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ORIGINAL ARTICLE

Population pharmacokinetics and exposure–overall survival analysis of the transforming growth factor-β inhibitor galunisertib in patients with pancreatic cancer

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Abstract

Purpose To evaluate the exposure–overall survival (OS) relationship in patients with advanced pancreatic cancer treated with galunisertib plus gemcitabine (GG) or gemcitabine plus placebo (GP).

Methods Galunisertib 300 mg/day was given orally as intermittent dosing and gemcitabine as per label. Galunisertib exposure metrics for each patient in the GG arm ($n = 99$) of a phase 2 study of pancreatic cancer were calculated. Parametric survival models were used to identify influential baseline and response covariates on OS.

Results The population pharmacokinetics dataset included data from 297 patients/healthy subjects (age: 22–84 years, weight: 39–126 kg) across multiple studies, including this pancreatic cancer study. Galunisertib was rapidly absorbed with peak concentrations attained within 0.5–2 h and had an elimination half-life of 8 h. Between-subject variance on apparent clearance was estimated to be 47%. Age was the only characteristic to have a statistically significant effect on apparent clearance. A parametric Weibull survival model with treatment effect (dose) estimated a hazard ratio of 0.796, after adjusting for patient baseline factors that were significantly associated with OS. There was also a flat daily exposure–OS relationship within the observed exposure range, once all significant baseline covariates were included. Response covariates, such as reduction in CA19-9, time on treatment, and cumulative exposure over treatment cycles were also identified as significant factors for OS for patients with pancreatic cancer.

Conclusions This analysis suggests that 300 mg/day galunisertib administered as 150 mg twice daily for 14 days on/14 days off treatment is an appropriate dosing regimen for patients with pancreatic cancer.

Keywords Pharmacokinetics · Pharmacodynamics · Randomized controlled trial · Anticancer drugs

Introduction

The transforming growth factor beta (TGF-β) signaling pathway plays an important role in cancer promotion and progression [1]. Pathological forms of TGF-β signaling promote tumor growth by inducing epithelial-to-mesenchymal transition, extracellular matrix remodeling, evasion of immune surveillance, metastasis, and chemoresistance [2–4]. TGF-β signaling is initiated by the binding of TGF-β to type I or type II TGF-β receptors, causing the heterotetramerization of both ligand and receptor. Upon heterotetramerization, downstream SMAD-dependent (canonical) and SMAD-independent (non-canonical) pathways can be activated [5]. Whole-genome sequencing analyses confirmed that TGF-β signaling was one of the recurrently mutated signal transduction pathways in pancreatic cancer [6]. Despite the steady

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increase in survival for most cancers, advances have been slow for pancreatic cancer, for which the 5-year relative overall survival (OS) rate is 7–8% [7, 8].

The efficacy of the pharmacological inhibition of the type I TGF-β receptor (TGF-βRI) in preclinical models of pancreatic cancer has previously been demonstrated [9]. Galunisertib is an oral small molecule inhibitor of TGF-βRI that specifically downregulates SMAD2 phosphorylation, abrogating activation of the TGF-β canonical pathway [4]. Galunisertib, as well as other inhibitors of the TGF-β signaling pathway, has demonstrated potent inhibition of canonical, and to a lesser extent, non-canonical pathways in a variety of in vitro carcinoma cell lines and preclinical models [9–12]. Due to cardiovascular toxicities in rats and beagle dogs [13], a pharmacokinetic/pharmacodynamic (PK/PD) approach, which integrated translational biomarkers and preclinical toxicity, was developed. This allowed for prospective definition of a therapeutic window for galunisertib, which was further characterized in human trials [14].

In a randomized, double-blind, phase 2 study (ClinicalTrials.gov; NCT01373164) to evaluate the efficacy of galunisertib in combination with gemcitabine (GG) in patients with advanced pancreatic cancer, patients who received galunisertib combination therapy showed an approximate 20% improvement in OS relative to patients who received gemcitabine plus placebo (GP) [15, 16]. Galunisertib is, to date, the most advanced signaling inhibitor of TGF-βRI under clinical development [3]. However, for optimal dose identification for cancer patients, it is important to understand the relationship between observed patient exposures and OS [17, 18].

Here, we describe a population PK meta-analysis across indications for galunisertib, which is necessary to describe individual patient exposure in the current pancreatic cancer (JBAJ) study. In addition, we report on the observed exposure–response (as measured by OS) relationship in patients with advanced pancreatic cancer treated with either GG or GP. The two key objectives of these analyses were (a) to characterize the PK of galunisertib in patients with cancer and in healthy subjects from a range of studies and indications, identifying patient factors and laboratory parameters that may influence galunisertib disposition, and (b) to explore the relationship between galunisertib exposure and OS, identifying important markers for survival benefit in patients with pancreatic cancer.

Materials and methods

Galunisertib population PK model

PK data from the current phase 2 study in patients with pancreatic cancer (JBAJ) were combined with data from five other studies for meta-analyses (Table 1). All studies were conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and were approved by the appropriate independent review boards. This analysis was conducted to establish a comprehensive database of galunisertib PK information to allow comparison of PK profiles of future studies to this database and thus identify possible PK-related efficacy and safety factors.

Galunisertib was administered as an oral tablet twice daily (BID) for 14 days on treatment and 14 days off treatment. In all studies, one cycle was defined as 28 days and constituted 14 days on/14 days off treatment. In the clinical pharmacology studies, only single doses were administered. Subjects in all studies included in the meta-analyses, apart from the food effect study, took galunisertib on an empty stomach. Samples of approximately 4 mL of venous blood were collected and used for measurement of galunisertib concentrations using a liquid chromatography/mass spectrometry (LC/MS) method. Details of blood collection intervals are also provided in Table 1.

Plasma samples obtained during this study were analyzed for galunisertib using validated LC–API/MS/MS methods (BPLY215A and BPLY215B) at Intertek Pharmaceutical Services (El Dorado Hills and San Diego, California, USA). For BPLY215A, the lower limit of quantification was 0.0500 ng/mL and the upper limit of quantification was 10,000 ng/mL. For BPLY215B, the lower limit of quantification was 5000 ng/mL and the upper limit of quantification was 1000,000 ng/mL. All samples were initially analyzed using BPLY215B and those below the limit of quantification for this method (5000 ng/mL) were re-analyzed using BPLY215A. Samples above the limit of quantification were diluted and re-analyzed with BPLY215B to yield results within the calibrated range. The inter-assay accuracy (% relative error) during validation of BPLY215A ranged from − 3.778 to − 1.268%. The inter-assay precision (% relative standard deviation) during validation of BPLY215A ranged from 1.695 to 5.086%. The inter-assay accuracy (% relative error) during validation of BPLY215B ranged from − 2.22 to − 1.79%. The inter-assay precision (% relative standard deviation) during validation of BPLY215B ranged from 2.21 to 5.07%. Galunisertib was stable for up to 148 days (ARLY215A) and 109 days (ARLY215B) when stored at approximately − 20 °C. Galunisertib was stable for up to 753 days (ARLY215A) and 1147 days (ARLY215B) when stored at approximately − 70 °C. Long-term storage stability was conducted by the sponsor, except for the 753-day assessment (ARLY215A).

A population PK model was developed for galunisertib by fitting a model to concentration–time data using NONMEM version 7.3 (ICON Development Solutions, Leopardstown, Dublin, Ireland) in conformity with the Food and Drug Administration's (FDA) Guidance for Industry:

Table 1 Summary of studies included in the population PK analysis

Study	Indication	Galunisertib dose (mg/day)	Dosing regimen (mg/day)	PK blood sampling collection intervals (h)	*N*
JBAJ (NCT01373164)	Part A: solid tumors Part B: pancreatic cancer	Phase 1b: 80, 160, 300 Phase 2: 300 Doses in both parts given BID	Galunisertib: 300 mg/day (days 1–14) Gemcitabine: 1000 mg/m^2 once weekly for up to 7 weeks, 28-day cycle	Part 1b, cycle 1: Day 1: predose, 0.5, 2, 3, 6 Day 7: predose, 0.5, 2, 3, 6 Day 14: predose, 0.5, 2, 3, 6, 24, 48 Part 2, cycle 1: Day 1: predose, 0.5–2, 3.5–6 Day 7: predose, 0.5–2 Day 14: predose, 0.5–2, 3.5–5, 24, 48	113
JBAH	Solid tumors; 2nd GBM	40, 80, 160, 240, 300 Doses given BID	Galunisertib monotherapy (Part A) 40, 80, 160, 240, 300 Galunisertib + lomustine (Part B): 160, 300 14 days on/14 days off = 1 cycle (28 days)	Cycle 1: Day 1: predose, 0.5, 2, 3, 6 Day 3: predose, 2 Day 6: predose, 2 Day 14: predose, 0.5, 2, 3, 6 Day 15: 24 Day 16: 48 Cycle 2: Day 1: predose, 0.5, 2, 3, 6 Day 14: predose, 0.5, 2, 3, 6 Day 15: 24	37
JBAH-RBA	Solid tumors	150 single dose	Galunisertib monotherapy	In 3 periods with different formulations Predose, 0.5, 1, 2, 3, 5, 8, 12, 24, 48	13
JBAL	2nd GBM	300 doses given as 150 mg BID	Galunisertib + lomustine 14 days on/14 days off = 1 cycle (28 days)	Cycle 1: Day 1: predose, 0.5–2, 3.5–5 Day 3: predose Day 14: predose, 0.5–2, 3.5–5 Day 15: 24 Day 16: 48	114
JBAU Food effect study	Healthy subjects	150 single dose	Galunisertib monotherapy	In 2 periods (fed/fasted) predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72	14
JBAM 14C study	Healthy subjects	150 single dose	Galunisertib monotherapy	Predose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144	6

BID twice per day, *2nd GBM* second-line treatment glioblastoma multiforme, *PK* pharmacokinetics, *RBA* relative bioavailability

Population Pharmacokinetics [19]. Plasma concentrations below the quantification limit of the assay were treated as missing values and were not included in the analysis. In the PK observations, there were only 62 samples (beyond Day 1 predose) below the limit of quantification out of a total of 3097 observed galunisertib concentrations. Due to the small percentage (2%) of samples below the quantification limit, treating them as missing will not influence the analysis. In general, missing values of independent variables (demographic and laboratory) were imputed by the last observation carried forward method. Different structural models were tested, such as 1-, 2-, and 3-compartment PK models. Data analysis was conducted using the PREDPP subroutine ADVAN4 (TRANS4) and the first-order conditional estimation method with interaction. A series of pharmacostatistical models were systematically evaluated to identify the model that best described the data. Inter-subject variability was evaluated on all parameters. With each combination of structural model, and inter-subject variability model, combined additive and proportional residual error models were added. Selection of the most appropriate base model was based upon agreement between predicted and observed plasma concentrations, randomness in the weighted residuals versus the predicted values, convergence of the estimation

and covariance routines, reasonable parameter and error estimates based upon the known PK of the compound, good precision of the parameter and error estimates, and decreases in the minimum objective function (MOF) (− 2* log likelihood of the data; − 2LL) of at least 7.88 points ($p < 0.005$).

Stepwise covariate modeling was implemented using Perl-speaks-NONMEM version 7.3 [20]. The criterion for forward inclusion was a *P* value no greater than 0.005 (Δ7.879 MOF for inclusion of one parameter) with a backward deletion threshold of 0.001 (Δ10.828 MOF for exclusion of one parameter). Patient/healthy subject factors included were age and body weight at baseline, body mass index, sex, alcohol use status, smoking status, caffeine use status, study, fed/fasting status, and drug formulation. A visual predictive check (VPC) was performed on the base and final models to investigate agreement between the observed and predicted concentrations.

The final covariate population PK model was used to simulate individual patient concentration predictions over time and calculate individual patient exposure for patients with pancreatic cancer in study JBAJ.

Exposure–OS analysis

Study JBAJ was a two-part study: phase 1b was an open-label, multicenter, dose-escalation phase; phase 2 was a 2:1 randomized, double-blind, placebo-controlled phase of GG versus GP. In phase 1, galunisertib (80, 160, or 300 mg/day given in two daily doses) was administered in combination with 1000 mg/m^2 of gemcitabine. In phase 1b, patients with metastatic solid malignancies that had not responded to anticancer therapies and/or were amenable to gemcitabine therapy were included. Phase 2 included patients with advanced or metastatic pancreatic adenocarcinoma at first presentation or after local relapse who were considered eligible for first-line chemotherapy with gemcitabine. The primary objective of the phase 2 part of study JBAJ was to compare OS in patients with Stage II–IV unresectable pancreatic cancer when treated with GG (galunisertib 300 mg/day plus gemcitabine 1000 mg/m^2) versus GP (placebo plus gemcitabine 1000 mg/m^2). Secondary objectives included evaluation of the galunisertib PK profile and comparison of biomarker responses.

Potential baseline clinical prognostic factors together with plasma exposure (measured in Cycle 1) were evaluated for their impact on OS. The relationship between exposure and OS was identified using three metrics; exposure at steady state (area under the curve from time 0 to 24 h after drug administration at steady state [$AUC_{0–24,ss}$]), minimum concentration at steady state ($C_{min,ss}$), and maximum concentration at steady state ($C_{max,ss}$). All of these metrics were analyzed with respect to their relationship to OS as continuous variables using parametric time-to-event models. Here, we report only $AUC_{0–24,ss}$. Although there were planned off-treatment periods (14 days on treatment, 14 days off treatment) within a cycle, exposure at steady state (as observed on day 14 for each individual patient) was assessed as constant in OS analyses. Steady-state exposure, following galunisertib twice daily dosing and $t_{1/2}$ of approximately 8 h, is achieved within 2 days of dosing in most patients. Hence, assuming constant AUC_{ss} for the first 14–15 days of a cycle is appropriate. However, in the exposure–OS analysis we have also assumed the same constant exposure for the planned off-treatment period. It is not clear how this assumption affected results, especially as time period to event/censoring varied between a cycle and up to 21 treatment cycles.

Potential clinical prognostic and predictive factors measured at baseline were evaluated for their impact on the exposure–OS relationship. Continuous laboratory variables were categorized according to quartile values and/or less than or equal to median observed baseline values (specifically for TGF-β1 levels) calculated across all patients. Assessing reductions in carbohydrate antigen19-9 (CA19-9) or TGF-β1 levels can help with evaluating possible antitumor activity [21, 22]. Patients were considered to be CA19-9 responders if they had a reduction of ≥ 20% in CA19-9 levels in the first 12 weeks of treatment, in contrast to ≤ 8 weeks in other assessments [23, 24]. Based on a study suggesting that galunisertib reduces TGF-β in hepatocellular carcinoma [21, 25], TGF-β was assessed similarly to CA19-9. Reductions in CA19-9 and TGF-β, cycles on treatment and cumulative exposure over the treatment course were all considered as potential explanatory covariates of OS. Cumulative exposure was calculated without taking dose modifications into consideration. However, this is not considered to be important as the overall mean dose intensity of galunisertib/placebo was similar between treatment groups (99% in the GP group and 96% in the GG group based on tablet count).

In addition, we assessed whether observed exposure differed in patients with baseline TGF-β level as a categorical covariate (≤ 4220 pg/mL vs. > 4220 pg/mL). These additional analyses were carried out on all patients and then separately on patients who stayed on treatment for at least 3 months. The cutoff point of 3 months was chosen to exclude patients with very poor prognoses, whose data might have masked any existing exposure–OS relationship.

Univariate and multivariate Cox regression analyses were performed to evaluate the exposure–efficacy relationship for the efficacy end point, OS, and to estimate the hazard ratios between patients treated with galunisertib plus gemcitabine and patients treated with placebo and gemcitabine. Exposure parameters, such as $AUC_{0–24,ss}$, were evaluated with patients categorized into groups dependent on their exposure quartiles. It is possible that due to the relatively small sample size in each quartile as well as the shape of the survival curve, the assumption of proportional hazards made

in the Cox regression models was not appropriate. Hence, to investigate this, a parametric model, including baseline hazard and $AUC_{0-24,ss}$ as a continuous variable was fitted to the data to further explore the exposure–OS relationship in study JBAJ. Parametric models, specifically Weibull and exponential models, were used to interpret the data.

The effects on survival probability of selected identified important baseline covariates, with entry p value of 0.2 and exit p value of 0.2, were investigated. Those covariates are a mixture of categorical [Eastern Cooperative Oncology Group (ECOG) performance status and presence of liver metastasis] and continuous factors ($AUC_{0-24,ss}$, CA19-9, and age). The effect of continuous covariates at different time cutoff points (2, 6, 12, and 24 months) were plotted using Monte Carlo simulations using the variance–covariance matrix.

Results

This phase 1b/2 study, mainly in patients with pancreatic cancer, was conducted in 24 centers across six countries. There were 14 patients with evaluable PK observations (excluding four screen-failure patients) in the phase 1b part of the study. Of the 199 patients who entered phase 2, 156 were randomly assigned 2:1 to study treatment, yielding 104 and 52 in the GG and GP arms, respectively. Of the 104 patients in the GG arm, only 99 patients had measured galunisertib concentrations. These patients, together with the 52 patients from the GP arm, were included in the exposure–OS analyses ($N = 151$).

Galunisertib population PK model

A total of 297 patients/heathy subjects were included in the population PK analysis (Table 1). The age of the population ranged from 22 to 84 years (mean = 60 years) at study entry and weight ranged from 39 to 126 kg (mean = 75.1 kg). The majority of subjects were Caucasian ($n = 189$, 63.0%). By indication, patients presented with second-line glioblastoma (48.5%), pancreatic cancer (33.3%), and other cancers (11.4%). The remainder of the population (6.7%) was healthy.

The median predicted concentrations generally closely followed the median observed concentrations, with a slight deviation at later time points, where less data were available. The 5th and 95th percentiles were generally well predicted, although they were slightly underpredicted at earlier time points, notably around the peak concentrations (Fig. 1). The PK of galunisertib was best described by a two-compartment model with first-order absorption and elimination rate, assuming a log-normal distribution of inter-patient variability. Galunisertib was rapidly absorbed with peak concentrations attained within 0.5 to 2 h and an elimination half-life of 8 h. Mean population apparent clearance of galunisertib was 35 L/h and the steady-state apparent volume of distribution was 190 L. The between-subject variance was estimated to be 47% on the population-based apparent total

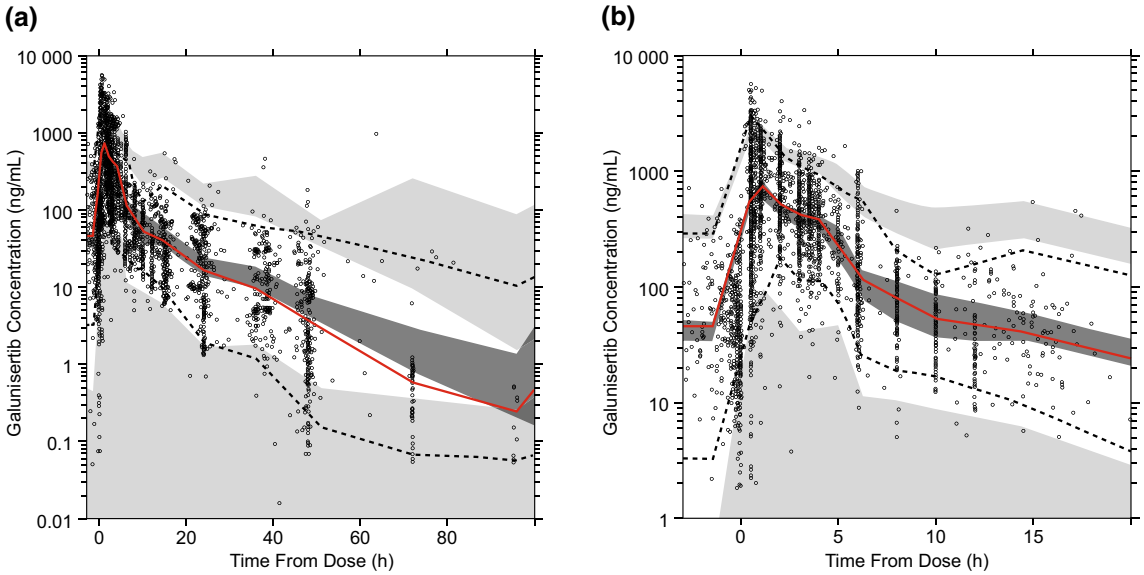

Fig. 1 Visual predictive check (prediction corrected) for **a** final model (entire concentration–time profile) and **b** final model (only 18 h post-dose). Solid red line: median of observed concentrations; dashed black lines: 5th and 95th percentiles of observed concentrations; dark gray-shaded area: confidence interval for the median of simulated data; light gray-shaded areas: confidence intervals for the 5th and 95th percentiles of simulated data. Observed data and simulations following 300 mg/day, administered as 150 mg twice daily, at steady state

clearance (CL/F). Shrinkage on CL/F and Ka was 5% and 14%, respectively.

The final PK model included effects of food and formulation on absorption rate and of age on the CL/F (Table 2a). Although the effect of age on CL/F between-subject variability was small (reducing inter-patient variability from 49% down to 47%), it was statistically significant and kept in the final model. CL/F decreased with age in a linear fashion. Galunisertib systemic exposure was not influenced by weight (median 72 kg, range 39–126), sex (22% female), race (63% Caucasian), smoking status (24% smokers), and consumption of alcohol (29% consuming) or caffeine (33% consuming). The absorption rates in fasted subjects with high shear wet granulation (HSWG) and roller compaction slurry-milled (RCS) formulation were estimated to be 1.18 h^{-1} and 0.467 h^{-1}, respectively, whereas in fed and fasted subjects with HSWG formulation, the absorption rates were 0.309 h^{-1} and 1.18 h^{-1}, respectively. This was expected and supported by the conclusions from a separate food effect study and the relative bioavailability study (data from both studies included within the meta-dataset), where, although exposure was not changed in either case, Cmax and, for one of the formulations, tmax were reduced by approximately 20%, which was not clinically meaningful with chronic dosing of galunisertib. Plots of the included factors (as listed in Table 2a) against Ka and CL/F from the final model are available in Supplementary Materials (Figure

Table 2 (a) Mean population, inter-patient, and covariate parameters in the final population PK model (b) and mean and relative SE estimates from the full Weibull model

Parameter	Estimate (relative SE %)	Inter-patient variability for PK (relative SE %)
(a)		
Absorption rate constant		
Ka (h^{-1})	1.18 (13)	156% (12)
Effect of food on Ka	–0.738 (6.3)	NE
Effect of RCD formulation on Ka	–0.49 (8.2)	NE
Effect of RCS formulation on Ka	–0.604 (14)	NE
Clearance		
CL/F (L/h)	34.9 (3.4)	47.1% (13)
Effect of age on CL/F ($year^{-1}$)	–0.0122 (26)	NE
V of D for 1st compartment (L)	79.9 (6.8)	NE
V of D for 2nd compartment (L)	110 (11)	NE
Inter-compartment clearance (L/h)	6.68 (7.6)	NE
Residual error (additive)	0.188 (43)	
Residual error (proportional)	76.0% (2.1)	
Parameter	Estimate	Relative SE (%)
(b)		
λ_{OS} (1/month)	0.0478	8.6
α_{OS}	1.38	6.9
$_{3}AGE1$ (1/year)	0.0351	41.6
$_{4}AGE75$ (1/year)	− 0.659	52.4
$_{5}CA19$ (1/KU/L)	0.0000124	25.2
$_{6}ECOG1$	− 0.469	46.7
$_{7}ECOG2$	1.03	32.8
$_{8}LMPB$	− 0.463	44.7
$_{9}PREGEM$	− 1.12	41
$_{10}DOSE$	0.228	93.9

(a) Apparent clearance is age dependent as follows: CL/F = 34.9 × (1 − 0.0122 × (age-61))

(b) OS model: objective function value: 788.016; termination message: minimization successful. Number of function evaluations used: 274; number of significant digits in the final estimate: 4.3

Age1 age (years) at baseline as continuous covariate, *Age75* age at baseline cutoff 75 years, *CA19* carbohydrate antigen19-9 in kU/L,*CL/F* apparent clearance, *D* distribution, *ECOG 1/2* Eastern Cooperative Oncology Group performance status 1 or 2, *h* hour, *Ka* absorption constant, *GEM* gemcitabine, *LMPB* liver metastasis at baseline (yes; no), *NE* not estimated, *OS* overall survival, *PK* pharmacokinetics, *Q* inter-compartment clearance, *RCD* roller compaction dry-milled, *RCS* roller compaction slurry-milled, *SE* standard error, *V* volume

S1). Additionally, the final population PK model goodness of fit plots are also available in Supplementary Materials (Figure S2).

Final PK model parameter estimates were used to simulate galunisertib PK profiles for individual JBAJ patients and calculate individual patient exposure (AUC_{0-24}), $C_{max,ss}$, $C_{min,ss}$, and time to maximum concentration at steady state ($T_{max,\ ss}$). The calculated median (25th–75th) population exposure at steady state was 5560 ng h/mL (3820–7910 ng h/mL) with C_{max} and T_{max} of 904 ng/mL (668–1194) and 1.5 h (1–2.5), respectively. Although there was one patient with very high exposure, the predicted $AUC_{0-24\ ss}$ for patients with pancreatic cancer in study JBAJ following a 300-mg/day dose (administered as 150 mg BID) was within the therapeutic window (3730 to 8380 ng h/mL) defined previously [14]. These exposure metrics were used in exposure–OS analyses, reported below.

Exposure–response (OS) relationship in patients with pancreatic cancer

It appeared from the OS data that there was not a constant relative hazard, which makes Cox regression an inappropriate method to use. To address this, parametric models were explored; of these, Weibull described the data best. In this parametric analysis, although there are assumptions on distributional form of base hazard and hazard over time, there is no need for the proportional hazard assumption. Using the Weibull parametric model, OS data were adequately described and it was possible to investigate the important covariates including exposure as a continuous potential covariate. The Weibull model (Eq. 1) provided a good fit to the data; significant covariates, including treatment effect (dose) were included (Table 2b).

$$\begin{aligned} h_{\text{death}}(t) = {} & \lambda_{\text{OS}}\alpha_{\text{OS}}(t)^{\alpha_{\text{OS}}-1} \cdot \exp\big(_{3\text{AGE1}}(\text{AGE} - 67.5) \\ & +_{4\text{AGE75}}\text{AGE75} +_{5\text{CA19}} (\text{CA19} - 533) \\ & +_{6\text{ECOG1}}\text{ECOG1} +_{7\text{ECOG2}} \text{ECOG2} +_{8\text{LMPB}} \text{LMPB} \\ & +_{9\text{PREGEM}}\text{PREGEM} +_{10\text{DOSE}} \text{DOSE}\big), \end{aligned} \quad (1)$$

$$S(t) = \exp^{-h(t)\cdot t},$$

where ECOG1 = 1 for baseline ECOG 0, and 0 otherwise; ECOG2 = 1 for baseline ECOG 2; and 0 otherwise; PREGEM = 1 for previous gemcitabine treatment, and 0 otherwise; LMPB = 1 for no baseline liver metastasis, and 0 otherwise; AGE = age at baseline as continuous covariate; AGE75 = 1 for age (years) at baseline ≤ 75 years, 0 otherwise; CA19 = CA19-9 as continuous covariate; DOSE = 1 for GP, 0 for GG.

Including the treatment effect as a significant covariate, the hazard ratio (90% confidence interval) was estimated as 0.796 (0.56, 1.13). For the treatment comparison, a hazard ratio < 1 indicates a lower risk of death in the GG treatment group compared with the GP treatment group. From the Kaplan–Meier OS curve and 90% VPC, based on 100 parametric model simulations predicting OS probability for each treatment arm, the model was able to predict the observed OS in both arms of the study (Fig. 2).

In the analysis of potential covariates of OS, a flat relationship between exposure ($AUC_{0-24,ss}$) at steady state and OS was apparent when considering exposure as a covariate and once all significant covariates (namely ECOG, pre-treatment with gemcitabine, age [continuous], baseline CA19-9 [continuous], and liver metastasis [binary]) were included (Fig. 3a). Similar results were found for $C_{max,ss}$ and $C_{min,ss}$ (data not shown). The age-to-survival probability relationship was not linear and there appeared to be an inflection point around 65 to 75 years of age where the slope changed (data not shown). A categorical cutoff by age (patients > 75 years and patients ≤ 75 years) was found to be a significant covariate in the analysis. Unusually, patients > 75 years of age (small number of patients, $n = 19$ in the GG arm) appeared to have a higher survival probability compared with younger patients, especially at later time points (Fig. 3b). The survival curve differences were primarily driven by approximately 14 of 19 patients in the GG arm, aged > 75 years. There might have been other reasons, for example, different tumor mutations, but it was not possible to identify these within our dataset. We therefore selected age as an inflection point. Patients with liver metastasis on study entry fared worse than those without liver metastases (Table 2b). Patients with an ECOG performance status of 2 at baseline had a lower probability of survival compared with patients with an ECOG status of 0 or 1 (Table 2b). Patients with high levels of CA19-9 (as a continuous variable) at baseline had a lower survival probability compared with patients with lower CA19-9 levels (Table 2b). TGF-β baseline levels were not found to be a significant prognostic marker for OS. Observed exposure was lower and appeared less variable in patients with baseline TGF-$\beta \leq 4220$ pg/mL ($AUC_{0-24,ss} = 5719$ ng h/mL, % coefficient of variation [CV] = 49; $n = 51$) than in patients with TGF-β > 4220 pg/mL ($AUC_{0-24,ss} = 7674$ ng h/mL, CV = 76; $n = 23$).

Further analysis of OS, including concentrations of the two biomarkers over time, revealed that CA19-9 reduction (defined as at least one occurrence of a ≥ 20% reduction from baseline in the first 12 weeks of treatment) was a significant explanatory factor of OS, whereas TGF-β reduction (collected only during the first three treatment cycles) was not a significant covariate. Additionally, time on treatment (number of cycles) was identified as a significant covariate of OS, but cumulative exposure was not. Baseline factors CA19-9, age, and pre-treatment with

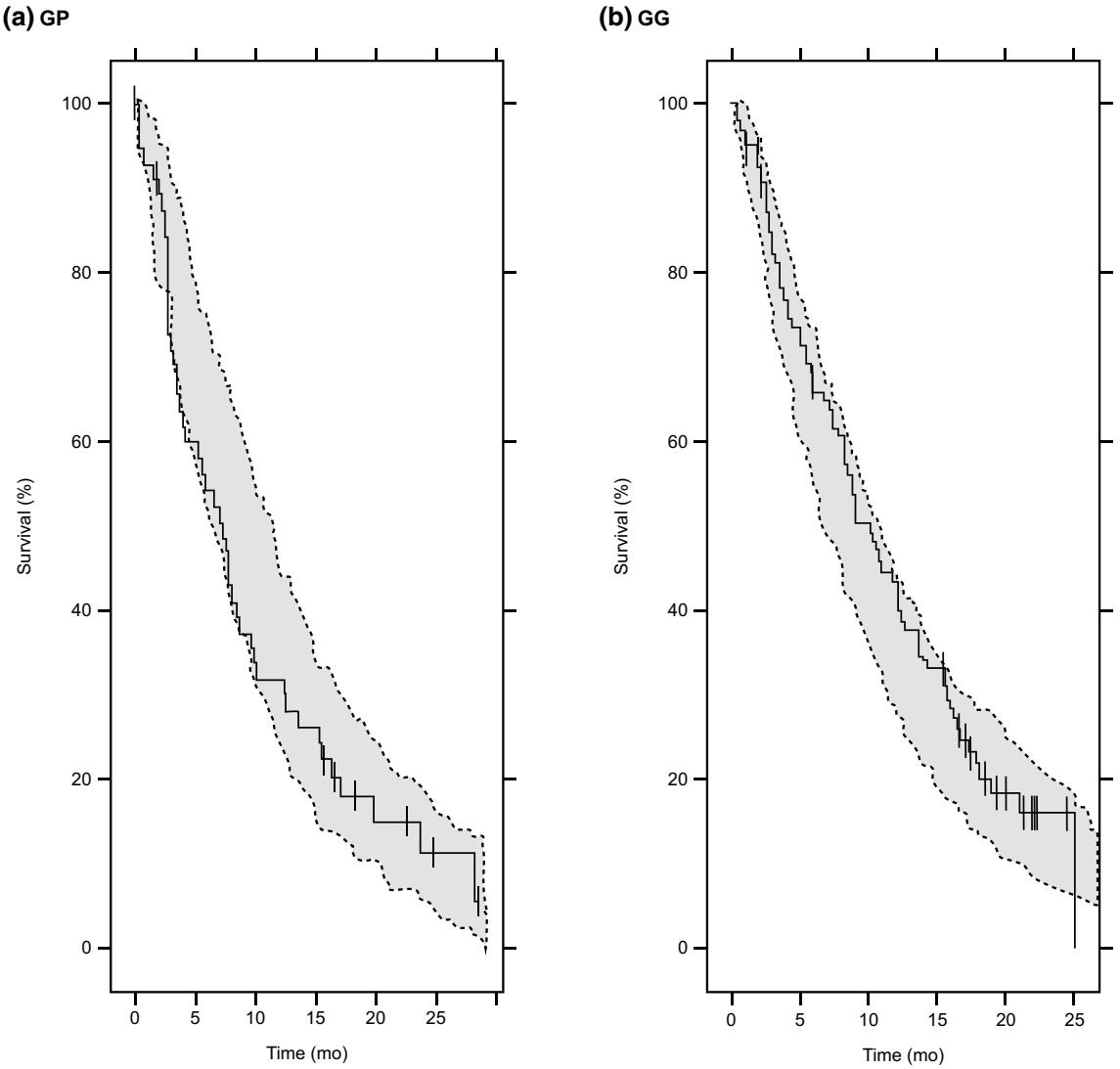

Fig. 2 Exposure–overall survival analysis: Parametric model—survival probability over time in **a** gemcitabine plus placebo (GP) and **b** galunisertib plus gemcitabine (GG) treatment arms. Visual predictive check for the Kaplan–Meier OS curve (based on 100 simulations). The observed Kaplan–Meier curve (solid line) from study JBAJ is compared to the 90% confidence interval (gray area) derived from parametric Weibull model simulations predicting OS probability. The censored values are shown with short black lines on the solid curve. *OS* overall survival

gemcitabine remained significant covariates for OS within this model.

Investigating only patients who survived for ≥ 3 months in additional analyses (not reported here in detail), time on treatment (number of cycles), and cumulative exposure ($AUC_{0–24,ss}$) over the treatment course (Fig. 4a) were both found to be independent significant response markers for OS. Baseline CA19-9, pre-gemcitabine treatment, and CA19-9 reduction (Fig. 4b) were also found to be important covariates in this subgroup. In the CA19-9 reduction analysis, 20% reduction at week 12 was treated the same even at observations < 12 weeks and hazard at week 1 was dependent on observations not available until week 12. This may explain underprediction in earlier months and overprediction at later months (Fig. 4b).

Discussion

This exploratory phase 2 study showed that the novel combination of GG was more effective than the standard of monotherapy gemcitabine for OS [15] and the magnitude of effect was encouraging for future studies. We assessed whether known baseline factors, such as ECOG and liver metastasis, influenced OS. Specific investigation was carried out to assess whether OS was influenced by variability

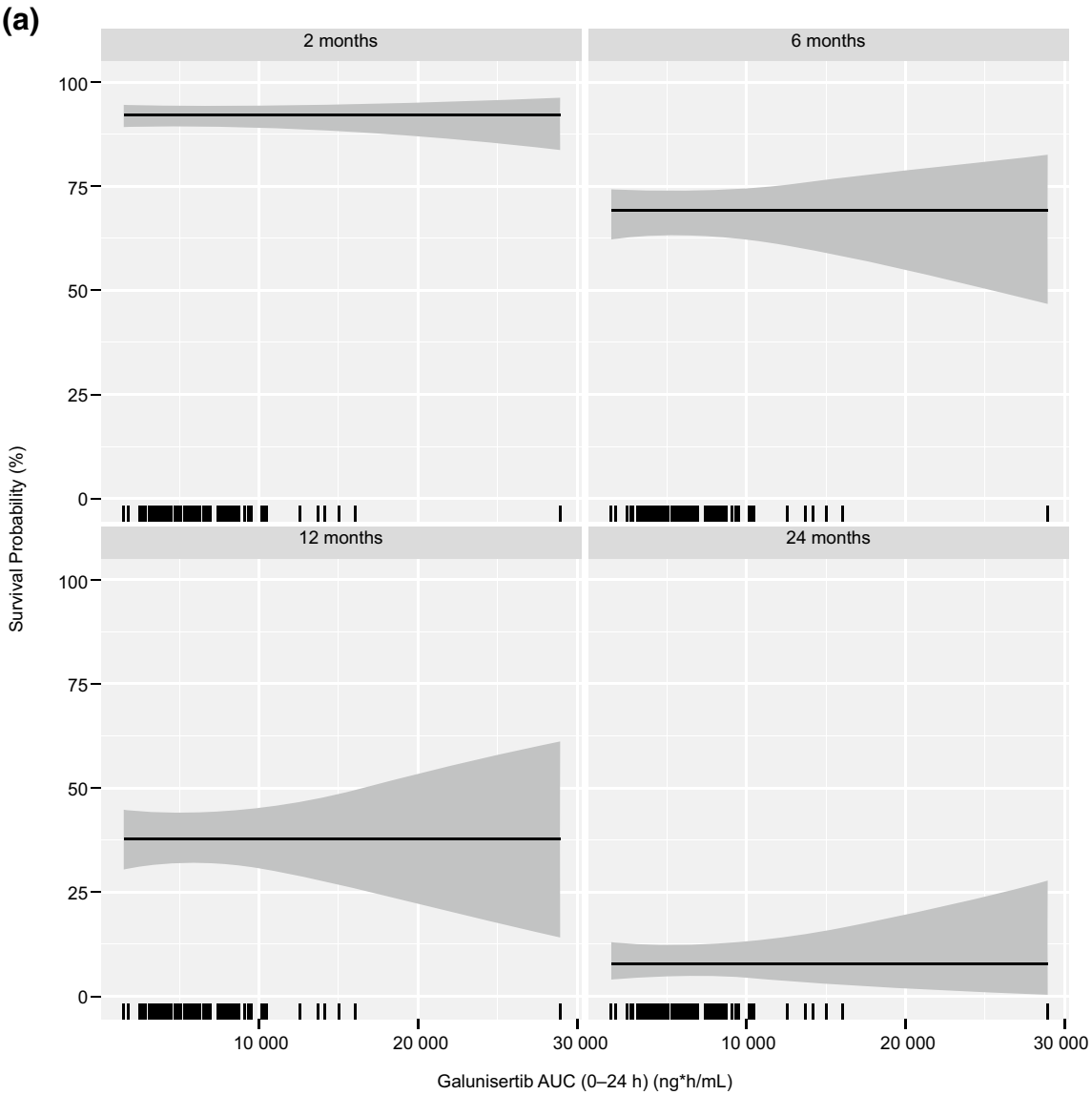

Fig. 3 Potential and identified covariates for overall survival by baseline factors: **a** exposure and **b** age. **a** Model-predicted survival probability (black solid line) at 2, 6, 12, and 24 months against exposure ($AUC_{0-24,ss}$). Short black lines on the *x*-axis indicate observed exposure in each patient from study JBAJ. **b** Visual predictive check (shaded area) for the Kaplan–Meier overall survival curve (solid line) stratified by the significant categorical covariate age (patients ≤ 75 years and patients > 75 years). Note different *x*-axis scales. $AUC_{0-24,ss}$ area under the curve from time 0–24 h, at steady state

in achieved galunisertib plasma exposures (on a per-patient level) following a 300-mg/day dose. To characterize variability in galunisertib PK, we developed a population PK model, using all available galunisertib plasma concentration observations over time from a range of studies. In the population PK analysis, galunisertib PK was evaluated in 277 patients with solid tumors and 20 healthy subjects using a population modeling approach. This was carried out to elucidate and quantify major sources of inter-patient variability for galunisertib PK.

Galunisertib was rapidly absorbed into the systemic circulation with a time to maximum concentration of up to 2 h, which is consistent with the findings for other small molecule inhibitors [26, 27]. We found that there was a small, but statistically significant, effect of age on CL/F; food consumption and formulation also affected the rate of galunisertib absorption. Our analysis showed that there was an underprediction of maximal concentrations of galunisertib in some patients. However, by plotting the VPC and scaling the *x*-axis to only 18 h, the majority of observations were captured within the prediction intervals. At later

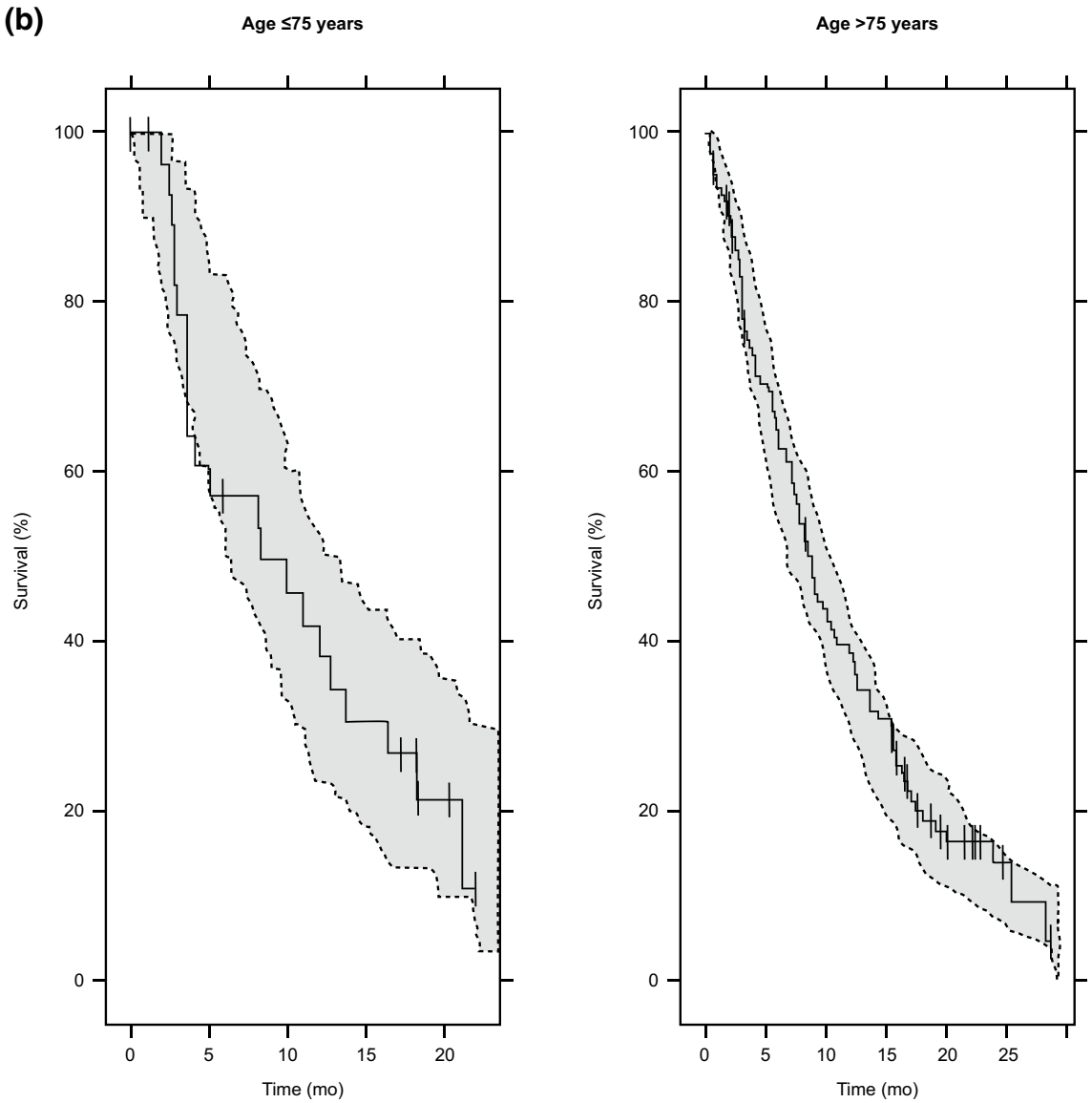

Fig. 3 (continued)

time points, beyond 50 h post-dose, inter-patient variability was overestimated, reflecting perhaps the smaller number of observations made. Exposure (AUC_{ss}), rather than $C_{max,ss}$, was related to both safety (daily and different intermittent schedules were used in rat and dog studies, where the main non-monitorable toxicity was valvulopathy) and preclinical efficacy of galunisertib [13, 14]. If this observation in preclinical species holds true for patients as well, this underprediction of maximum concentration is less of a concern with chronic dosing.

Other than the effect of age on clearance, none of the patient demographic characteristics were found to be significant covariates for galunisertib PK. Overall, the PK in patients with pancreatic cancer were similar to the PK observed in patients with other cancer types to date, and were within the predefined therapeutic window [14]. Due to systemic exposure of galunisertib being directly related to non-monitorable toxicity in animals, it is important that the inter-patient variability in exposure was found to be moderate at 47% [14]. Apparent clearance of galunisertib decreased with age in a linear fashion. As with other small molecule inhibitors, the renal clearance of galunisertib is low [27]; only 6% of the galunisertib dose was recovered in urine as the intact parent drug (data on file, Eli Lilly and Company).

In the pancreatic cancer phase 2 study (JBAJ), we used a randomized design emphasizing the experimental arm and enriching the control arm. We pooled data from the

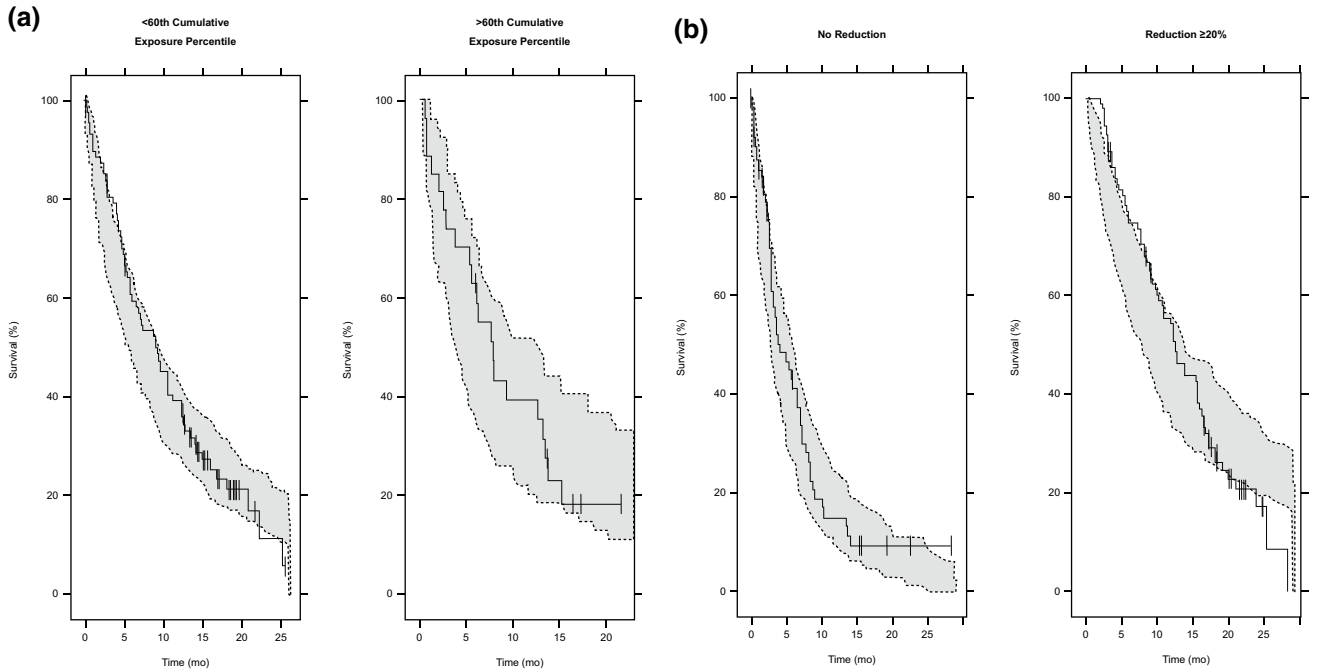

Fig. 4 Identified response markers for overall survival in patients with pancreatic cancer: **a** cumulative exposure ($AUC_{0–24,ss}$) and **b** CA19-9 reduction in patients surviving ≥ 3 months. Visual predictive check (shaded area) for the Kaplan–Meier overall survival curve (solid line) based on 100 simulations and stratified by covariate values. Note different *x*-axis scales. $AUC_{0–24,ss}$ area under the curve from time 0–24 h, at steady state

control arm of other trials of patients with similar characteristics, allowing for a smaller study sample size in study JBAJ [15]. Here, we investigated the relationship between individual patient-observed galunisertib exposures and OS and whether there were any trends in plasma exposure, even following only one dose level (300 mg/day), leading to an improved survival benefit.

On review of Kaplan–Meier analyses, whereby median OS time within each exposure quartile was estimated, there were no clear separations between the OS curves in the first three quartiles and higher exposure was not associated with longer survival. Indeed, patients in the highest quartile of exposure had the shortest median OS (6.7 months). This was shorter than the median OS observed in the GP arm (7.6 months), suggesting that other factors may have been more influential in predicting the OS of patients in this quartile. We therefore employed parametric models to investigate the exposure–OS response relationship, where exposure could be added as a continuous explanatory variable. Other patient characteristics were also integrated into the model enabling an assessment of exposure to be made after adjusting for these covariates. Although assumptions have been made on the functional form of distributions for base hazard and hazard over time in parametric models, there is no need for a constant proportional hazard assumption in these models, in contrast to the usual semi-parametric Cox regression model. We identified that the Weibull model [28] best described the data.

Important covariates for OS were pre-treatment with gemcitabine, baseline liver metastasis, ECOG status, CA19-9, age continuous, and age categorical (≤ 75 and > 75). There was a treatment effect (GP vs. GG), but higher exposure within the 300-mg/day dose group was not associated with an improvement in OS. These findings were consistent for all three exposure measures. The flat relationship between exposure, together with the significant dose effect, and OS, after adjusting for the baseline factors that were significantly associated with OS, suggests that the chosen dose of galunisertib (300 mg/day) achieved sufficient plasma galunisertib levels for the treatment of pancreatic cancer in the study JBAJ.

A 20% reduction in CA19-9 over 12 weeks was identified as an important marker of response to treatment. This is consistent with previous findings in patients with pancreatic cancer [23, 24]. A reduction of the TGF-β in response to galunisertib exposure has also been associated with improved OS in patients with hepatocellular carcinoma [25], although we did not identify this to be an important covariate in our study. However, $AUC_{0–24,ss}$ did appear to be lower and less variable in patients with baseline TGF-β ≤ 4220 pg/mL. Owing to the relatively small sample size and the exploratory nature of the analyses, the interpretation of the TGF-β

results should be approached with caution. Additionally, time on treatment (number of cycles) was found to be a significant marker for OS. Investigating only patients who survived for ≥ 3 months, we found that time on treatment and cumulative exposure ($AUC_{0-24,ss}$) over the treatment course were both independently significant response markers for OS.

A limitation of this study of galunisertib PK is that data were restricted to 297 patients from six different studies. In future meta-analyses, all galunisertib plasma concentration data could be combined with data from studies where PK was measured in different cycles in larger numbers of patients. Exposure response could also be assessed in terms of progression-free survival, which has the advantages of smaller sample sizes and shorter follow-up times [29]. This study did not consider hepatic impairment function as a potential covariate, which could be of importance given the low renal clearance of galunisertib. Inclusion of patients with varying degrees of hepatic function impairment would also facilitate estimation of inter-occasion variability, inter-patient variability on other parameters, and better parameter precision estimates. Similarly, OS analyses were limited to the collected baseline and response markers, and we did not consider and/or correct for immortal time bias. We did not assess the exposure–response relationship with markers associated with inflammatory processes in pancreatic cancer or immune subgroups, i.e., patients with pre-existing CD4 T cells. This last consideration becomes important in studies with immune-targeting agents.

In conclusion, this meta-analysis suggests that the PK of galunisertib was similar in patients with different types of solid tumors. For patients with pancreatic cancer, galunisertib 300 mg/day (given as 150 mg BID) provides the desired PK plasma exposure, with steady-state concentrations consistently within the predefined therapeutic window. We report a survival advantage for patients treated with the combination of galunisertib plus gemcitabine, with an estimated hazard ratio of 0.796 after adjusting for patient baseline factors. In addition, patients who show a > 20% reduction in CA19-9 over the first 12 weeks on treatment have a better survival probability. Such a model can facilitate the design of future trials and help predict anticipated effects of galunisertib when used clinically.

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Author contributions All authors participated in the interpretation of the study results, and in the drafting, critical revision, and approval of the final version of the manuscript. Ivelina Gueorguieva, Josep Tabernero, Michael M. Lahn, Ann Cleverly, and Karim A. Benhadji were involved in the study design. All authors were involved in data collection and interpretation. Josep Tabernero and Davide Melisi were investigators in the study. Ivelina Gueorguieva, Timothy H. Waterhouse, Colin Miles, and Ann Cleverly conducted the statistical analysis. The authors confirm that the principal investigators for this paper were Dr Josep Tabernero and Dr Davide Melisi, and that they had direct clinical responsibility for patients.

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Compliance with ethical standards

Conflict of interest Ivelina Gueorguieva, Ann Cleverly, Timothy H. Waterhouse, Colin Miles, and Karim A. Benhadji are current employees of and own shares in Eli Lilly and Company. Michael M. Lahn was an employee of Eli Lilly and Company during the design and conduct of the study and currently owns shares in Eli Lilly and Company. Josep Tabernero has had consultant/advisory roles for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Eli Lilly and Company, Imclone, MSD, Merck Serono, Millennium, Novartis, Roche, Sanofi, Symphogen, and Taiho. Davide Melisi has received research funding from Celgene, Incyte, and Shire, and has a consulting role with Baxter, Eli Lilly and Company, Incyte, and Shire. Teresa Macarulla received honoraria for consultancy from Baxalta, Baxter, Celgene, Genzyme, Roche, Sanofi, Shire Pharmaceuticals, Tesaro, and QED Therapeutics, and has received travel/accommodation compensation from Bayer, H3 Biomedicine, Merck, and Sanofi. Valeria Merz has no conflicts of interest to disclose.

Role of the sponsor Eli Lilly and Company was involved in the study design, data collection, data analysis, and preparation of the manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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