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ORIGINAL REPORT

Model-Based Prediction of Phase III Overall Survival in Colorectal Cancer on the Basis of Phase II Tumor Dynamics

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ABSTRACT

Purpose
We developed a drug-disease simulation model to predict antitumor response and overall survival in phase III studies from longitudinal tumor size data in phase II trials.

Methods
We developed a longitudinal exposure-response tumor-growth inhibition (TGI) model of drug effect (and resistance) using phase II data of capecitabine (n = 34) and historical phase III data of fluorouracil (FU; n = 252) in colorectal cancer (CRC); and we developed a parametric survival model that related change in tumor size and patient characteristics to survival time using historical phase III data (n = 245). The models were validated in simulation of antitumor response and survival in an independent phase III study (n = 1,000 replicates) of capecitabine versus FU in CRC.

Results
The TGI model provided a good fit of longitudinal tumor size data. A lognormal distribution best described the survival time, and baseline tumor size and change in tumor size from baseline at week 7 were predictors ($P < .00001$). Predicted change of tumor size and survival time distributions in the phase III study for both capecitabine and FU were consistent with observed values, for example, 431 days (90% prediction interval, 362 to 514 days) versus 401 days observed for survival in the capecitabine arm. A modest survival improvement of 39 days (90% prediction interval, −21 to 110 days) versus 35 days observed was predicted for capecitabine.

Conclusion
The modeling framework successfully predicted survival in a phase III trial on the basis of capecitabine phase II data in CRC. It is a useful tool to support end-of-phase II decisions and design of phase III studies.

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INTRODUCTION

Drug development in general, and specifically in oncology, is considered an inefficient process[1]; this is the reason that the US Food and Drug Administration launched the Critical Path Initiative,[2] which aims to modernize this process. To date, decision making and trial design during early oncology drug development remains an empirical process. Antitumor activity in early phase II studies typically is evaluated by using objective response rate (ORR), and achievement of a predefined ORR is the main decision criteria for proceeding to phase III clinical trials and to inform phase III study design. Observation of response in phase II, indeed, is associated with positive results in subsequent phase III.[3,4] However, ORR estimates in typical, small, noncomparative, phase II trials are generally pretty imprecise and uninformative to make go–no go decisions and to support the design of phase III clinical trials.[5,6] In addition, ORR or progression-free survival (PFS) end points preclude the conduct of adequately powered, randomized, phase II studies to establish dose-response relationships and/or to compare alternative schedules. There clearly is a need for new end points and methods to improve the selection of candidate drug/regimen in early clinical studies.[5-8] The use of relative change in tumor size from baseline has been proposed to compare treatments and to make decisions on the basis of a smaller number of patients in randomized, phase II studies.[9,10] In the Critical Path Initiative,[2] the concept of model-based drug development is supported as holding "vast potential to support more efficient and effective development of drugs" (Executive Summary, p ii). In this manuscript, we developed a modeling framework that comprised a longitudinal exposure-response tumor growth inhibition (TGI) model to evaluate

antitumor effect on the basis of continuous tumor size measurements and a survival model that used change in tumor size as the main predictor for survival together with prognostic factors.

The combination of these models, together with the use of drug-specific and disease/patient-specific parameters, allow scaling of drug effect across patient populations and drug development phases (eg, phase II to phase III). This approach was evaluated retrospectively in metastatic colorectal cancer (mCRC) with capecitabine (considered an investigational drug in this work) in an attempt to predict survival outcome of a phase III study of capecitabine versus fluorouracil (FU; the standard reference drug) on the basis of capecitabine phase II data and historical FU phase III data.

METHODS

Trials and Data

Capecitabine data came from a randomized, phase II study designed to test three dosing schedules of capecitabine as first-line therapy in patients with advanced and/or metastatic CRC.[11] Data (ie, tumor size measurements for target lesions, dosing histories) from the intermittent regimen (arm B; capecitabine 1,255 mg/m^2 twice daily for 14 days followed by a 7-day rest period; n = 34) that was additionally selected for testing in phase III studies were used to develop the TGI model for capecitabine. The ORR was 24% (95% CI, 11% to 41%). FU (reference drug) historical data were obtained from the FU arm (n = 301) of a large, randomized, phase III trial conducted to determine whether the intermittent regimen of oral capecitabine was at least as active as bolus intravenous (IV) FU plus leucovorin (FU/LV) as first-line treatment for mCRC.[12] This open-label, randomized, parallel-group study compared capecitabine 1,250 mg/m^2 (same regimen as arm B intermittent regimen) to FU/LV administered according to the Mayo Clinic regimen, which consisted of a rapid IV injection of LV 20 mg/m^2 followed by an IV bolus injection of FU 425 mg/m^2 FU daily on days 1 to 5 every 4 weeks. Tumor size measurements for target lesions, dosing histories, and dates of death and censoring from the FU arm were used to develop the TGI model for FU and for the drug-independent survival model. In this arm, ORR was 15.5% (95% CI, 11.6% to 20.1%).

Model Development

TGI model. A model accounting for the dynamics of tumor growth, antitumor drug effect, and resistance to drug effect was developed on the basis of a previously published simulation model.[13] The model describes tumor size (ie, sum of the longest diameters of target lesions according to the RECIST [Response Evaluation Criteria in Solid Tumors Group] criteria) as a function of time and drug exposure and accounts for the natural growth of the tumor and drug action on the tumor (ie, cell kill driven by drug exposure). The model incorporates a first-order tumor growth rate, as we did not find any evidence of Gompertz growth (as used by Iliadis et al[13]). In addition, a resistance process was incorporated to describe the regrowth of tumor apparent in some patient profiles.

The model is described by the differential equation below:

$$\frac{dy(t)}{dt} = K_L \cdot y(t) - K_D(t) \cdot \text{Exposure}(t) \cdot y(t) \quad y(0) = y_0 \qquad (1)$$

with

$$K_D(t) = K_{D,0} \cdot e^{-\lambda t} \qquad (2)$$

in which y(t) is the tumor size at time t, y_0 is the baseline tumor size, K_L is the tumor growth rate, $K_D(t)$ is the drug-constant cell kill rate that decreases exponentially with time (according to λ) from an initial value of $K_{D,0}$ to account for the progressive development of resistance, Exposure(t) is the drug exposure at time t. Because no pharmacokinetic data were available, the daily dose was used as a metric for exposure to drive drug effect.

Interpatient variability in the model parameters (K_L, K_D, and λ) was assumed to be lognormally distributed, and patient specific estimates were given by, for example, K_L:

$$K_{Li} = K_L \cdot \exp(\eta_i^{K_L}) \qquad (3)$$

in which K_L is the typical value for the population and η_i^{KL} is an interpatient random effect that follows a normal distribution with a mean of 0 and variance of ω^{2KL}. An additive, normally distributed residual error, with a mean of 0 and variance σ^2, accounted for measurement error and all residual unexplained sources of variability. The model parameters were estimated in a nonlinear, mixed-effect analysis, in which data from all patients were analyzed simultaneously by using the NONMEM program (version V, level 1.1; GloboMax, Hanover, MD). Parameters were estimated by using the first order conditional estimation algorithm with interaction.[14] Of note, this model incorporates drug-specific (K_D and λ) and disease-specific parameters/characteristics (K_L, y_0).

Survival model. A survival model was developed to describe the survival time (T) distribution as a function of covariates. The probability density function that best described the observed survival time was selected among normal, lognormal, Weibull, logistic, log-logistic, exponential, and extreme[15] by using difference in log-likelihood and goodness of fit plots of the alternative models. In the case of a lognormal distribution, log(T) is normally distributed with a mean of α and variance of σ^2.

The following predictors for α were incorporated in the model: tumor size at baseline (a measure of disease characteristics) and relative change in tumor size from baseline at first post-treatment visit (around week 7; a measure of drug effect), which was calculated as the following:

$$\frac{y(0) - y(\text{week7})}{y(0)} \qquad (4)$$

in which y(week 7) is the TGI model–predicted tumor size at week 7. Week 7 response was selected, as data were available for most patients. Model parameter estimation was done by using the CensorReg function in S-Plus. Of note, the survival model can be considered a drug-independent model that relates a biomarker response (ie, change in tumor size) and prognostic factors (ie, baseline tumor size) to a clinical end point (ie, survival time).

Simulation and Assessment of the Modeling Framework

The models were used to simulate tumor size at week 7 and survival across replicates (n = 1,000) of an independent phase III study (ie, the validation study) of capecitabine versus FU/LV that used the same dosing regimen for both drugs.[16] This study was also designed to demonstrate that capecitabine was at least as active as bolus IV FU/LV. The data analysts (L.C., P.G., and R.B.) were blinded for any study result before simulating the study. The distributions of simulated relative change in tumor size from baseline (ie, median and quartiles at week 7 across individuals) and survival time (ie, Kaplan and Meier plots and median estimates) across replicates of the simulated phase III study were compared with observed ones. For each of the replicates, model parameters were drawn from model parameter uncertainty distributions; individual patient TGI model parameters were computed in sampling individual random effects from corresponding interpatient normal distributions; residual error was added to predicted tumor sizes; and patient survival times were drawn from the parametric survival model probability density function.

Capecitabine and FU responses in the phase III study were predicted from phase II capecitabine data and FU historical phase III data by using drug-specific parameters; disease-specific, drug-independent parameters; and patient characteristics according to the scheme given in Figure 1.

RESULTS

Tumor Size Model

The longitudinal tumor size data (ie, sum of larger target lesions diameters at each visit) observed in 34 patients treated with capecitabine (arm B[11]) are illustrated in the Appendix Figures A1 (online only).

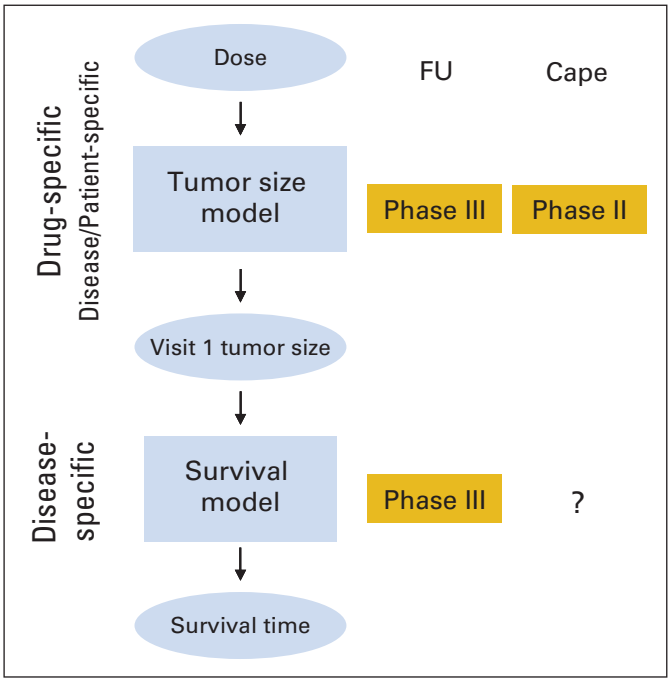

Fig 1. Scheme for simulating a phase III study on the basis of phase II data of an investigational agent (here, capecitabine [Cape]) and historical phase III data of a reference drug (fluorouracil [FU]).

A large range of baseline sizes was observed together with a variety of profiles during drug treatment.

The tumor size model provided a good fit of both capecitabine and FU data. The fit of the model to capecitabine data is illustrated in the Appendix Figures A2 through A3 (online only).

Parameter estimates are listed in Table 1 for both capecitabine and FU. Model parameters are well estimated with estimations and standard errors (SEs) typically less than 30% except for the rate constant for resistance appearance for capecitabine (SE, 58%) and for some of the interpatient variances, particularly for capecitabine. The larger uncertainty of estimates for capecitabine is due to the smaller number of patients in the phase II study. This uncertainty is accounted for in the simulation process. Of note, the K_L estimate is 40% faster in the capecitabine data set (ie, phase II patients) compared with that of the phase III patients (ie, FU data set), which reflects differences in disease progression among the patient populations. K_D for two drugs cannot be readily compared, as it depends on dose and dosing schedule. The dynamics for resistance appearance are different for both drugs, but are more uncertain for capecitabine.

Table 1. Tumor Growth Model Parameter Estimates

Parameter	Study Data: Capecitabine Phase II (n = 34) Estimate	Capecitabine Phase II (n = 34) Relative SE (%)	FU Phase III (n = 252) Estimate	FU Phase III (n = 252) Relative SE (%)
Tumor growth rate				
K_L, week^{-1}	0.021	27.6	0.015	25.4
Cell kill rate				
K_D, g^{-1} × week^{-1}	0.025	19.9	0.058	17.0
Resistance appearance				
λ, week^{-1}	0.053	57.7	0.042	28.7
Interpatient variance				
ω^{2KL}	0.499	36.9	0.556	27.8
ω^{2KD}	0.388	67.0	0.540	43.7
$\omega^{2\lambda}$	1.260	126.2	0.450	55.5
Residual error				
σ, mm	11.83		14.9	

Abbreviations: Fu, fluorouracil; KL, tumor growth rate; K_D, drug-constant cell kill rate; λ, resistance appearance rate; ω^2, variance of interpatient variability; σ, standard deviation of residual error.

Table 2. Survival Model Parameter Estimates

Parameter	Estimate	Relative SE (%)	Wald *P*
Intercept*	6.27	1.3	< .00001
Baseline tumor size, mm^{-1}	−0.0038	20.3	< .00001
Change in tumor size at week 7	1.61	17.4	< .00001
σ	0.699	NA	NA

Abbreviations: σ, SE of the lognormal distribution; NA, not available.
*Survival time analyzed in days.

Survival Model

The survival model was developed on the basis of the FU arm of the historical phase III study.[12] From the 301 patients included in the study, 245 patients with observed tumor size at week 7 were used to build the survival model. The lognormal distribution best described the survival time. Baseline tumor size (ie patient characteristic) and change in tumor size from baseline at week 7 (ie, drug effect) were significant predictors of survival time. Parameter estimates of the survival model are listed in Table 2. Model parameters are well estimated. Baseline tumor size and change from baseline at week 7 (median, 6.9 weeks; range, 1 to 10 weeks) are highly significant predictors, and their effects are well estimated. As expected, larger baseline tumor size was associated with poorer prognosis, and larger tumor shrinkage at week 7 predicted longer survival.

Simulation

An independent validation phase III study[16] was simulated by using the modeling framework. Consistent with the process described in Figure 1, patient characteristics (ie, baseline tumor size), dosing histories, and model parameters for simulating the two arms were obtained as listed in Table 3.

Survival times for early-dropout patients (ie, patients who dropped out before first tumor assessment and could not be simulated with the model) were resampled from observed survival times (n = 39 [13%]; median survival, 200 days; 95% CI, 117 to 303 days) in the historical study.[12]

After completion of the simulations, actual study results were compared with simulations. Simulated week 7 change in tumor size from baseline in the capecitabine arm is shown in Figure 2. Observed median and quartiles (25% and 75% quartiles) were well within the predictive distribution of the model (model-predicted median, 0.115; 90% prediction interval, 0.045 to 0.191; observed value, 0.061). Good performance of the model also was observed for the FU arm; the

Table 3. Sources of Patient Characteristics and Parameter Estimates to Simulate an Independent Phase III Study

Variable	Samples and Estimates Sources by Treatment	
	Capecitabine	FU
Baseline tumor size*	Sampled[12]	Sampled[12]
Dosing history	Sampled[11]†	Sampled[12]‡
Drug-specific parameters K_D and λ§	Estimated[11]; in Table 1	Estimated[12]; in Table 1
Tumor growth rate, K_L‖	Estimated[12]; in Table 1	Estimated[12]; in Table 1
Survival model parameters¶	Estimated[12]; in Table 2	Estimated[12]; in Table 2
Early-dropout patient survival#	Sampled[12]	Sampled[12]

Abbreviations: FU, fluorouracil; K_D, drug-constant cell kill rate; λ, resistance appearance rate; K_L, tumor growth rate.

*Baseline tumor sizes typical for phase III patients taken from historical data[12] (median, 71 mm; range, 12 to 331 mm).

†Assumes same dose intensity in the phase III arm as observed in the phase II study.[11]

‡Assumes same dose intensity in the simulated study as observed in the historical study.[12]

§Drug-specific parameters estimated from phase II data[11] for capecitabine and historical phase III data[12] for fluorouracil.

‖Disease-specific parameters estimated from historical phase III data.[12] Allows to scale capecitabine tumor size predictions from phase II to phase III patients.

¶Drug-independent model parameters estimated by using historical phase III data.[12]

#Assumes same pattern for early dropout in the two phase III studies.

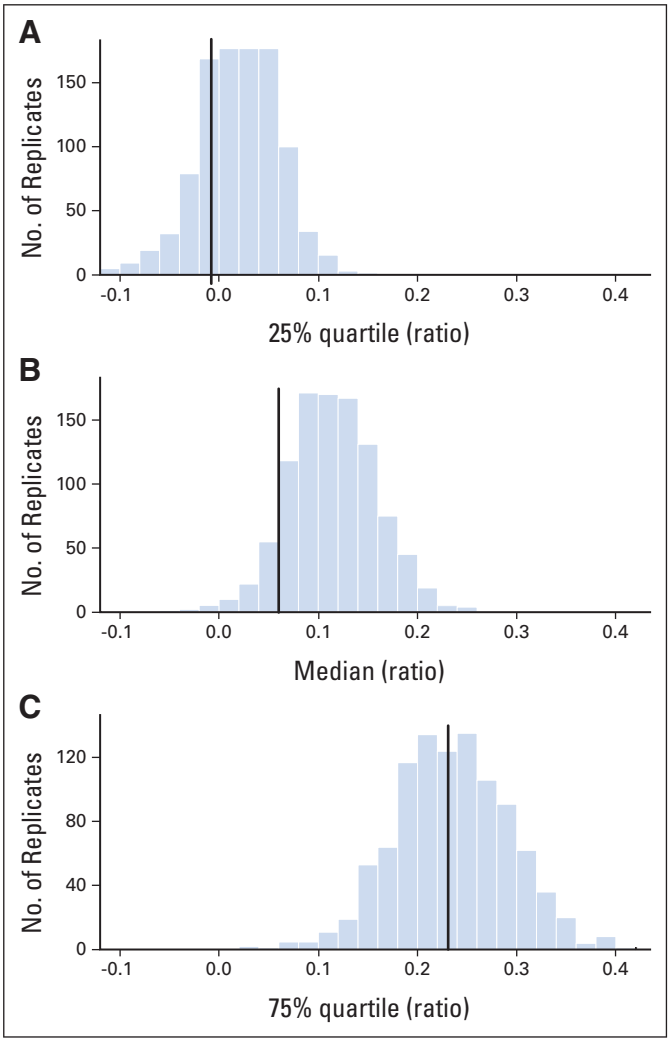

Fig 2. Distribution of predicted tumor size reduction (relative to baseline) compared with observations (vertical lines) for capecitabine in the phase III study.[16] Simulations were performed by using the tumor-growth inhibition model, capecitabine-specific parameters, disease-specific growth rate, and baseline tumor sizes, as described in Table 3.

model-predicted median was 0.047 (90% prediction interval, 0.027 to 0.070) compared with an observed median value of 0.053.

Survival prediction is shown in Figure 3 for the capecitabine arm. The observed Kaplan-Meier curve is well within the 90% prediction interval. The observed median survival (90% prediction interval) in the two arms were 431 days (362 to 514 days) versus 401 days for capecitabine and 392 days (342 to 444 days) versus 366 days for FU. Capecitabine treatment would result in a potential survival improvement of 39 days (−21 to 110 days) versus 35 days observed compared with patients treated with FU.

DISCUSSION

A modeling framework to analyze phase II data from investigational treatments and to simulate expected survival in phase III studies in an attempt to support end of phase II decisions has been proposed. The approach utilizes longitudinal tumor size data to estimate drug- and disease-specific parameters by using a TGI model, and it uses historical survival data to develop a drug-independent survival model that incorporates prognostic factors and predicted change in tumor size from baseline. The modeling framework succeeded in predicting survival in a phase III trial of capecitabine versus FU in patients with CRC [16] on the basis of capecitabine phase II data[11] and historical FU data.[12] This approach assumes that drug- and disease-specific parameters/models can be used and combined (as shown in Fig 1 and as summarized in Table 3) to predict antitumor drug effect and expected survival for an investigational agent in phase III patients on the basis of early phase II data. The small survival difference predicted by the model between the capecitabine and FU arms (39 days, although uncertain) and that observed in the actual study (35 days)[16] may not have been expected on the basis of the large response rate observed in phase II.[11] In this specific example, the small survival difference is due to the choice of drugs. However, a predicted lack of difference might be of importance in making end-of-phase II decisions and in designing phase III studies. Additional validation of the approach is warranted with different agents and in other tumor types. We also developed a similar approach (ie, TGI model combined with drug-independent survival model) in metastatic breast cancer,[17] and investigators at the US Food and Drug Administration independently developed a drug-independent survival model in non–small-cell lung cancer (NSCLC) by using data from four pivotal trials.[18] In both our metastatic breast cancer model and the US Food and Drug Administration NSCLC model, an early measure of change in tumor size from baseline (weeks 6 to 8) was a significant predictor in the survival models. Of note, the US Food and Drug Administration database[18] included agents with a variety of mechanisms of action, including a best supportive care arm. Change in tumor size is a more informative, patient-level, continuous

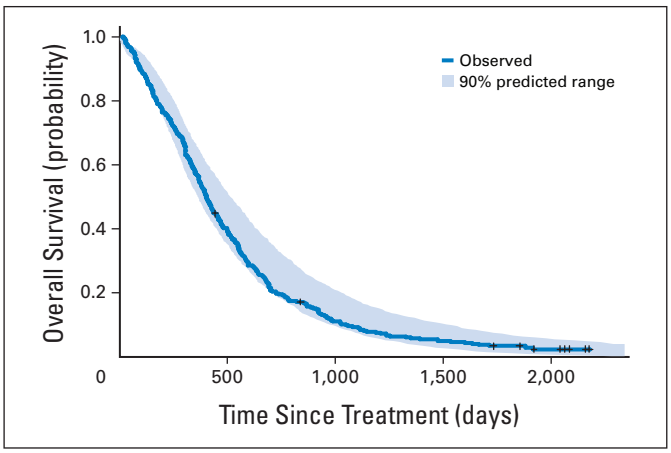

Fig 3. The 90% prediction interval (light blue area) and observed (line) survival curve for capecitabine in the phase III study. Simulations were performed by using the drug-independent survival model, the week 7 tumor size reduction predicted by the tumor-growth inhibition model, and baseline tumor sizes, as described in Table 3.

end point that can be assessed in small, randomized, early phase II studies, and it seems to be a better predictor of survival than ORR. In a recent study, week 8 response also was found to predict for survival in NSCLC.[19] TGI models have been used to analyze tumor xenograft data[20] and also longitudinal tumor size data in clinical studies.[18,21] The US Food and Drug Administration model[18] does not explicitly incorporate exposure-driven drug effect parameters and does not have the same potential as the more mechanistic model proposed here (eg, to perform dose-response simulations and predictions of drug effect in different patient populations). The indirect-response model recently proposed by Tham et al[21] incorporates exposure-driven drug effect, as in our model. The modeling framework we are proposing is, to the best of our knowledge, the first attempt to assess drug effect by using early phase II clinical data and by using a drug-independent survival model to simulate expected survival in a phase III setting.

The modeling framework proposed in work is a useful tool to compare expected clinical response of new compounds to reference treatments, to maximize learning from early phase II studies,[22] and to support end-of-phase II decisions and design of phase III studies. The modeling framework currently is being investigated in the simulation of other clinical end points of interest beyond survival (ie, ORR and PFS). Dose-response simulations also can be performed after the adjunction of a model to simulate dose intensity over time. This approach is in line with US Food and Drug Administration Critical Path Initiative[2] recommendations to use model-based approaches to support decision making during drug development. Early change in tumor size as a primary end point in phase II studies[10] combined with survival simulations might be a powerful approach to support end-of-phase II decisions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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