Mathematical model to predict the patient responses to combined radiotherapy with CTLA-4 immune checkpoint inhibitor

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Immune checkpoint inhibitor (ICI) is an emerging treatment option for cancer treatment. Recent studies show that adding radiotherapy (RT) to ICI improves the patient outcome. However, near-infinite parameter combination (combination sequencing, radiation dose, patient selection, etc.) is a significant caveat for clinical trial design. Here I propose the framework describing interactions between the immune system and tumor based on patient blood samples and clinical trial outcomes. The cell compartments described by ordinary differential equations include irradiated and non-irradiated tumors, inactivated tumors, and circulating lymphocytes. An immune activation term was estimated based on tumor size changes in a phase 1/2 clinical trial for the immune checkpoint inhibitor targeting CTLA-4 pathways (Tremelimumab trial registered as NCT01008358 on the National Clinical Trials database, www.clinicaltrials.gov). To report the outcome in the cohorts, I used similar concepts as RECIST 1.1 guidelines, converted to our dynamic simulations: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Their CR, PR, and SD rates were reported as 0, 18%, 59% with a maximum deviation of ±10%. Our model was able to reproduce the observed outcomes when values of q were randomly drawn from a double normal distribution with mean 40 and 55 and standard deviation 0.3 (Figure 1). The separated two distributions indicate that only 10% of patients are responded to tremelimumab if the treatment condition is not sufficient enough to increase the CTLA-4 effectiveness (q). This interpretation was in accordance with the benchmarking dataset showing only some of the patients respond to monotherapy of tremelimumab. On the other hand, the results also suggested that the effectiveness of the immune checkpoint inhibitor can be maximized in the optimized combination treatments guided by the model. Our simulations showed that for ICI-RT combination approaches in metastatic patients, the fraction of irradiated tumor load has a large impact on treatment efficacy and has to be included when analyzing treatment efficacy. Furthermore, the framework captures heterogeneity among patients regarding tumor mass, lymphocyte counts, and sensitivity to RT and ICI, and could be used to guide patient selection and clinical trial design to maximize the efficacy of ICI-RT combination regimen.
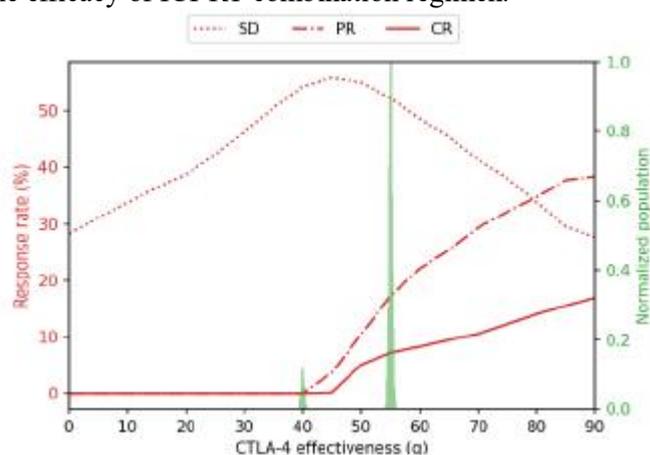

Fig. 1. The response rate for fixed immune checkpoint inhibitor (ICI) effectiveness (q) and the estimated population density with corresponding q. SD: stable disease, PR: partial response, CR: complete response..