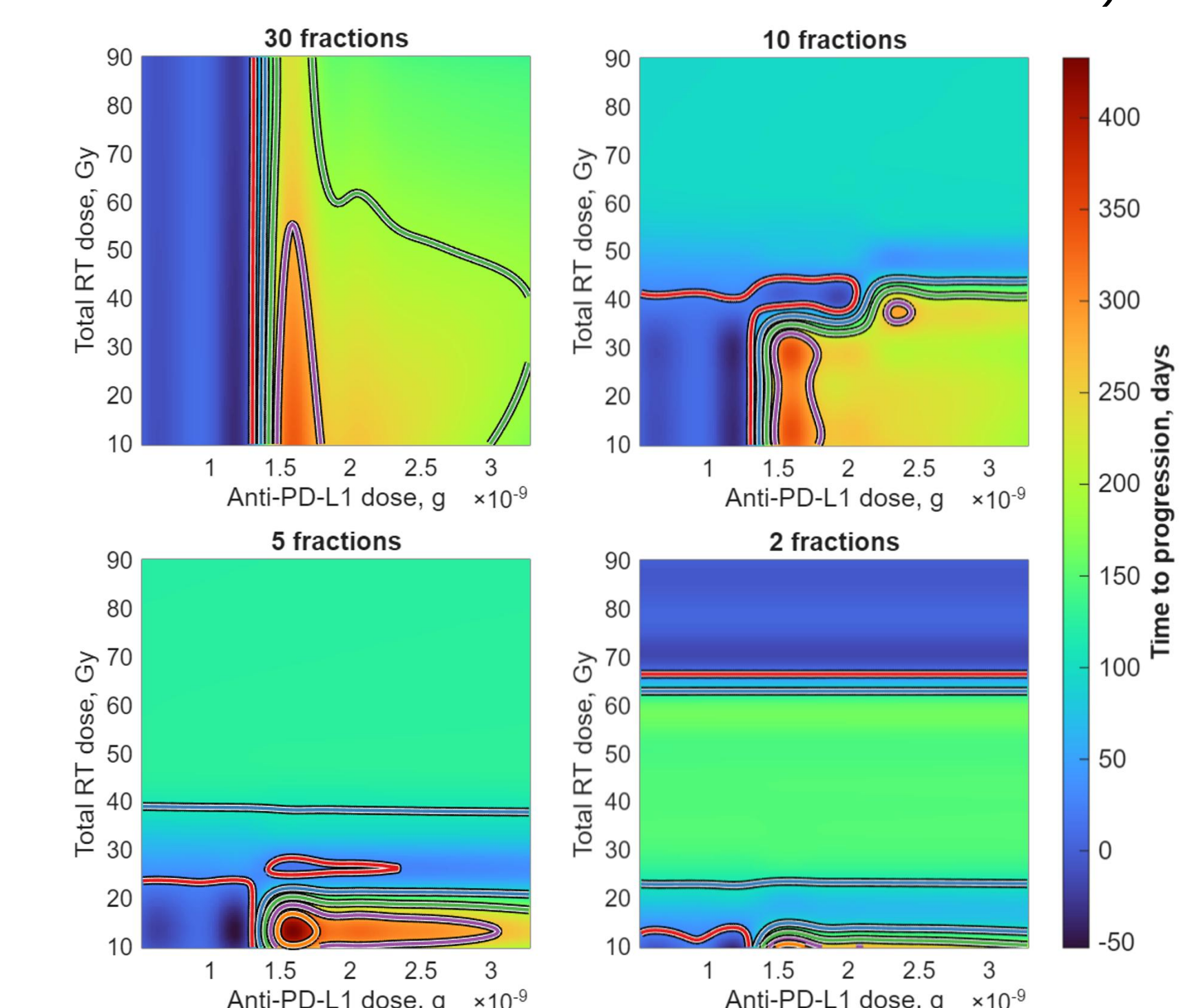


Figure 5: TTP depends on interplay between RT dose and IT dose. Heatmaps of time to progression (days) as a function of total RT dose and anti-PD-L1 dose, for RT delivered in varying fraction counts. Contour lines mark equal TTP values across all panels.

The full report and additional information can be accessed by scanning the QR code.

