ARTICLE

Prediction of overall survival in patients across solid tumors following atezolizumab treatments: A tumor growth inhibition–overall survival modeling framework

Phyllis Chan1 | Mathilde Marchand2 | Kenta Yoshida1 | Shweta Vadavkar1 | Nina Wang1 | Alyse Lin1 | Benjamin Wu1 | Marcus Ballinger3 | Nitzan Sternheim4 | Jin Y. Jin1 | René Bruno5

1Department of Clinical Pharmacology, Genentech, Inc., South San Francisco, California, USA
2Certara, Marseille, France
3Department of Clinical Science, Genentech, Inc., South San Francisco, California, USA
4Department of Product Development, Genentech, Inc., South San Francisco, California, USA
5Department of Clinical Pharmacology, Genentech/Roche, Marseille, France

Correspondence
Phyllis Chan, Clinical Pharmacology, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA.
Email: chan.hui-min@gene.com

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Abstract
The objectives of the study were to use tumor size data from 10 phase II/III atezolizumab studies across five solid tumor types to estimate tumor growth inhibition (TGI) metrics and assess the impact of TGI metrics and baseline prognostic factors on overall survival (OS) for each tumor type. TGI metrics were estimated from biexponential models and posttreatment longitudinal data of 6699 patients. TGI-OS full models were built using parametric survival regression by including all significant baseline covariates from the Cox univariate analysis followed by a backward elimination step. The model performance was evaluated for each trial by 1000 simulations of the OS distributions and hazard ratios (HR) of the atezolizumab-containing arms versus the respective controls. The tumor growth rate estimate was the most significant predictor of OS across all tumor types. Several baseline prognostic factors, such as inflammatory status (C-reactive protein, albumin, and/or neutrophil-to-lymphocyte ratio), tumor burden (sum of longest diameters, number of metastatic sites, and/or presence of liver metastases), Eastern Cooperative Oncology Group performance status, and lactate dehydrogenase were also highly significant across multiple studies in the final multivariate models. TGI-OS models adequately described the OS distribution. The model-predicted HRs indicated good model performance across the 10 studies, with observed HRs within the 95% prediction intervals for all study arms versus controls. Multivariate TGI-OS models developed for different solid tumor types were able to predict treatment effect with various atezolizumab monotherapy or combination regimens and could be used to support design and analysis of future studies.
INTRODUCTION

The use of tumor dynamics model-based approaches has become increasingly attractive to evaluate treatment response for decision-making through the course of clinical development in oncology.\(^1^\)–\(^3^\) Model-based tumor dynamics metrics (including early shrinkage, time to regrowth, on-treatment growth rate, or the full dynamic profile) have been demonstrated to predict overall survival (OS) in different types of solid tumors, including colorectal cancer,\(^4^\)–\(^6^\) breast cancer,\(^7^\)–\(^8^\) non-small cell lung cancer (NSCLC),\(^9^\)–\(^11^\) locally advanced and metastatic urothelial carcinoma (mUC),\(^12^\)–\(^13^\) renal cell carcinoma (RCC),\(^14^\)–\(^15^\) and several other tumor types\(^16^\)–\(^19^\) for a variety of treatments. Leveraging tumor dynamics as a biomarker to predict OS in phase II trials with cancer immunotherapy (CIT) is not a novel concept, but longitudinal tumor response to CIT treatment may elicit different patterns compared with treatments with other mechanisms of action, such as delayed responses or increased tumor burden before regression.\(^10^\)–\(^12^\)–\(^13^\)–\(^16^\)

Atezolizumab is a humanized immunoglobulin G1 monoclonal antibody that targets human programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells (ICs) and tumor cells (TCs) and inhibits PD-L1 interaction with programmed death 1 (PD-1) and B7.1 receptors, thereby sending inhibitory signals to T cells.\(^20^\)–\(^22^\) Atezolizumab is approved to treat locally advanced or metastatic NSCLC, mUC, extensive-stage small-cell lung cancer (SCLC), locally advanced or metastatic triple-negative breast cancer (TNBC), and unresectable hepatocellular carcinoma (HCC) by the US Food and Drug Administration (US FDA) and/or the European Medicines Agency.\(^23^\)–\(^24^\)

The association between tumor growth inhibition (TGI) metrics and OS for atezolizumab was previously investigated in patients with NSCLC who progressed during or following prior platinum chemotherapy, using atezolizumab and control (docetaxel) data from a phase II trial (POPLAR) for model development and a phase III trial (OAK) as external evaluation.\(^10^\) A TGI-OS model, with on-treatment tumor growth rate constant (KG) as estimated using time profiles of the sum of longest diameters (target lesions per response evaluation criteria in solid tumours [RECIST] 1.1), albumin (ALB), and number of metastatic sites as independent prognostic factors, was able to predict the OS hazard ratio (HR) in subpopulations of patients with varying baseline PD-L1 expression in both trials. This model will be referred to herein as the “historical” OS model. In POPLAR and OAK, slower KG in the atezolizumab arm when compared with the docetaxel (control) arm predicted the OS benefit, whereas the other TGI metrics (i.e., time to growth, early change in tumor size, and tumor shrinkage rate constant), as well as classical clinical end points of overall response rate (ORR) and progression-free survival (PFS), did not predict the observed difference in OS in the two studies.\(^10^\) Although the link between tumor dynamics and OS was shown for other CITs,\(^12^\)–\(^13^\)–\(^16^\)–\(^19^\) this is the only analysis where the difference in TGI metrics (namely KG) across treatment arms in randomized studies was shown to predict treatment effect (HR of investigational treatment vs. control) on OS. Among the various tumor dynamic-based approaches to predict OS, the use of KG estimates seems to be quite promising as demonstrated in many studies.\(^5^\)–\(^10^\)–\(^15^\)–\(^18^\)–\(^25^\)

Limitations of the previous atezolizumab study\(^10^\) are the use of only one tumor type and the model development was based on data from a single clinical trial. To determine whether the TGI-OS platform can be generalized, the

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
The association between tumor growth inhibition (TGI) metrics and overall survival (OS) for atezolizumab was previously investigated in patients with non-small cell lung cancer from a phase II trial for model development and a phase III trial as external evaluation.

WHAT QUESTION DID THIS STUDY ADDRESS?
Whether the TGI-OS platform could be generalized for atezolizumab by the inclusion of 10 clinical studies across five solid tumor types.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
The TGI-OS models predicted the treatment effects of atezolizumab-containing and control arms based on the comparison of hazard ratios. The tumor growth rate was the most significant predictor of OS across tumor types, and inflammatory status and tumor burden were also strong predictors.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
Identification of patient-level baseline prognostic factors and early on-treatment information can be leveraged to predict longer term survival benefit in cancer immunotherapy studies in multiple cancer types and support early development decisions with combination treatments.
inclusion of other studies and tumor types should be explored. The objectives of our analysis were to develop multivariate TGI-OS models to predict the OS distribution and the benefit of atezolizumab-containing treatments compared with controls in 10 clinical studies stratified by five solid tumor types. The goal is to identify appropriate patient-level baseline prognostic factors as well as individualized, early on-treatment information in the form of KG to predict longer term survival benefit in CIT studies in multiple cancer types and to identify patients who are most likely to benefit from these therapies. Ultimately, a successful confirmation of the TGI-OS platform can facilitate application across other CITs to support phase II study design, end-of-phase II decisions, and phase III planning and analysis particularly with combination treatments.1–3

METHODS

The clinical trial protocols of the 10 trials have been previously described26–35 and are summarized in Table 1. Across all trials, patients in the atezolizumab-containing arm received either atezolizumab intravenously at 840 mg every 2 weeks (IMpassion130, triple negative breast cancer [TNBC]) or 1200 mg every 3 weeks (the other nine trials). The 10 trials were conducted in five solid tumor types—NSCLC, SCLC, TNBC, RCC, and mUC—in accordance with the Declaration of Helsinki after approval by institutional review boards or independent ethics committees. All patients provided written informed consent.

Tumor lesions were measured using computed tomography or magnetic resonance imaging at baseline and at regular intervals afterward (approximately every 6–9 weeks for 1 year and then every 9–12 weeks thereafter until disease progression, death, or loss of follow-up). Longitudinal tumor size data, defined as the sum of the longest diameters of target lesions at each visit according to RECIST 1.1, were used for the estimation of TGI metrics. Patients with at least baseline and one postbaseline tumor size measurements were defined as evaluable, and data from patients who only had baseline tumor assessments were excluded from the analysis.

TGI modeling methods have been previously published.10 Briefly, the biexponential TGI model proposed by Stein et al.18 was fit to the longitudinal tumor size data set by tumor type. In the model, TS0 is the model-estimated tumor size at the start of treatment (time = 0), KG is the tumor growth rate constant (1/week), and KS is the tumor shrinkage rate constant (1/week). The model was implemented as a nonlinear mixed effect model using NONMEM version 7.4. In each of the models by tumor type, a log-normal distribution was used to characterize the interindividual variability of KG and KS by treatment, with a common log-normal distribution for TS0 within the same tumor type, and an additive residual error was described by a normal distribution. TGI model evaluation was conducted using standard goodness-of-fit plots. Individual post hoc parameter estimates from the model were used as TGI metrics in the subsequent TGI-OS modeling.

The TGI-OS model was developed and evaluated as previously described.10 The impact on OS from a predefined list of potential covariates, which consisted of individual baseline prognostic factors for each tumor type (Table S1) and TGI metrics, was first explored using the Kaplan–Meier method. Baseline prognostic factors investigated across the five tumor types included variables associated with tumor burden (baseline tumor size [SLD], number of metastatic sites [MET], liver metastasis), inflammatory status (ALB, neutrophil-to-lymphocyte ratio [NLR], C-reactive protein [CRP]), and general prognostic factors (Eastern Cooperative Oncology Group performance status [ECOG], lactate dehydrogenase [LDH], alkaline phosphatase). In addition, race (White vs. non-White or Asian vs. non-Asian) and tumor-specific variables, such as hemoglobin, time since initial diagnosis, calcium, and sarcomatoid histology for RCC, were also tested in tumor-specific TGI-OS models. PD-L1, which is expressed on TCs and tumor-infiltrating ICs on a wide variety of cancer expressions and is targeted by atezolizumab, was scored by immuno-histochemistry as percentage of PD-L1–expressing TC (TC3 ≥ 50%, TC2 ≥ 5%, and <50%, TC1 ≥ 1% and <5%, and TC0 < 1%) and as percentage of PD-L1–expressing tumor area for IC (IC3 ≥ 10%, IC2 ≥ 5%, and <10%, IC1 ≥ 1% and <5%, and IC0 < 1%).36

Univariate screening of the covariates was evaluated using Cox regression analyses, and all significant covariates with a significance level of p < 0.05 per the log-likelihood ratio test were included in the full model. If several covariates relating to the same variable were significant in the Cox analysis, such as dichotomizing race to White versus non-White or Asian versus non-Asian, only the one with the best likelihood improvement was retained in the full model. The continuous covariates were not normalized by median values.

The full model parameters were estimated based on a parametric survival regression. The probability density function that best described the observed survival times was selected among normal, log-normal, Weibull, logistic, log-logistic, and exponential by using the difference in Akaike information criterion of the alternative models. Backward stepwise elimination of the full model was performed using a significance level of p < 0.01, and this resulted in the final model, in which all covariates were significant. The TGI-OS models were developed independently by tumor type, and model development and evaluation were implemented in R version 3.6.3 (R Foundation for Statistical Computing).

The model performances were evaluated using a simulation-based approach. Baseline prognostic factors as well as KG were resampled from observed values in the analysis data set for each tumor type. Model parameters were sampled from the estimated mean values and uncertainty in parameter estimates from the TGI-OS model for
| Trial name   | ClinicalTrials.gov identifier | Tumor type | Atezolizumab-containing arm (A) | Control arm (C) | Number of patients enrolled (A/C) | Number of TGI-evaluable patients (A/C) | Tumor assessment schedule | Tumor assessment among TGI-evaluable patients | Number of postbaseline tumor size assessments (A/C) |
|-------------|-------------------------------|------------|-------------------------------|-----------------|----------------------------------|----------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| OAK         | NCT02008227                  | NSCLC      | Atezolizumab                  | Docetaxel       | 421/401                          | 388/363                                | q6w for 36 weeks, then q9w     | 5277                                         | 2546/1653                                      |
| POPLAR      | NCT01903993                  | NSCLC      | Atezolizumab                  | Docetaxel       | 142/135                          | 129/123                                | q6w for 36 weeks, then q9w     | 1309                                         | 669/388                                       |
| IMpower130  | NCT02367781                  | NSCLC      | Atezolizumab + carboplatin + nab-paclitaxel | Carboplatin + nab-paclitaxel | 472/232                          | 441/214                                | q6w for 48 weeks, then q9w     | 4451                                         | 2868/929                                      |
| IMpower150  | NCT02366143                  | NSCLC      | Arm A: Atezolizumab + carboplatin + paclitaxel | Carboplatin + paclitaxel + bevacizumab | 402 (Arm A)/400 (Arm B)/360 (Control) | 377 (Arm A)/369 (Arm B)/369 (Control) | q6w for 48 weeks, then q9w     | 8007                                         | 2312 (Arm A)/2668 (Arm B)/1921 (Control)     |
| IMpower131  | NCT02367794                  | NSCLC      | Arm B: Atezolizumab + carboplatin + nab-paclitaxel | Carboplatin + nab-paclitaxel | 343/340                          | 311/317                                | q6w for 48 weeks, then q9w     | 6197                                         | 2057/1312                                     |
| IMpower132  | NCT02657434                  | NSCLC      | Atezolizumab + cisplatin/cisplatin/carboplatin + pemetrexed | Cisplatin/cisplatin + pemetrexed | 292/286                          | 241/239                                | q6w for 48 weeks, then q9w     | 2168                                         | 968/721                                       |
| IMpower133  | NCT02763579                  | SCLC       | Atezolizumab + carboplatin + etoposide | Placebo + carboplatin + etoposide | 198/196                          | 189/187                                | q6w for 48 weeks, then q9w     | 1969                                         | 862/731                                       |
| IMvigor211  | NCT02302807                  | mUC        | Atezolizumab                  | Chemotherapy (vinflunine vs. taxane:paclitaxel and docetaxel) | 459/443                          | 382/362                                | q9w for 54 weeks, then q12w   | 2822                                         | 1204/874                                      |
| IMpassion130 | NCT02425891                 | TNBC       | Atezolizumab + nab-paclitaxel | Placebo + nab-paclitaxel | 452/438                          | 439/422                                | q8w for 12 months, then q12w  | 4171                                         | 1843/1467                                     |
| IMmotion151 | NCT02420821                 | RCC        | Atezolizumab + bevacizumab    | Sunitinib       | 454/461                          | 425/421                                | At 12 weeks after randomization, followed by q6w until Week 78, then q12w after 78 weeks | 7076                                         | 3355/2873                                     |

**Note:** Atezolizumab is given at 1200 mg q3w except in IMpassion130, where atezolizumab is given 840 mg q2w.

*Abbreviations:* mUC, metastatic urothelial carcinoma; NSCLC, non-small cell lung cancer; q#w, every # weeks; RCC, renal cell carcinoma; SCLC, extensive-stage small cell lung cancer; TNBC, triple-negative breast cancer.
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each of the simulated study replicate. Censoring was sim-
ulated by sampling patient study duration from a uniform
distribution based on observed censoring data as shown in
Figure S1. Simulation results of the TGI-OS model were fur-
ther summarized as OS HR by comparing the atezolizumab-
containing arm(s) to the respective control arm of each
clinical trial. OS distributions and HR of the atezolizumab-
containing arm versus control of each trial were simulated
1000 times.

The performance of the TGI-OS model for NSCLC was
further evaluated using external validation by randomly split-
ting the data from 70% of the patients into a training set and
30% into a testing set and using the model developed from
the training set to predict the OS outcome of the patients in
the testing set. The model performance was evaluated based
on the concordance index (c-index).37

RESULTS

Data from one phase II and nine phase III atezolizumab trials
were included in the analysis. Among these 10 trials, treat-
ment consisted of atezolizumab monotherapy, atezolizumab
in combination with chemotherapy (e.g., carboplatin), and/
or targeted therapy (e.g., bevacizumab), and the active con-
trol arm generally included the corresponding combination
treatment, chemotherapy (e.g., docetaxel), or targeted ther-
apy (e.g., sunitinib), as shown in Table 1. A total of 6699 of
the 7367 patients randomized (90.0%) to the 10 trials were
considered TGI evaluable. The numbers of randomized and
TGI-evaluable patients by trial are listed in Table 1. Of the
five tumor types included in the analysis, the majority of the
data (57%) were in NSCLC. A total of 43,447 baseline and
posttreatment tumor assessments from the TGI-evaluable pa-
tients were used for TGI model development, with an average
of 6.49 tumor assessments per patient. The median duration
of tumor assessments ranged between 123 days (mUC) and
380 days (RCC), and the majority of OS data with censoring
was up to 405 days of follow-up, except in RCC, where the
median OS had not been reached (Figure S1). The difference
between the median duration of tumor assessment and OS
duration ranged from 129 days (mUC) to 407 days (TNBC),
with a median of 275 days across tumor types. Within each
trial, the atezolizumab-containing treatment arm is gener-
ally associated with longer duration of tumor assessment, as
shown in Figure S1, as the patients who had slower disease
progression were more likely to continue clinical visits.

The biexponential TGI models were fitted to tumor
type-specific data. An example model was included in the
Supplementary Material. The TGI model was sufficiently
flexible to capture different patterns of tumor dynamics ob-
served for NSCLC as well as for the other four solid tumor
types. Example model fits of individual tumor size data are
illustrated in Figure S2, and the goodness-of-fit plots for the
longitudinal tumor data are shown in Figure S3, indicating no
bias across time or tumor size as well as demonstrating good
correlations between observed and predicted values among
the five tumor-specific models.

The final TGI model parameter estimates by tumor type
are shown in Table S2. All parameters are estimated pre-
cisely regardless of treatment type or tumor type, with a
relatively low standard error <10% for KG and <13% for
KS. Overall, individual parameter estimates were not re-
duced to the population mean, and particularly for KG, the
estimated shrinkage values38 were generally below 20%, in-
dicating the data were informative for individual parameter
estimations.

A comparison of KG distributions between treatments
for NSCLC is shown in Figure 1. Across tumor types, mUC
has faster tumor shrinkage with larger KS, and SCLC has
the slowest tumor regrowth with smaller KG, irrespective
of treatment type. The typical TGI profiles stratified by
treatment and trial are shown in Figure 2.

Along with the predefined lists of baseline prognostic
factors, individual KG estimates were considered as co-
variates for the TGI-OS model development. Previously,

![FIGURE 1](image_url)  
Model-estimated KG comparison between treatments in patients with non-small cell lung cancer. Dots indicate individual model-estimated KG, ends of boxes indicate 25th and 75th percentiles (i.e., interquartile range), horizontal lines indicate medians, and ends of whiskers indicate 1.5 times the interquartile range. Atezo, atezolizumab; B, bevacizumab; C/C, cisplatin/carboplatin; CnP, carboplatin + nab-paclitaxel; CP, carboplatin + paclitaxel; Doce, docetaxel; KG, tumor growth rate constant; P, pemetrexed.
KG has been shown to be a strong predictor of OS in atezolizumab trials for NSCLC. Exploration of the association between KG and OS data was conducted using Kaplan–Meier analysis and is shown in Figure S4. In all tumor types, a trend of inverse correlation is observed between tumor growth and survival, with the slowest KG (lowest quartile of log(KG)) having the longest OS.

TGI-OS models for each tumor type were developed using univariate screening, followed by backward elimination. The parameter estimates of the final TGI-OS models based on a log-normal probability density function are shown in Table 2 for NSCLC and in Table S3 for other tumor types. KG was the most significant predictor of OS across all five tumor types.

Several baseline prognostic factors were highly significant across multiple tumor types (Table 3), such as inflammatory status (CRP, ALB, and/or NLR in all tumor types), tumor burden (SLD, MET, and/or liver metastasis in all tumor types), ECOG (four tumor types, excluding RCC), LDH (two tumor types), and race in terms of Asian versus non-Asian (two tumor types).

According to TGI-OS models, survival probability increases when CRP, NLR, SLD, or the number of metastatic sites decreases, and ALB increases. In addition, IC/TC PD-L1 expression groups and line of treatment were significant prognostic factors for NSCLC, in which the data combined both first-line and later lines of treatment. Four tumorspecific variables were also significant prognostic factors for RCC. Statistical summaries of the significant prognostic factors by trial and by treatment for NSCLC and by tumor type for the other models are shown in Table S4. Notably, 40.8% (N = 196) of patients in the IMpower132 trial for NSCLC had missing IC or TC PD-L1 expression information, but when combined with the rest of the NSCLC data, only 4.9% of patients (203 of 4179) had missing IC or TC information.

The predictive ability of the TGI-OS models was evaluated by comparing the 95% prediction intervals (PIs) of simulated survival distributions with observed distributions, stratified by treatment type (Figure S5). The overlapping of the curves suggests that the models can reasonably reproduce the observed survival distributions in all treatment types across the five tumor types.

The TGI-OS models were also evaluated by simulating OS HR by atezolizumab treatment arm versus appropriate control in each trial, conditional on the individual baseline prognostic factors and estimated KG, as shown in Figure 3. The model-predicted HRs indicate good model performance across all 11 comparisons from 10 trials, with observed HRs within the 95% PIs for all trial arms.

The results of the external validation by randomly splitting the data show that the c-index of the training (0.753) and of the testing sets (0.754) are the same or similar to the c-index of the model developed using the full set of data (0.754), indicating a good and consistent predictive accuracy of the model. The model evaluation using OS HR based on the testing set is shown in Figure S6. External validation for the other tumor types was not conducted due to the relatively small sample sizes.

**DISCUSSION**

Model-based estimates of on-treatment growth rate (KG) have been found to predict for OS in a variety of tumor types.
and treatments. More recently, KG was found to be the only tumor dynamic metric able to predict survival benefit in one phase II study and one phase III study of atezolizumab versus chemotherapy in second and later lines of therapy for NSCLC, whereas other model-based metrics or classical end points (ORR, PFS) did not. US FDA scientists found that KG was inversely associated with OS in 24 randomized NSCLC clinical trials with CPIs or targeted therapies, although they did not develop a predictive model, suggesting that KG estimates from early tumor dynamic data might serve as an earlier end point in clinical studies.

The present analysis aimed to confirm the use of KG in predicting long-term survival benefit as well as to identify baseline prognostic factors that are common or specific across five solid tumor types using data from 10 atezolizumab randomized clinical trials.

Because the majority of data in the analysis was collected from patients with NSCLC (N = 3872 TGI-evaluable patients), a tumor-specific model was constructed from a large NSCLC data set of 27,409 tumor assessments, enabling a robust evaluation of the impact of a diverse set of patient characteristics. Comparing to the historical atezolizumab TGI-OS model that was developed from a phase II trial, in addition to ALB and the number of metastatic sites, the updated model incorporated the additional independent baseline prognostic factor effects of CRP, LDH, NLR, ECOG, race, presence of liver metastases, and PD-L1 expression (IC or TC > 0), which were investigated in the previous analysis but deemed not to be significant. This phenomenon was probably attributed to the narrow range of the covariate values available or to the small sample size in each subgroup for the previous analysis, thereby causing a decrease in power in detecting the effect on OS from these covariates. The updated NSCLC model also differentiated the effects between the first-line and later lines of treatment, mainly by using a more comprehensive data set for model development, as opposed to the previous analysis, where only data for second and later lines of therapy were available. The directions of effect from the significant covariates on OS are consistent with the general knowledge of the trends between these prognostic factors and patient survival (e.g., higher ECOG score is associated with worse prognosis). In contrast, tumor burden, age, sex, body weight, histology (non-squamous vs. squamous), and smoking history were not independent significant baseline prognostic factors in the historical or in the updated multivariate TGI-OS model.

PD-L1 expression was determined to be a significant covariate in the TGI-OS model for NSCLC. PD-L1 expression is the most widely accepted predictive biomarker for treatments with immune checkpoint inhibitors; however, its role is not clear, particularly in the combination treatment setting. Because PD-L1 expression information in terms of IC/TC groups was missing in a large number of patients in one of the NSCLC trials (IMpower132), a sensitivity analysis was conducted by excluding IC/TC from the TGI-OS model development. The results of the sensitivity analysis showed that the same set of covariates besides IC/TC were selected for the final model after backward elimination, and parameter estimates were similar to the model incorporating IC/TC groups (Table S5), with similar model evaluations using OS HR estimates.
(Figure S7). On the other hand, because IC/TC information is specific to immune checkpoint inhibitors targeting PD-1 receptors, the TGI-OS model without the IC/TC group in the sensitivity analysis could be applied to NSCLC trial data based on treatments with other mechanisms of action. The c-index of the model without IC/TC is 0.752, which is similar to that of the model with IC/TC (0.754), further confirming the good predictive accuracy of both models.

The most impactful covariate (second to KG) in the updated NSCLC model was CRP, which was not available previously for the development of the historical model that only used data from one clinical trial. This is consistent with results from a separate analysis based on data from two of the trials included in the current analysis.40 CRP was also a significant baseline prognostic factor in the TNBC model. CRP is an inflammation biomarker, routinely used in clinical practice for monitoring patients with cancer, and studies show an association between elevated CRP levels with a poor response and worse survival in epithelial cancers, such as liver, lung, colorectal, and breast cancers.41–44

Another biomarker that was shown to be a significant covariate in the TGI-OS models from four of five tumor types is ALB, where hypoalbuminemia is a known risk factor for poor prognosis in patients with cancer45 and may be associated with cancer cachexia and impaired response to checkpoint inhibitors.46 A similar association between ALB and OS have been identified in patients with locally advanced urothelial carcinoma or mUC treated with durvalumab13 and in Asian patients with NSCLC treated with motesanib.9

In the five tumor-type specific TGI-OS models developed in the current analysis (i.e., NSCLC, SCLC, TNBC, mUC, and RCC), KG was the most significant covariate in predicting OS, showing that increasing KG is associated with decreasing survival time. This is similar to an analysis conducted by the US FDA using data from 24 NSCLC trials.25 In the current analysis, atezolizumab-containing treatments had lower median KG, that is, slower growth, than treatments from the respective control arms, and this is consistent with the observation that the atezolizumab-containing arms have shown significant or numerical improvements in OS over control in all of the trials.26,27,29,33,34 Therefore, the exposure-driven treatment effects were assumed to have been captured by the estimated KG, and the subsequent survival model can be considered treatment independent.1,2 The biexponential TGI model was able to provide an adequate fit to the observed tumor size data, indicating that the individual post hoc estimates of KG described the individual longitudinal profiles well. No covariates were investigated for the TGI model (and KG), as the objective of the analysis was to simulate OS, conditional on TGI metrics and baseline prognostic factors.

Tumor dynamics has been studied as an early efficacy marker for other CITs as well as for chemotherapy and targeted
therapy. Among CIT treatments, tumor growth patterns were investigated with pembrolizumab, ipilimumab, nivolumab, durvalumab, and bevacizumab across melanoma, NSCLC, mUC, and kidney cancer types, and all reported a strong association between survival and tumor response metrics, such as early tumor size change, KG, or KS,13,15,16,47,48 supporting the validity of TGI-OS correlation in CIT. Although tumor growth rate in terms of KG was the most significant TGI metrics in predicting OS for atezolizumab-containing treatments, other TGI metrics should be explored when applying the TGI-OS framework to molecules and study designs (e.g., patient population or trial follow-up duration) not investigated previously.

A similar model-based framework has been applied to other NSCLC9,11,25,40 and breast cancer8 analyses as well as in other tumor types such as prostate15,18 and ovarian cancer.19 In most cases, the analysis focuses on a single tumor type. The strength of the current analysis lies in its conglomeration of five different tumor types and thereby providing a wealth of support for the TGI-OS platform in various solid tumor types. In addition, it is the first study where TGI-OS models have been shown to predict OS treatment benefit across a wide variety of trials and tumor types. Although the analysis data originated from atezolizumab trials, the analysis is not restricted to atezolizumab monotherapy because various treatment types were included in the analysis due to the different treatments used in the control arms and in combination with atezolizumab. However, whether the TGI-OS platform will apply to other anticancer treatments with different mechanisms of action remains to be determined, and external validation studies with other data sets are warranted. Furthermore, the association between tumor growth rates and OS could be explored using novel modeling approaches, such as machine learning.40,49

One limitation of the current work is that the two-stage approach may suffer from selection bias due to patients with progressing-only disease dropping out early in the trial. Joint modeling has been shown to address this issue based on a simulation study.50 However, in an analysis conducted using observed clinical data, the difference in model predictions between the joint model and two-stage approaches might not be clinically meaningful.51 Recent research indicates that

![Figure 3](image-url)

**Figure 3** Hazard ratios of atezolizumab-containing arm versus control by study based on simulations of the tumor growth inhibition–overall survival models. N indicates number of tumor growth inhibition–evaluable patients in each group and arm (atezolizumab/control) with nonmissing covariates. Squares indicate observed hazard ratios, circles indicate median model-predicted hazard ratios, and bars indicate 95% prediction intervals (PIs) based on 1000 replicates. 1L, first line; 2+L, second or later line; Atezo, atezolizumab; B, bevacizumab; C/C, cisplatin/carboplatin; CE, carboplatin+etoposide; Chemo, chemotherapy; CI, confidence interval; CnP, carboplatin+nab-paclitaxel; CP, carboplatin+paclitaxel; Doce, docetaxel; mUC, metastatic urothelial carcinoma; nP, nab-paclitaxel; NSCLC, non-small cell lung cancer; P, pemetrexed; PBO, placebo; RCC, renal cell carcinoma; SCLC, extensive-stage small cell lung cancer; TNBC, triple-negative breast cancer.
competing risks joint models may be needed to correct for dropouts (by inducing informative censoring) when simultaneously modeling longitudinal biomarker and terminal event data. These questions require further evaluation with regard to the objectives of the modeling effort. The impact of follow-up on TGI metrics estimates and OS HR predictions at the study level to support decisions based on early data cuts is being assessed using both two-stage and joint models. We contend that TGI metrics derived based on two-stage models are more actionable to support trial decisions, whereas current SLD (or SLD slope)-based joint models are more suitable to perform patient-level dynamic predictions and enable personalized health care.

In conclusion, our study results provide further support that tumor dynamic model-based metrics (such as KG) could help support early decisions between alternative treatments, select the most promising combinations in future CIT clinical trials, and predict the probability of success of a phase III clinical trial.

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CONFLICT OF INTEREST

P.C., K.Y., S.V., N.W., A.L., B.W., M.B., N.S., J.Y.J., and R.B. are employees and stockholders of Genentech, Inc. M.M. is employed by Certara Strategic Consulting.

AUTHOR CONTRIBUTIONS

P.C., M.M., K.Y., B.W., M.B., N.S., J.Y.J., and R.B. wrote the manuscript and designed the research. P.C., M.M., and K.Y. performed the research. S.V., N.W., and A.L. analyzed the data.

ORCID

Phyllis Chan https://orcid.org/0000-0003-1509-1526
Kenta Yoshida https://orcid.org/0000-0003-4967-3831
René Bruno https://orcid.org/0000-0003-0200-039X

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Additional supporting information may be found online in the Supporting Information section.

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