

A generic modeling framework for dose regimen optimization and patient selection in radioligand therapy

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Background

The radioligand therapy (RLT) is emerging as an essential pillar in cancer care, with clinical benefits already established for some advanced cancers [1, 2].

RLT offers great potential as a treatment option by focusing on targeting the tumor or its microenvironment, while minimizing damages to the surrounding non-tumor tissues. The targeting is achieved by e.g., selective tumor receptor expression, binding of an isotope linked ligand, and radiation induced breaks in the tumor DNA leading to cell death [3]. However, heterogeneity (e.g., receptor expression profiles, tumor perfusion rates, etc.) within targeted patient populations has made variability a competing factor in understanding of the dose-response relationship, and difficulty in identifying the ‘ideal’ dose and patient population in the drug development process. Additional factors leading to difficulty in defining the ideal treatment options include the inter-relation between the dose, the regimen and schedule, the role of cell repair rate differences across individual, and the non-tumor External Beam Radiation Therapy (EBRT) thresholds. One significant challenge in early oncology trials is to define, balance and understand these features within the Phase I population for support of the Phase II protocol design, i.e., to identify the appropriate dosing regimens and patient subgroups early and assess potential treatment options within the context of the high variability and the current safety EBRT thresholds.

Modelling and simulation-based approaches can provide a tool to support decision making regarding patient selection and dose regimen optimization in RLT. This approach can be initiated at the early stage of clinical trials, continuously leveraging available data from multiple sources. As new data arrives from dosed cohorts, the established models can be continuously refined to guide decision making. Here, we present a generic modelling and simulation framework and illustrate how modeling and simulation can be used to support RLT development via simulation scenarios.

Objective

To illustrate how the proposed modelling and simulation framework can aid in the decision criteria for both patient selection and dose regimen optimization in RLT development.

Method

Data: This analysis used data from the LuMIERE trial that was designed with 2 parts [4]. Patient selection for treatment with 177Lu-FAP-2286 was based on 68Ga-FAP-2286 positron emission tomography (PET) scan for determining tumor Fibroblast activation protein (FAP) expression [5]. Phase 1 part was designed to evaluate the safety and establish the recommended intravenous (IV) Phase 2 dose (RP2D) for 177Lu-FAP-2286 monotherapy in participants with FAP expressing solid tumors. In Phase 1, patients with positive uptake of 68Ga-FAP-2286 received a fixed dose of 177Lu-FAP-2286 IV administered every 6 weeks for a maximum of 6 doses. Doses ranged between 3.7 and 9.25 GBq (100-250 mCi). Phase 2 part was designed to further evaluate the safety and efficacy of 177Lu-FAP-2286 either as monotherapy or in combination with chemotherapy in multiple indications.

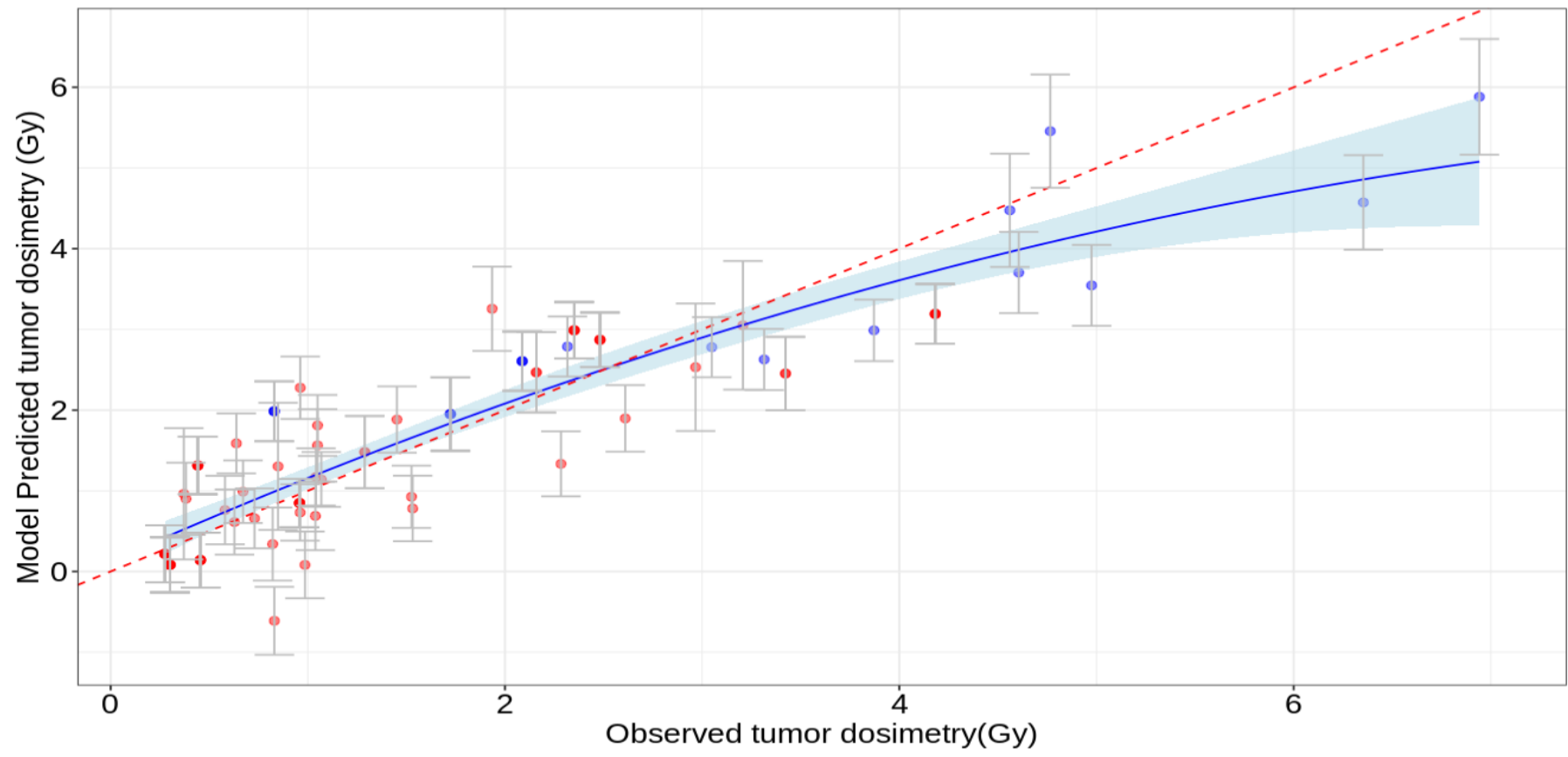
When this analysis was performed, the Phase 1 part of LuMIERE was ongoing, therefore, only data available from the Phase 1 part was used to develop the initial models and perform simulation scenarios.

Model development aimed to establish an integrated model characterizing the chain of events from the administered drug activity to patient response (efficacy & safety) to be used in a simulation framework for both dose optimization and patient stratification. Mixed-effects PKPD models, empirical regression models, and decision tree models were developed and linked for dosage simulation and design (e.g., fractionation, cycle duration). Patient specific factors (e.g., age, weight, renal function, cancer type, etc.), tumor and non-tumor dosimetry, blood drug exposure, and imaging assessment (gallium uptake) were all included in the analysis. The developed modeling and simulation framework provided utility for understanding the inter-relationship between the optimal dose regimen (maximum lesion uptake and minimal non-tumor uptake) to cancer type and lesion characteristics (e.g., lesion location, lesion size), and the utility of this in various stratified patient populations.

Model application: The developed model was used to illustrate the dose and schedule optimization, with consideration of the dose in term of dosimetry distribution in target tissues, in various patient groups, and the impact of certain lesion characteristics.

Results

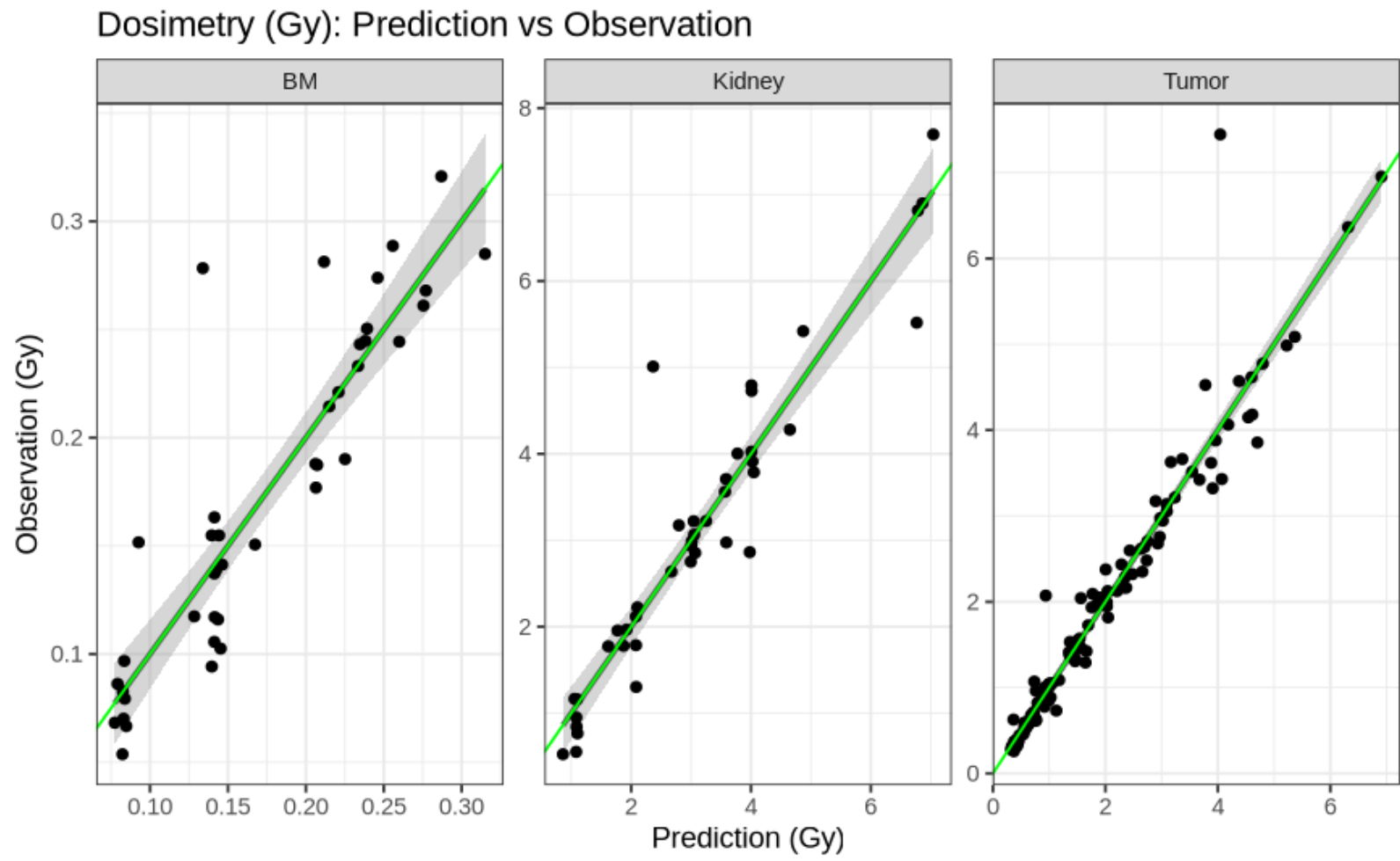
- Data from 24 patients with various cancer types were used in the analysis. 22 patients had blood PK measurements, 22 patients had kidney and tumor (121 lesions in total) and other organ dosimetry related measurements, and 23 had whole body dosimetry related measurements which was used as a proxy for bone marrow dosimetry.
- The mean value of Gallium standard uptake value (SUVmean) with other patient and lesion specific baseline characteristics (including lesion location, cancer type etc.) provided a reasonable individual lesion dosimetry prediction (Figure 1).



Blue point: lesion with indication 1; Red point: lesion with indications other than indication 1; Blue solid line: the mean predicted value from the model with 95% confidence interval; Bar: the 95% confidence interval of the predicted value

Figure 1: Observed and model predicted tumor dosimetry

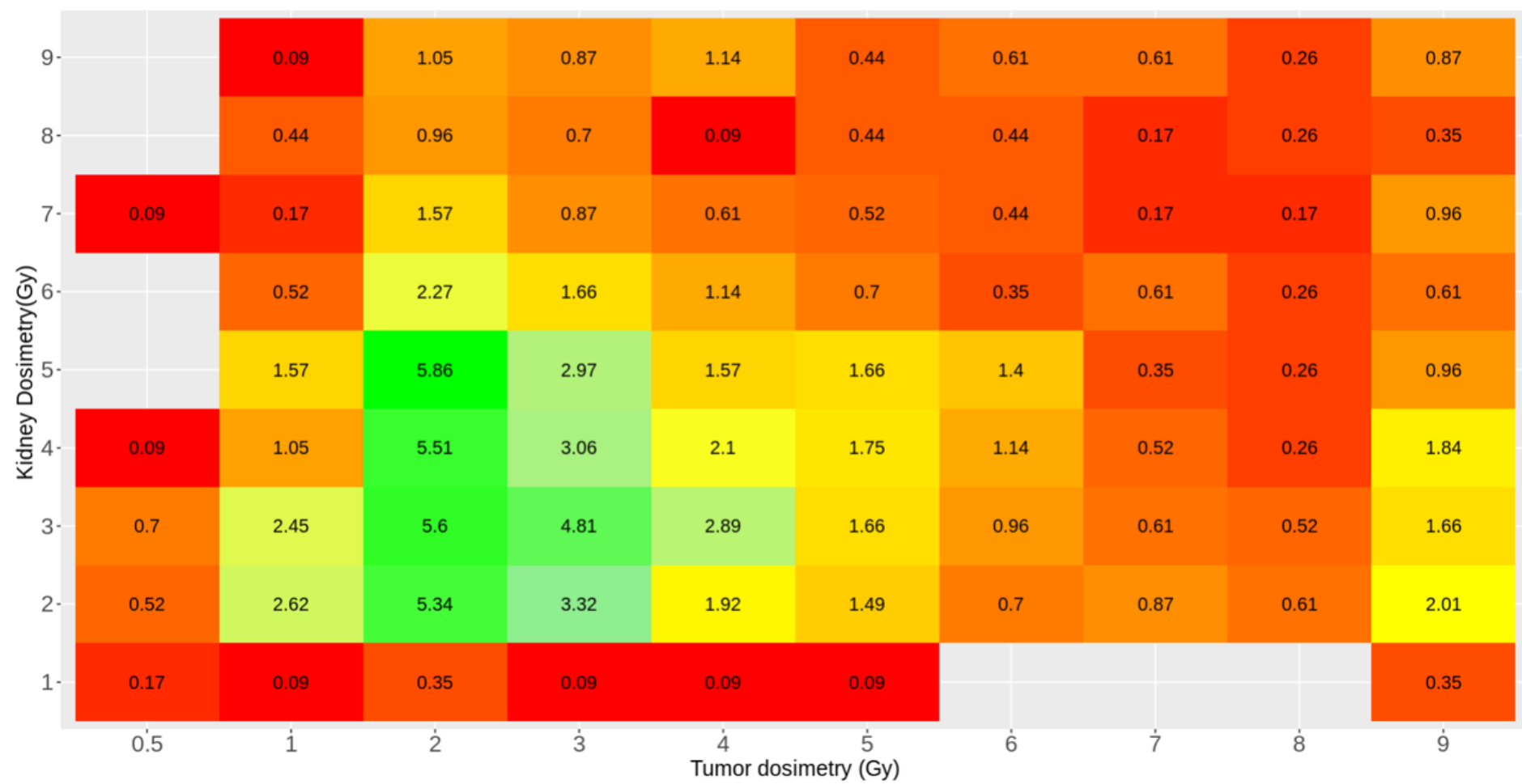
- Analysis indicated both linear and non-linear relationships existed between the administrated drug activity, blood exposure and organ dosimetry. This correlation between blood exposure and organ dosimetry was highly organ dependent. The model-based analysis was able to capture both the tumor and non-tumor dosimetry accurately, with utility of a range of models including turnover models and direct response models (Figure 2)



BM: bone marrow dosimetry; Black point: individual level dosimetry for BM and kidney, lesion level dosimetry for tumor; Green solid line: linear regression between predicted and observed dosimetry with 95% confidence interval in grey.

Figure 2: Observed and model predicted tumor and organ dosimetry

- A simulation scenario using the fully integrated PKPD model compared the dosimetry of tumor and non-tumor organ distribution across a range of doses, cancer types and fractionation schemes (Figure 3). Additional results indicated that the absorbed dose of tumor, kidney, bone marrow were correlated through patient specific characteristics (and possibly appropriate biomarkers), which could have relevance for patient selection, dose optimization and study design.



The number in the grid represents the proportion of patients in the simulation (n=500).

Figure 3: Dosimetry distribution across both kidney and tumor for a specific dose regimen, patient population and cancer lesion morphology.

Conclusions

The proposed modeling and simulation framework aligned the injected drug activity to the features specific to the patient population. Preliminary results highlighted the value of such a fully integrated model-based approach throughout the drug development process. Using this approach and integrating data throughout the clinical program may lead to more efficient effectively designed trials with the identification of highly specific patient populations or sub-populations where the risk benefit is more favorable.

References

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Disclosures

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