Modeling progression and treatment of prostate cancer using the Thales QSP software platform

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OBJECTIVE

- Metastatic, castration resistant prostate cancer (mCRPC) is an aggressive form of prostate cancer in which patients progress despite androgen deprivation therapy
- **The objective was to create a QSP platform model of mCRPC with an associated virtual population of mCRPC patients by training and validating to clinically relevant measures from many clinical trials simultaneously**
- This model and virtual population can be used to evaluate new therapies for treating mCRPC patients

METHODS

- A QSP model of mCRPC was developed using Thales, a QSP modeling platform specifically designed to facilitate, model, predict, and aid in the design of clinical trials
- The model includes immune cells, cancer cell killing, cytokine effects, and prostate-specific antigen (PSA) as a biomarker
- Virtual patients had primary and metastatic lesions, each with 3 distinct tumor microenvironments varying in size, growth, immune penetration, and drug PK/PD
- Parameters were aligned with existing mCRPC models or estimated from public data
- A virtual population of 100 mCRPC patients was generated by fitting and validating data from 9 clinical trials with 11 therapeutic compounds (monotherapy/combination)
- Key clinical measures the model predicts include tumor diameter, serum PSA, RECIST1.1, ORR, BOR, 50%/90% PSA decreases, time/duration of response, and survival (PFS, OS)

RESULTS

Model Predictions of Best Overall Response Data

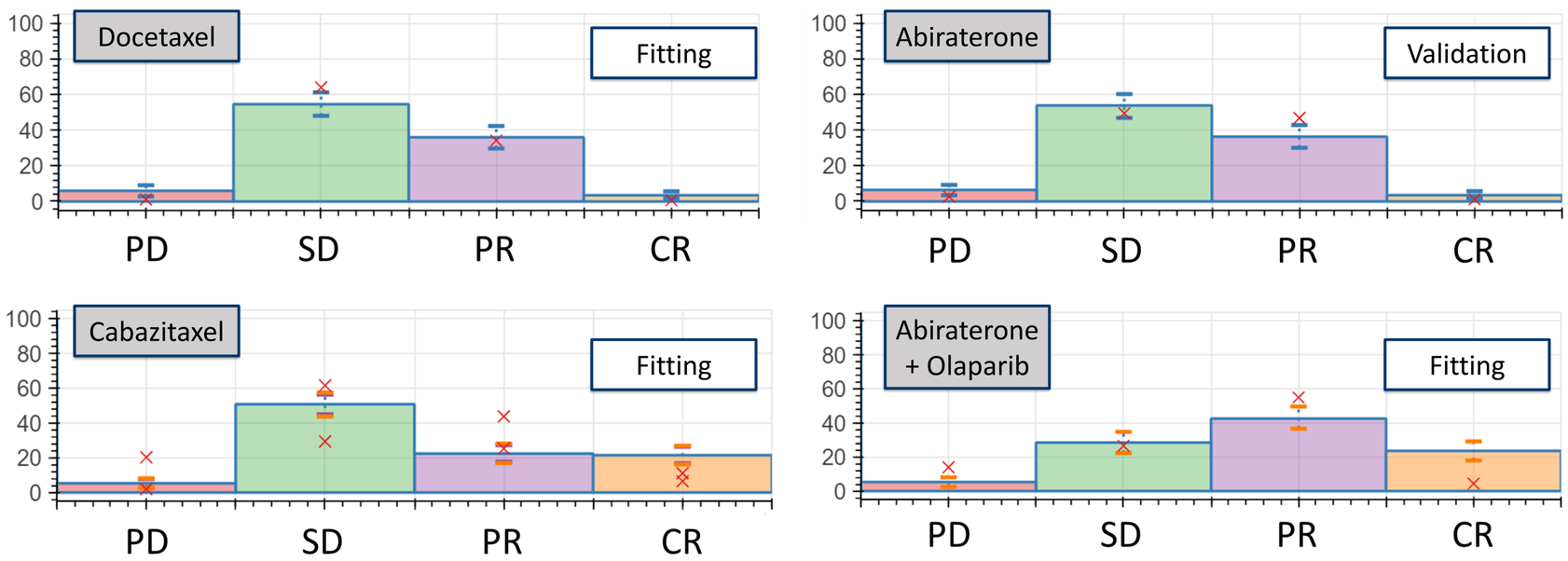


Figure 1: Top left – Docetaxel 75mg/m2 q3w; top right – Cabazitaxel 25mg/m2 q3w; bottom left - Abiraterone 1000mg qd; bottom right – Abiraterone 1000mg qd + Olaparib 300mg bid. Categories are BOR and definitions are based on the RECIST1.1 criteria: PD – at least 20% increase in sum of tumor diameters with absolute increase of at least 5mm; SD – not CR, PR, nor PD; PR – at least 30% decrease in sum of target tumor diameters; CR – no remaining detectable tumors. Bars represent the model predictions as a percentage of the full virtual population, x represent clinical trial endpoint data. 90% confidence intervals of model predictions are also shown. Clinical trial data taken from [1], [2], [3].

Model Predictions of Prostate Specific Antigen Data

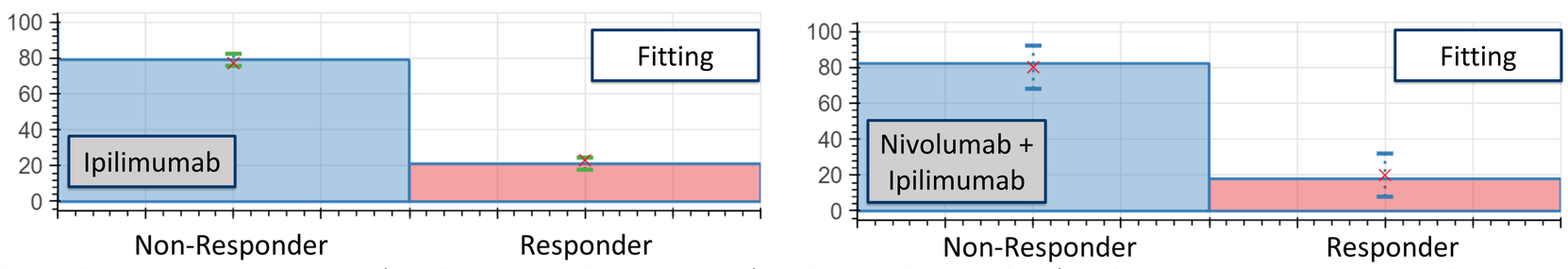


Figure 3: Left – Ipilimumab 10mg/kg q3w; right – Nivolumab 1mg/kg q3w + Ipilimumab 3mg/kg q3w followed by Nivolumab 480mg q4w. Categories are percent of patients who achieved a 90% (left plot) or 50% (right plot) decrease from baseline PSA levels. Bars represent the model predictions as a percentage of the full virtual population, x represent clinical trial endpoint data. 90% confidence intervals of model predictions are also shown. Clinical trial data taken from [5], [6].

- The model is capable of accurately predicting clinical endpoint for various drugs and dosing regimens including BOR, ORR, and PSA decreases
- Note that these results are for a single global population fit to all of these (and other) data simultaneously; hence, the generated virtual population can predict responses to novel compounds
- Altogether, data from 9 different clinical trials spanning 11 different therapies with multiple dosing regimens are simultaneously included as fitting and validation targets to train and validate the global virtual population (see references for some of the therapies and trials); Thales is capable of handling various types of data common in clinical trials natively
- The model also accurately predicts cytokine, immune cell, and PSA levels for healthy individuals, and can be extended to include mCRPC subtypes using biomarkers, disease phases, or genetic mutations

Model Predictions of Overall Response Data

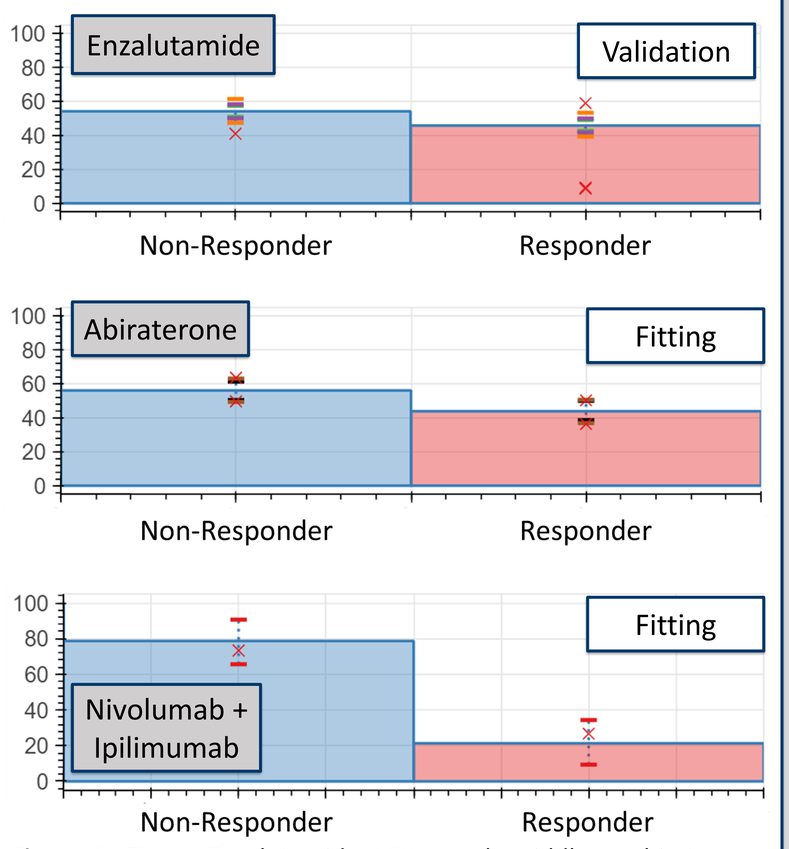
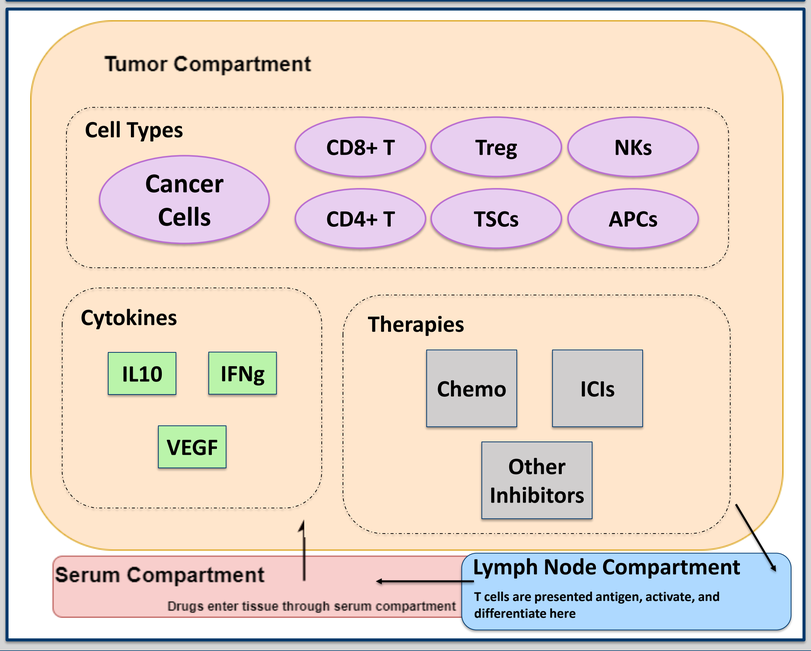


Figure 2: Top – Enzalutamide 160mg qd; middle – Abiraterone 1000mg qd; bottom - Nivolumab 1mg/kg q3w + Ipilimumab 3mg/kg q3w followed by Nivolumab 480mg q4w. Categories are ORR based on the RECIST1.1 criteria – responder is PR or CR, non-responder is SD or PD. Bars represent the model predictions as a percentage of the full virtual population, x represent clinical trial endpoint data. 90% confidence intervals of model predictions are also shown. Clinical trial data taken from [3], [4],[5].



CONCLUSION

- These results provide proof-of-concept that mCRPC progression and treatment can be modeled using a QSP platform model
- The model and virtual population accurately predict clinical endpoint data for many clinical trials and therapeutic regimens simultaneously
- Additional therapies could be added to further train the population, both enhancing model performance and allowing clinically relevant predictions for novel compounds such as optimal first-in-human dose, special populations of interest, or novel therapeutic combinations
- The mCRPC model extends our solid tumor modeling library, which contains a curated set of processes common to many solid tumor indications

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