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Original Research

Directional inconsistency between Response Evaluation Criteria in Solid Tumors (RECIST) time to progression and response speed and depth

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Abstract ***Aim:*** We seek to characterize how faster tumour shrinkage rate (k) can lead to paradoxically shorter Response Evaluation Criteria in Solid Tumors (RECIST) time to progression ('TTP20' – tumour size exceeding its minimum by 5 mm and 20%) [1] and, therefore, progression-free survival (PFS). Specifically, we investigate under what conditions this paradoxical behaviour occurs, what fraction of patients satisfy these conditions, whether this phenomenon can invert population-level PFS hazard ratio, and consistency of an alternative time-to-event benefit metric with k.

Methods: We use a mathematical model treating tumour burden as decreasing drug-sensitive and increasing drug-resistant cell subpopulations. We fit this model to data from several clinical trials with different indications [2]. We simulated a more effective treatment and recorded whether patients' TTP20 increased or decreased. We performed a study-level analysis to compare the relationship of speed and depth of response with TTP20 for both the administered 'control' and simulated 'more effective' drug. We propose and test an alternative benefit metric: the model-projected time that tumour size reaches 120% of baseline (TTB120).

Results: Depending on indication, 3–27% of patients are estimated to have a paradoxically inverse relationship between k and TTP20. Simulated head-to-head studies show that TTP20-based PFS can favour the less effective drug. In contrast, TTB120 always favours the more effective drug.

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Conclusion: We demonstrate the paradoxical behaviour of RECIST TTP20 – as an exemplar of percent-change-from-nadir based cancer progression criterion – both in theory and in observed patient data at the individual and trial level. We propose an alternative tumour size–based criterion (TTB120) that is directionally consistent with tumour shrinkage rate.

1. Introduction

The Response Evaluation Criteria in Solid Tumors (RECIST) are accepted as pragmatic and robust criteria in the determination of patient status in the context of treatment and drug development for solid tumours [1,3]. The criteria are based on unidimensional measurements of a 'target' subset of measurable lesions integrated with qualitative assessments of the remainder of the disease, including the potential appearance of new lesions. Over the years, these criteria have come to dominate the assessments of solid tumours [4], and many modifications have been applied to optimize the criteria for different tumour types [5,6] and treatments [7]. However, there have also been persistent calls about shortcomings [6] and concerns about the predictive power during drug development leading to numerous efforts to identify suitable, alternative measures [8–12].

We use modelling and simulation of clinical tumour size (TS) data to reveal a potential pitfall in the current drug evaluation criterion of RECIST 1.1. Although the conventional paradigm assumes that increased anti-tumour effect results in a longer time to progression (TTP) and improved progression-free survival (PFS), we show that this is often not the case because of a fundamental mathematical property of the RECIST definition of disease progression. Specifically, we demonstrate a paradoxically inverse relationship between the TS-based RECIST TTP metric ('TTP20' = time to increase of 20% and at least 5 mm from nadir) and speed and depth of response. TS data from clinical trials are put into a mathematical modelling framework and *in silico* experiments demonstrate that this directional inconsistency could happen in real patients and can drive changes in study-level PFS results. We explore why this paradoxical behaviour of the TTP20 metric has not been noticed before. We end by proposing an alternate model-based clinical benefit metric as a potential replacement for the quantitative component of the RECIST criteria for progression in the absence of new lesions that is directionally consistent with speed and depth of response and can potentially be used as an improved surrogate for patient benefit from a study drug.

While we focus on RECIST criteria in the current work, our observations in principle apply to any patient benefit metric containing a time to 'fixed percent increase in disease burden from nadir' criterion. Some of the many examples are irRC [13], irRECIST [14], iRECIST [7], mRECIST [5], modified RECIST for malignant mesothelioma [15], RANO for brain metastases in the solid tumours [16], PCWG2 [17], and PCWG3 [18] in prostate cancer, revised responses for lymphoma including a revised response in 2007 [19], the 2014 Lugano Classification [20], LYRIC [21] and RECIL [6], and iwCLL 2008 [22] and 2018 [23] in chronic lymphocytic leukaemia.

We anticipate that our findings in this work based on the RECIST TTP20 metric are also relevant conceptually to the aforementioned examples.

2. Data sources and methods

2.1. Model of tumour burden dynamics

To determine the relationship between treatment efficacy and the RECIST 1.1 time to progression by target lesions (TTP20), we used a simple mathematical model (Eqn. (1)) that treats patient tumour burden as a decreasing drug-sensitive subpopulation of tumour cells and an independently growing drug-resistant subpopulation. This model has successfully described tumour dynamics in non–small cell lung cancer, melanoma [24], multiple myeloma [25], and ovarian cancer [26]. We represent the initial sum of diameters of the target lesions as SOD_0, and in the presence of drug, the net fitness of the drug-sensitive cells as an exponential decay or 'tumour shrinkage rate' $k > 0$, the net fitness of the resistant tumour cells as an exponential growth rate $g > 0$, and the initial fraction of drug-resistant cells by $0 \leq \phi \leq 1$. The sum of diameters (SOD) of target lesions over time t can then be approximated as:

$$SOD(t) = SOD_0\left[(1-\phi)e^{-kt} + \phi e^{gt}\right] \quad (1)$$

This model can account for the most frequently observed clinical responses of durable response ($\phi = 0$), 'primary' resistance ($\phi = 1$), and 'acquired' resistance (k, $g > 0$, $\phi < 1$).

2.2. Analysis of the mathematical consistency of time to progression with response speed/depth

To illustrate that TTP20 can be theoretically inconsistent with tumour shrinkage rate, we simulated the SOD

time course $SOD(t)$ for a single 'virtual patient' and recorded the time at which $SOD(t)$exceeds its lowest value by 20% and by at least 5 mm. To determine the effect of increased treatment efficacy on TTP20, we increased k incrementally from 0 to 0.1 while keeping constant the initial fraction of drug resistant cells $\phi = 0.01$ and the resistant cell regrowth rate $g = 0.01$ and then recorded the $SOD(t)$ trajectory (Fig. 1 inset), as well as the corresponding TTP20 for each choice of k (Fig. 1).

2.3. Evaluation of TTP20 inconsistency in individual patients

To assess whether inconsistency between k and TTP20 can happen in real patient populations, we used publicly available SOD data from patients in the control (standard of care [SoC]) arms of five clinical trials with four tumour histologies [2] (NCT00364013, OV1(N/A), OV2 (N/A), NCT00094081, NCT01193244; Table 1). For each patient, we fit the model to the observed change in SOD over time. All three possible nested models described in Section 2.1 were fit to each patient's SOD time course. We used the Akaike Information Criterion [27] to evaluate which model best fit the SOD data. Patients whose best-fit model had $R^2 < 0.6$ for all three of the models were removed from analysis to prevent overinterpretation of patients whose data were not well characterized. We then took each patient parameter set and determined the TTP20 of that patient assuming their SODs were observed continuously to isolate the effect of the TS trajectory on TTP20 irrespective of clinical sampling intervals. We then simulated the effect of a more effective treatment by increasing k. We assumed that the improved k treatment would have no effect on primary resistant ($\phi = 1$) patients and therefore their TTP20. If increasing k in a patient with $\phi < 1$ led to a *decrease* in TTP20 of at least 1 d, we flagged this patient as 'inconsistent.' We recorded the percent of patients falling into this category for each of the five different studies (see Table 1 and Fig. 2).

Table 1
Table of Project Data Sphere [2] control arm indications and standard of care treatments and the corresponding number of total patients measured and the number of patients whose parameter set found them to be susceptible to inconsistency between TTP20 and speed/depth of response.

Indication and drug	Total number of patients	Total number of 'inconsistent' patients, n (%)
Metastatic colorectal carcinoma treated with oxaliplatin + leucovorin	320	85 (26.6)
Epithelial ovarian carcinoma treated with topotecan	235	18(7.7)
Epithelial ovarian carcinoma treated with paclitaxel	107	11 (10.2)
Advanced head/neck cancer treated with radiation + cisplatin	361	11(3.0)
Progressive metastatic castration resistant prostate cancer treated with prednisone	167	5(3.0)

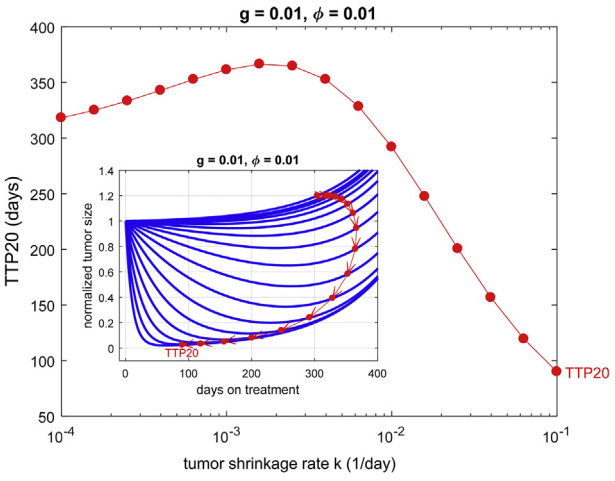

Fig. 1. Illustration of directional inconsistency between RECIST time to progression (as defined by 20% increase from nadir = 'TTP20') and tumour shrinkage rate k. For a simulated patient with a resistant cell growth rate g = 0.01 and initial resistant cell fraction of ϕ = 0.01, increasing k (indicated by red arrows, inset) from 0 to 0.001 results in increasing TTP20 as expected, but increasing k from 0.001 to 0.1 results in successively *decreasing* TTP20. As this illustration represents tumour burden as baseline normalized, the 5 mm minimum increase criterion for RECIST1.1 progression was not applied in this figure, but it was applied in all subsequent analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

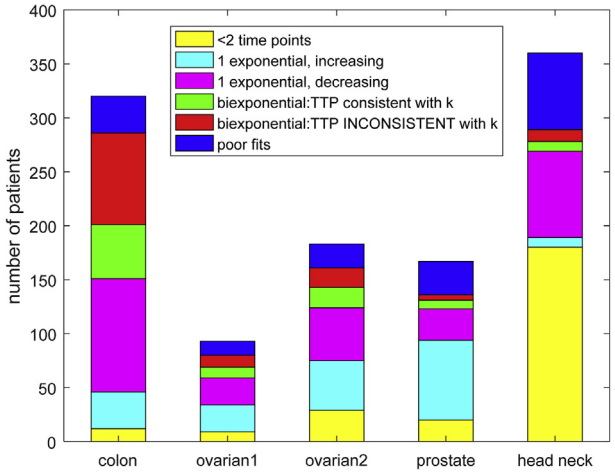

Fig. 2. Bar graph of numbers of patients in each TS time profile shape subset across studies, based on parameter estimation and AIC-based testing. The patients for which TTP20 and tumour shrinkage rate k are directionally inconsistent are indicated by red regions. These patients occur at a (conservatively estimated) rate of 27% in the colon cancer study, 8% in ovarian 1, 10% in ovarian 2, 3% in prostate, and 3% in the head and neck study. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2.4. Evaluation of TTP20 inconsistency in study-level results

We simulated a virtual more effective 'investigational treatment' arm by taking the same patient-level parameter sets in the colorectal carcinoma (CRC) population and increasing only the tumour shrinkage rate k for each patient by 10-fold to see if the frequency and magnitude of the TTP20 inconsistency could drive changes in study level results. For each patient and treatment (SoC and the virtual, more effective treatment), we computed the maximum percent tumour shrinkage (SOD_{min}/SOD_0), which we call the best response, and the resulting TTP20. We estimated the complete response rate by computing the percent of patients whose best response (SOD_{min}) went below 5mm, and the partial response rate by calculating the percent of patients whose SOD decreased at least 30% from baseline. We computed the TTP20 for each patient and the resulting hazard ratio (HR) of the two treatments. We produced the waterfall plot of depth of response and the Kaplan–Meier curve of PFS for both the administered SoC and the simulated investigational treatment.

2.5. Analysis of relationship between TTP20 and maximum percent tumour shrinkage

To understand why this inconsistency had not been previously observed, we first performed 'naïve' univariate regression on CRC patient TTP20 with respect to best response depth using estimated values from the CRC patients obtained from Section 2.3. We then plotted simulated TTP20 as a function of the best response (SOD_{min}/SOD_0) for several constant values of ϕ overlaid on these estimated patient values to demonstrate the non-linear relationship between the two metrics. We then performed multivariate linear regression on TTP20 with patient parameters ϕ, g, and k as additional predictors to correct for confounding factors.

2.6. Propose and evaluate alternate model-based metric 'TTB120'

We propose an alternate model-based end-point, the extrapolated time to SOD reaching 20% greater than baseline. This metric would require multiple TS assessments over time be fit to the evolutionary model, after which patient parameters would be used to simulate the SOD time course and thereby the expected time at which the patient's tumour reaches 20% larger than the SOD_0. This 'TTB120' value is our proposed tumour-sized based component of a time to event metric of patient benefit in the absence of new lesions. To evaluate the consistency of TTB120 with respect to k, we applied the methods of 2.2 to determine the effect of increasing k on TTB120 for a single virtual patient. We then applied the methods of Section 2.3 to assess whether TTB120 is consistent with k (and therefore response speed and depth) at the study level.

3. Results

3.1. Directional inconsistency between tumour shrinkage rate and TTP20

Our analysis reveals that there are model parameter combinations for which increasing k results in a paradoxically *shorter* TTP20. We demonstrate that for a theoretical patient with an initial resistant tumour cell fraction $\phi = 0.01$ and resistant growth rate $g = 0.01$, as we increase k from 0 to 0.1, the speed and depth of response consistently increases (Fig. 1 inset), but after an initial small increase, TTP20 actually *decreases* (Fig. 1).

3.2. A significant portion of real patients are susceptible to inconsistency between shrinkage rate and TTP20

When the evolutionary model was fit to patient TS data, we found that 'inconsistent' patients, that is, those who have a small increase in k leading to a decrease in TTP20, make up at least 3% (prostate cancer) to 27% (colorectal cancer [CRC]) of the total patient population (Fig. 2). These frequencies are conservative as patients who did not show signs of relapse ($\phi = 0$), patients who did not show signs of response ($\phi = 1$), and those whose TS data were not well-described by the tested models ($R^2 < 0.6$) were not considered as candidates to demonstrate 'inconsistency'; only patients who exhibit the response-and-relapse trajectory can exhibit the inconsistency.

3.3. Trial-level analysis reveals inconsistency between depth of response and TTP20

While the simulated 'investigational treatment' with a 10-fold higher k than the SoC produces a waterfall plot indicating deeper responses in CRC patients (Fig. 3A), Kaplan–Meier analysis on simulated PFS instead favours the SoC (HR = 1.21, 90% confidence interval [CI; 1.00, 1.46]; Fig. 3B).

3.4. Non-linear relationship between TTP20 and tumour shrinkage confounds correlational analysis

Univariate linear regression between patient maximum percent tumour shrinkage (SOD_{min}/SOD_0) and TTP20 appears to confirm that a worsened best response (corresponding to lower k) correlates with shorter TTP20, with an R-squared value of 0.066 and a p-value of 0.00159 (Fig. 4A). However, the theoretical relationship between TTP20 as a function of depth of response in terms of ϕ and g reveals a significant region of the curve

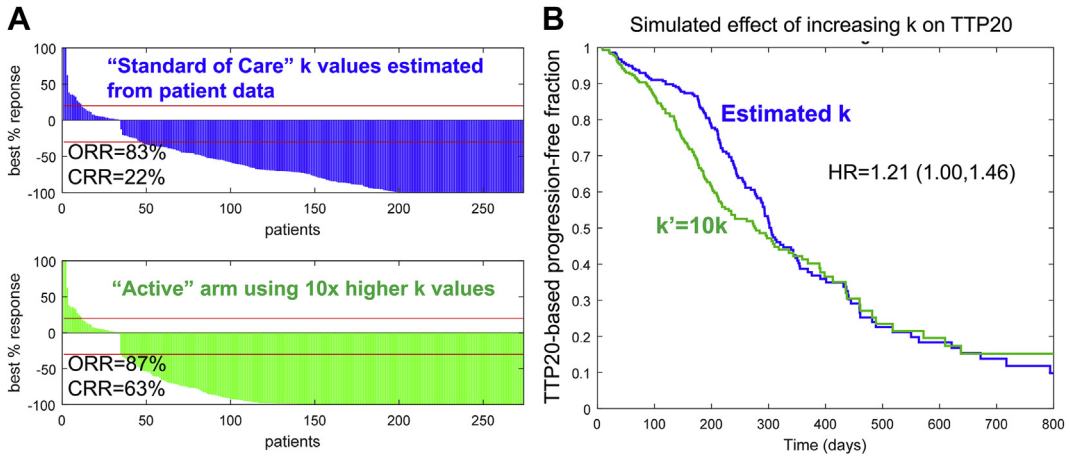

Fig. 3. (A) Waterfall plot of best depth of response in sum of the longest diameters for CRC patients, marked with red lines to indicate RECIST 1.1 criteria for partial response (30% below baseline) and progressive disease (20% above baseline). Blue indicates the evolutionary model predicted best response for patient trajectories fit to observed sum of the longest diameters, while the green indicates the evolutionary model predicted best response for a simulated 10× stronger tumour shrinkage rate which demonstrates the improved depth of response of this simulated regimen. (B) Kaplan–Meier curve of RECIST 1.1 criteria for progression-free survival predicted by the fit to the evolutionary model for the observed sum of the longest diameter trajectories in blue and the simulated 10× stronger tumour shrinkage rate in green to demonstrate that the observed Kaplan–Meier curve for the simulated treatment appears worse. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

where TTP20 increases as k decreases (best response worsens; (Fig. 4B, red curves). Overlay of CRC patient parameter sets indicates there exists a significant number of patients that would fall in this region (Fig. 4B, black stars). Multivariate regression considering all model parameters and best response as predictors confirms the inconsistency between TTP20 and k (Fig. 4C) with an R-squared value of 0.66 and a p-value of 8.47×10^{-28}. As expected, ϕ and g vary inversely with TTP20, as an increase in resistant fraction and resistant tumour cell growth rate are consistent with poor patient response and thus shorter TTP20. However, k also varies negatively with TTP20, consistent with our findings but inconsistent with conventional expectation.

3.5. Model-based metric TTB120 is directionally consistent with tumour shrinkage rate

Simulations demonstrate that TTB120 (Fig. 5A) is consistent with speed and depth of response in a virtual

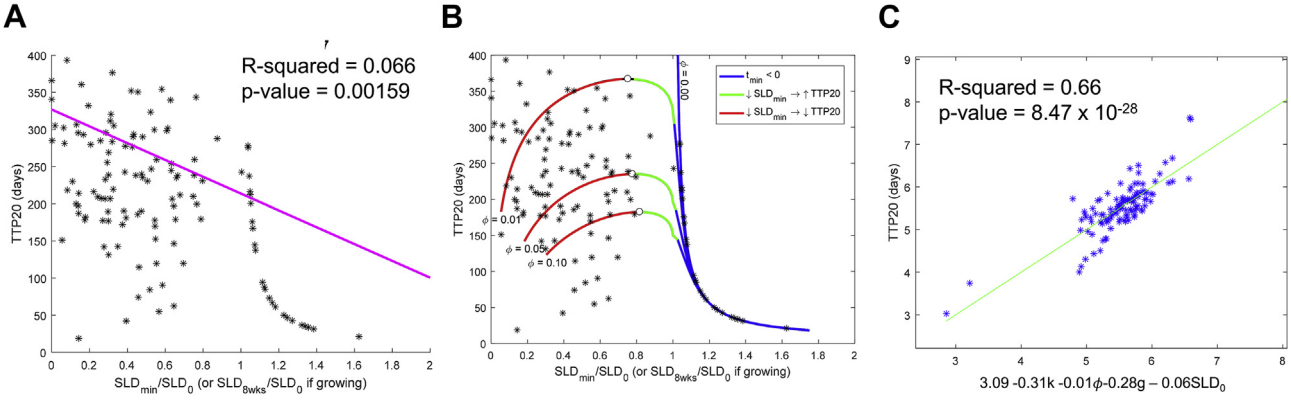

Fig. 4. (A) Results of the univariate regression on TTP20 versus best response (SOD_{min}/SOD_0) reveal a negative correlation between TTP20 and best response with an R-squared value 0.066 and a p-value of 0.00159. (B) Illustration of the theoretically directionally inconsistent relationship between RECIST 1.1 TTP20 versus best response (SOD_{min}/SOD_0) for a constant resistant regrowth rate g and constant initial resistant fraction ϕ, simulated at ϕ values increasing from 0 to 0.1. Black dots represent evolutionary model fitted colorectal patients TTP20 and best response (SOD_{min}/SOD_0). Red indicates region of inconsistency between shrinking tumours and shorter TTP20, green represents region of consistency between expected relationship between shrinking tumours and larger TTP20, and blue represents region where the tumour strictly grows. (C) Results of multivariate regression on TTP20 taking into consideration parameters ϕ, g, and k indicate expected negative correlations between resistant growth rate g and initial resistant fraction ϕ with TTP20 but also demonstrate the paradoxically negative correlation between tumour shrinkage rate and TTP20 for colorectal patient parameter sets (blue dots), with an R-squared value of 0.66 and a p-value of 8.47×10^{-28}. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

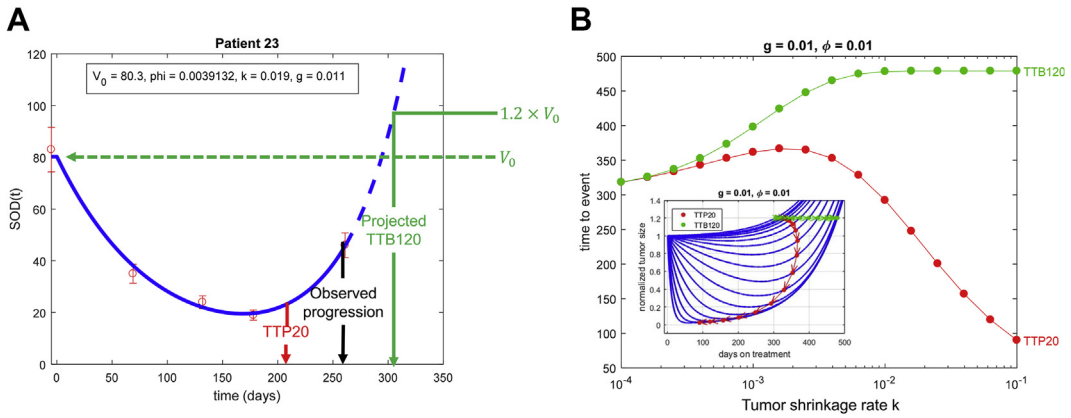

Fig. 5. (A) Illustration of the proposed model-based metric of TTB120, which utilizes the evolutionary model to predict out when a sum of diameter trajectory would reach 1.2 times its baseline SOD for an example patient in the colorectal set. The proposed metric allows for flexibility in changing a patient's regimen at the time of first observed relapse, while maintaining a metric for comparing benefit that doesn't penalize speed and depth of response. (B) Comparison of operating characteristics of proposed TTB120 metric (green) and RECIST TTP20 metric (red). Inset shows tumour size trajectories for increasing values of k (as indicated by arrows), with the addition of TTB120 events. Larger figure shows that TTB120 is directionally consistent with shrinkage rate k, in contrast to RECIST TTP20. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

patient (Fig. 5B). The simulated investigational treatment with 10-fold higher k than SoC is slightly favoured in Kaplan–Meier analysis using TTB120, but the difference is not statistically significant (HR = 0.98, 90% CI: [0.81,1.19]; Fig. 6). The population-level simulations varying k on the resulting HR between the original and 'new' treatment confirm that while TTP20 is directionally inconsistent in indicating patient benefit via HR, TTB120 is consistent with k (Fig. 7).

4. Discussion

While the potential for directional inconsistency between speed/depth of tumour response and time to RECIST progression has been alluded to by others [4], we know of no published efforts that have attempted to characterize the frequency and potential impact of this inconsistency in clinical studies.

We tested five different patient populations (consisting of 320 CRC, 100 and 200 ovarian, 175 prostate and 350 head & neck cancer patients) and reached a conservative estimate that 3–27% of these patients would potentially exhibit this directional inconsistency if they

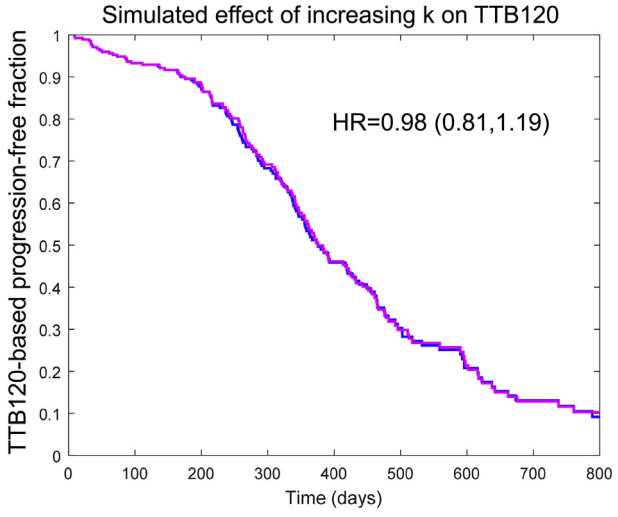

Fig. 6. Kaplan–Meier curve based on TTB120 metric comparing observed and simulated curves indicates that TTB120 is directionally consistent with speed and depth of response, with the simulated (tumour shrinkage rate = 10 × observed k treatment) appearing slightly better than the observed treatment with a hazard ratio of 0.98 (0.81, 1.19; not statistically significant).

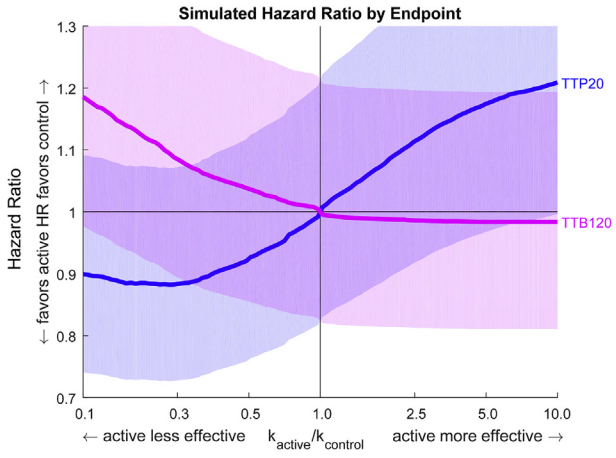

Fig. 7. Illustration of hazard ratios for the effect of increasing and decreasing tumour shrinkage rate k at the population level for the colorectal cancer trial demonstrating that RECIST TTP20 would result in a higher hazard ratio for a more effective drug, while the new projected TTB120 metric would result in a directionally consistent hazard ratio with more effective drug.

had been exposed to a more 'effective' treatment with higher tumour shrinkage rate (k) with all other parameters (resistant cell fraction ϕ and growth rate g) remaining equal. We focused on the CRC population for the remainder of the analyses.

Not only were at least 27% of the tested CRC patients susceptible to this directional inconsistency, but also these inconsistencies were of sufficient frequency and magnitude to invert the results of a simulated head-to-head PFS-based study between two similar treatments that differ only in k (Fig. 3B). Specifically, when comparing the time-to-progression distributions between patients taking the observed (Oxaliplatin + Leucovorin +5 FU) regimen (Table 1) and a more effective treatment having a 10-fold higher shrinkage rate, simulations showed that, while the more effective drug would result in faster and deeper anti-tumour responses (Fig. 3A), PFS analysis would favour the less effective drug, with a HR of 1.21 (1.00, 1.46; Fig. 3B).

To characterize the directional inconsistency phenomenon, we assumed that TS could be observed continuously (daily). While we expect that less frequent sampling would partially mask directional inconsistency, we propose that any patient benefit surrogate measure should be consistent with k irrespective of study design.

The reason previous analyses relating depth of response to progression time [28,29] have not detected this inconsistency is because they performed univariate linear analysis. Indeed, a linear regression through our own TTP20 estimates vs. best response depth appears to support consistent behaviour, but multivariate linear regression shows that k in fact correlates negatively with TTP20 once we correct for the other factors.

One may ask whether a given historical study failed to show a PFS advantage because of this directional inconsistency. As the available public data are either population level [30] or single arm [2], it was not possible for us to assess this possibility for a published study.

Finally, we propose an alternative metric 'TTB120,' the model-extrapolated time to reach 120% of baseline. To be clear, we are not proposing that patients be kept on a failing treatment longer than by RECIST criteria; rather, the described analysis indicates TTB120 is potentially a better surrogate for patient benefit than TTP20, the quantitative component of RECIST PFS in the absence of new lesions, because it is directionally consistent with response speed and depth for all patient populations and tumour shrinkage rates (Fig. 5B).

While we agree with recent findings that speed and depth of response are not particularly good predictors of long-term benefit compared to other metrics like tumour regrowth rate [31], we believe that treatment benefit surrogates should be directionally consistent with − if not particularly sensitive to − response speed and depth.

Given that these findings extend beyond RECIST to any time to progression metric for which progression occurs when disease burden exceeds a fixed percent increase relative to nadir, we hope that this work leads to further development of response surrogates that can provide more consistent assessments of the benefit that investigational agents can provide to cancer patients.

Conflicts of interest statement

K.J., A.G., and J.B. have no conflicts of interest to disclose. D.B. and A.S. are employed by Takeda Pharmaceuticals. A.C. is an officer of and owns stock in Fractal Therapeutics. D.W. is employed by and owns stock in Fractal Therapeutics. Both Takeda Pharmaceuticals and Fractal Therapeutics research and develop cancer drugs.

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