

PK/PD Modeling of Overall and Progression-Free Survival in Advanced Soft Tissue Sarcoma Patients Treated With Olaratumab in Combination with Doxorubicin.

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ABSTRACT

Background: Olaratumab (Olara), a recombinant human IgG1 monoclonal antibody, is a PGDFR α antagonist. Olara plus doxorubicin (Dox) improved survival vs Dox in an open-label, randomized Phase 2 soft tissue sarcoma (STS) trial (NCT01185964) (1). We characterized the exposure-response relationship of Olara for progression free survival (PFS) and overall survival (OS).

Methods: Patients received Dox (75 mg/m² Day 1) with (Arm A) or without (Arm B) Olara (15 mg/kg Days 1 and 8) for up to eight 21-day cycles. In Arm A, Olara monotherapy continued after Dox until disease progression, and Arm B patients could receive Olara after progressing with Dox. Data on patients in both Arm A (n=67) and Arm B (n=66) were used to develop the PFS and OS time-to-event models. Various hazard models were evaluated (exponential, Weibull, Gompertz, combined Weibull/Gompertz). The effect of Olara was explored using the average Olara serum concentration (Cavg) and trough Olara serum concentration in cycle 1 (Cmin1), both simulated using individual patient post-hoc PK parameters estimated by PopPK modelling. Additional covariates were evaluated for potential effects on PFS/OS.

Results: OS and PFS were both best described by survival models with an exponential hazard function. The effect of Olara on PFS/OS was captured by an inhibitory Emax function with Hill coefficient, regardless of the PK endpoint (Cavg or Cmin1) considered. The Olara EC50s for PFS (ECmin150 = 82 μ g/mL, ECavg50 = 179 μ g/mL) and those for OS (ECmin150 = 66.1 μ g/mL, ECavg50 = 134 μ g/mL) corresponded to the median and 25th percentile of Cmin1/Cavg in the study, respectively. The maximum predicted improvement in the hazard ratio for OS and PFS was 75% and 65%, respectively, and was predicted to be achieved within the range of Olara serum levels observed in the study. Baseline ECOG status and prior treatments were found to significant covariates for OS. No significant covariates were identified for PFS.

Conclusions: OS and PFS in STS patients receiving Dox alone or in combination with Olara were successfully described by the survival models developed in this study. Olara Cmin1 and Cavg showed a similar predictive role for Olara effect on PFS/OS. The survival models are consistent with a greater effect of Olara on OS than PFS. Maximum improvement in the OS HR was predicted to occur within the range of Olara serum levels achieved in the study.

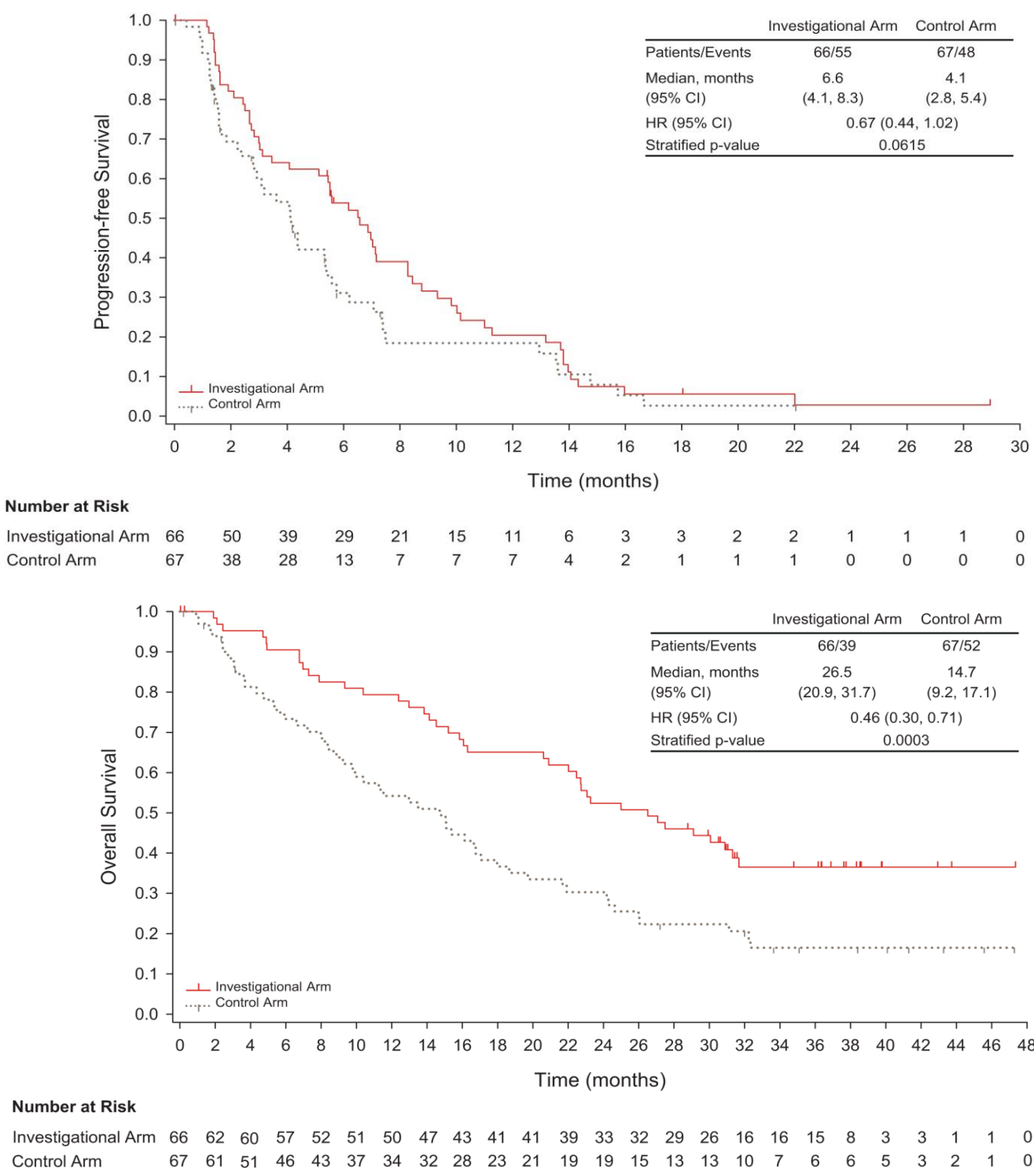
BACKGROUND & OBJECTIVE

Olaratumab (Olara), a recombinant human IgG1 monoclonal antibody, is a PGDFR α antagonist.

In a randomized Phase Ib/II trial (1), Olara (15 mg/kg) in combination with Doxorubicin (Dox) (75 mg/m²) met its primary PFS endpoint and achieved an improvement of 11.8 months in median OS that was highly statistically significant (HR = 0.46; p = 0.0003) (2) (Figure1).

Here we characterise the exposure-response relationship of Olara for overall survival (OS) and progression-free survival (PFS) when combined with doxorubicin in patients with advanced STS.

Figure 1. Kaplan-Meier Curves for PFS (upper panel) and OS (lower panel) of Investigational Arm versus Control Arm in STS patients



METHODS

PopPK model development

The PK model was developed in NONMEM VII using 1501 Olara serum observations from 171 patients across 4 Phase 2 studies:

- STS (n=95) and NSCLC (n=50) where Olara was dosed at 15 mg/kg on Days 1 and 8 of a 21-day cycle
- GBM and GIST (n=26) where Olara was dosed at 20 mg/kg in Day 1 of a 14-day cycle

Various structural models were tested, included models with target-mediated drug disposition term and linear clearance. Covariates were tested via step-wise covariate selection. The model was validated by visual predictive check (VPC) and bootstrap.

Survival model development

Overall survival (OS) and progression-free survival (PFS) in the STS Phase 2 study were described using a time-to-event modelling approach implemented using NONMEM Version 7.3 with Laplace estimation algorithm. Models were executed using PsN.

Various hazard models were tested including exponential, Weibull, Gompertz, and combined Weibull and Gompertz distributions of event times. The survival was calculated as the inverse of the exponent of the cumulative hazard from time=0 to time=j in the study according to the following equation:

$$Surv_t = e^{-\int_{t_0}^t haz_t \cdot dt}$$

where $Surv_t$ is the survival at time t and $haz_t \cdot dt$ is the hazard. The likelihood of event at time t (probability density function, pdf) was calculated as follows:

$$pdf = haz_t \times Surv_t$$

The effect of olaratumab as reflected by Cmin1 and Cavg was then evaluated separately on the OS and PFS survival models. The effect of olaratumab Cmin1 and Cavg was tested as a fractional decrease in the baseline hazard using the following relationship:

$$\frac{dHaz}{dt} = BASE_HAZ \cdot \left(1 - \frac{E_{MAX} \cdot Conc^{Hill}}{EC50^{Hill} + Conc^{Hill}}\right) \cdot \prod_n (1 + COV_n)$$

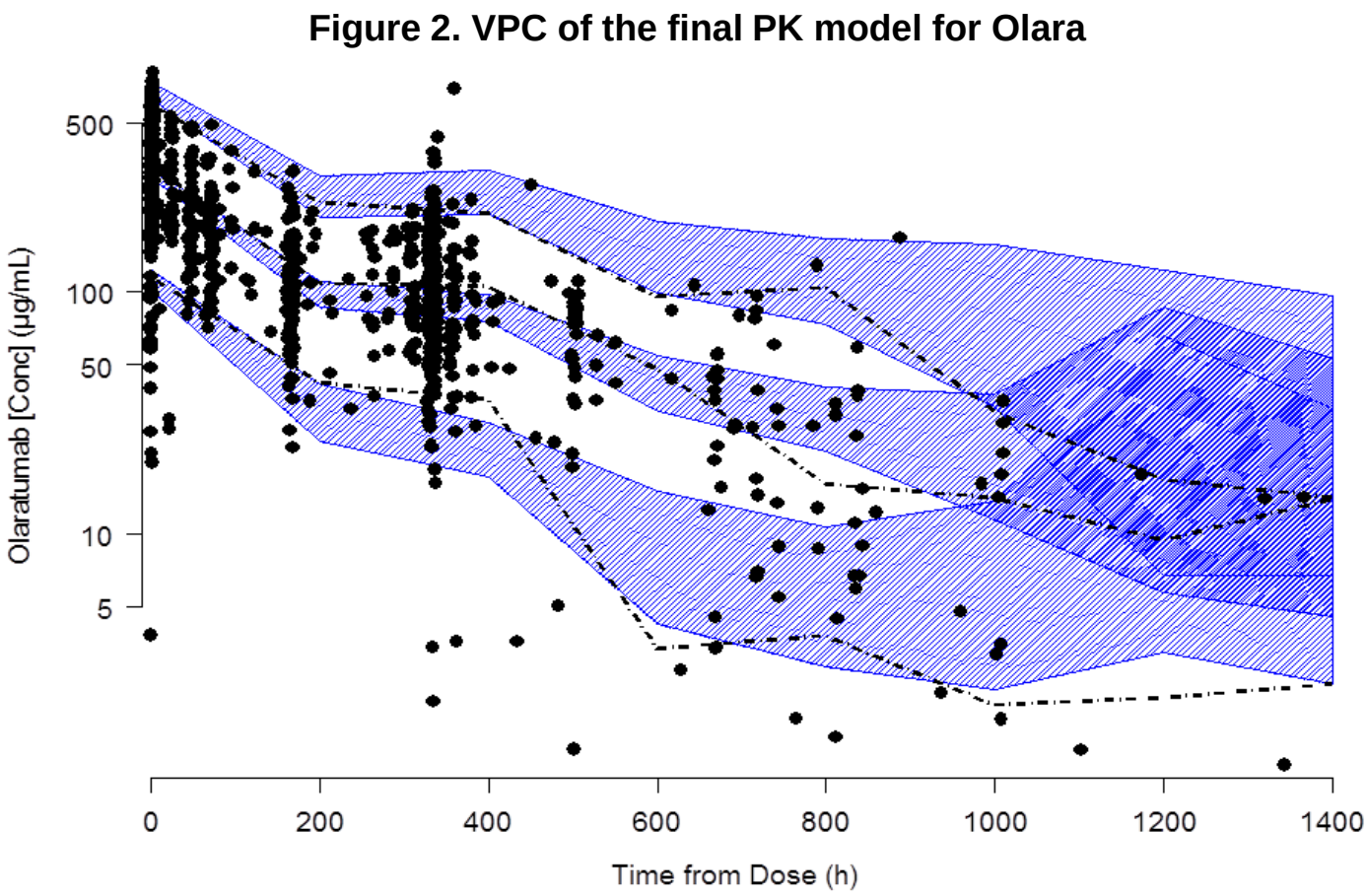
RESULTS

Olaratumab PopPK model

The PK of Olara in cancer patients was best-described by a 2-compartment model with linear elimination (Figure 2). Body Weight had a significant effect on both CL and V1 and Tumour Size had a significant effect on CL (Table 1).

Table 1. Olaratumab PopPK Parameter Estimates

Parameter Description	Population Estimate	Inter-Patient Variability
Structural Model		
CL (L/hr)	0.0233 (3.67)	33.3% (12.9)
V1 (L)	4.16 (1.79)	15.6% (30.1)
Q (L/hr)	0.0315 (25.8)	
V2 (L)	3.58 (13.2)	
Covariates		
WTE _{CL}	0.431 (10.2)	
WTE _{V1}	0.610 (12.9)	
TUMR _{CL}	0.00158 (25.8)	
Residual Error		
Proportional	22.5% (18.1)	
Additive	10.1 (15.5)	



Progression-Free Survival Model

PFS in the STS Phase 2 study patients was best described by a time-to-event model with a constant baseline hazard.

The effect of Olara was best captured by a inhibitory Emax model with Hill coefficient, and drug effect was similar regardless of whether Cmin1 or Cavg was used as the PK endpoint (Table 2, Figure 2, Figure 3):

- The EC50 corresponded to the median value of the PK endpoint in the study
- The maximum predicted improvement in the hazard ratio (HR) for PFS was approximately 60%

No covariates were found to have a significant impact on PFS

Table 2. PFS and OS Model Parameter Estimates (%SEE)

PK Endpoint	PFS		OS	
	Cmin1	Cavg	Cmin1	Cavg
Baseline Hazard				
BaseHaz	0.00604 (2.52)	0.00616 (2.63)	0.00205 (2.18)	0.00203 (2.26)
Drug Effect				
Emax	0.571 (15.4)	0.614 (14.5)	0.765 (8.63)	0.756 (9.07)
EC _{min1} 50 (ug/mL)	82.0 (6.15)		66.1 (12.1)	
EC _{avg} 50 (ug/mL)		179 (9.33)		134 (6.72)
Hill	8 (fixed)	8 (fixed)	8 (fixed)	8 (fixed)
Covariates				
EGRP _{Base}			0.862 (42.1)	0.802 (44.0)
PRVTR _{Base}			-0.583 (15.9)	-0.535 (19.1)

Figure 2. Observed versus predicted PFS in the study

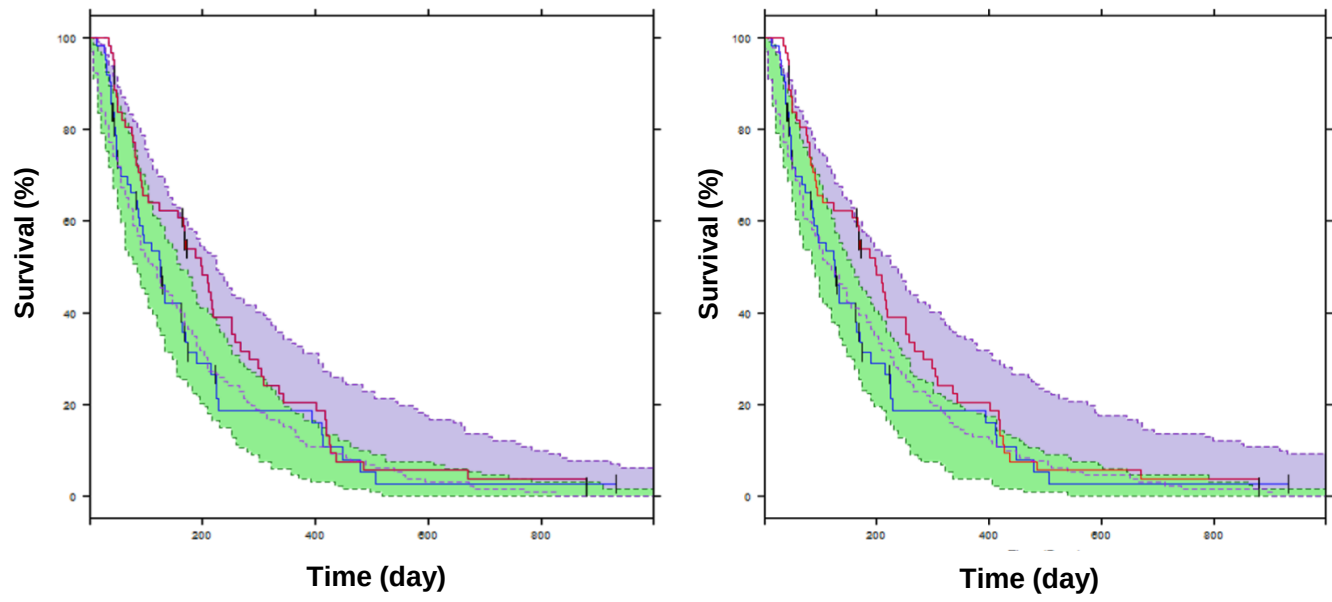
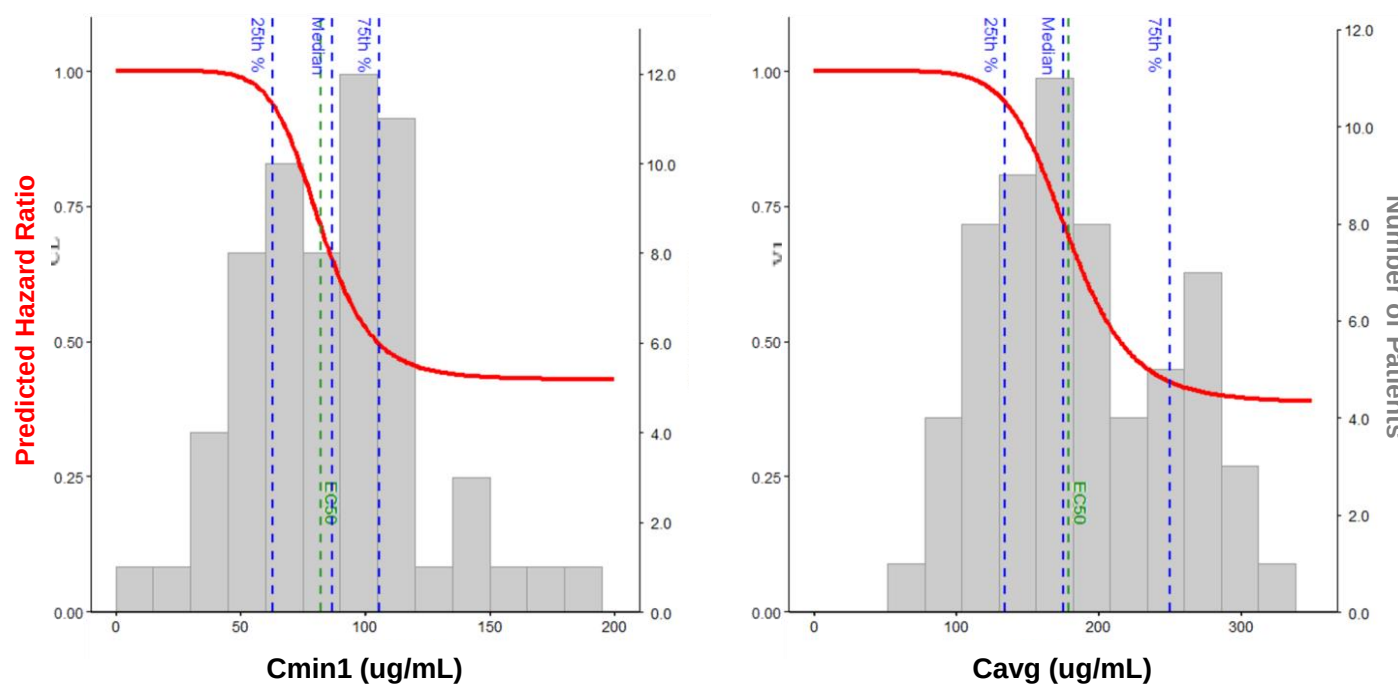


Figure 3. Predicted effect of Olara on the HR for PFS as a function of Cmin1 (left panel) or Cavg (right panel). The histograms describe the distribution of Cmin1 and Cavg in the study together with their quartiles (dashed blue lines) and the model-predicted EC50 (dashed green line)



Overall Survival Model

OS was also best described by a model with a constant baseline hazard and Cmin1 or Cavg had a similar predictive role for drug effect (Table 2, Figure 4, Figure 5).

Parameter estimates were consistent with the greater effect of Olara on OS (Table 2):

- The EC50 for OS corresponds to the 25th percentile of the PK endpoint studied (vs. median for PFS)
- The maximum predicted improvement in the hazard ratio (HR) for OS is approximately 75-77% (vs. 57-61% for PFS)

Emax was predicted to be achieved within the range of concentrations observed at the dose of 15 mg/kg tested in the study (Figure 5)

Significant covariates identified in the OS model were the ECOG prognosis score (0 vs. ≥ 1) and the number of lines of prior treatment.

Figure 4. Observed versus predicted OS in the study

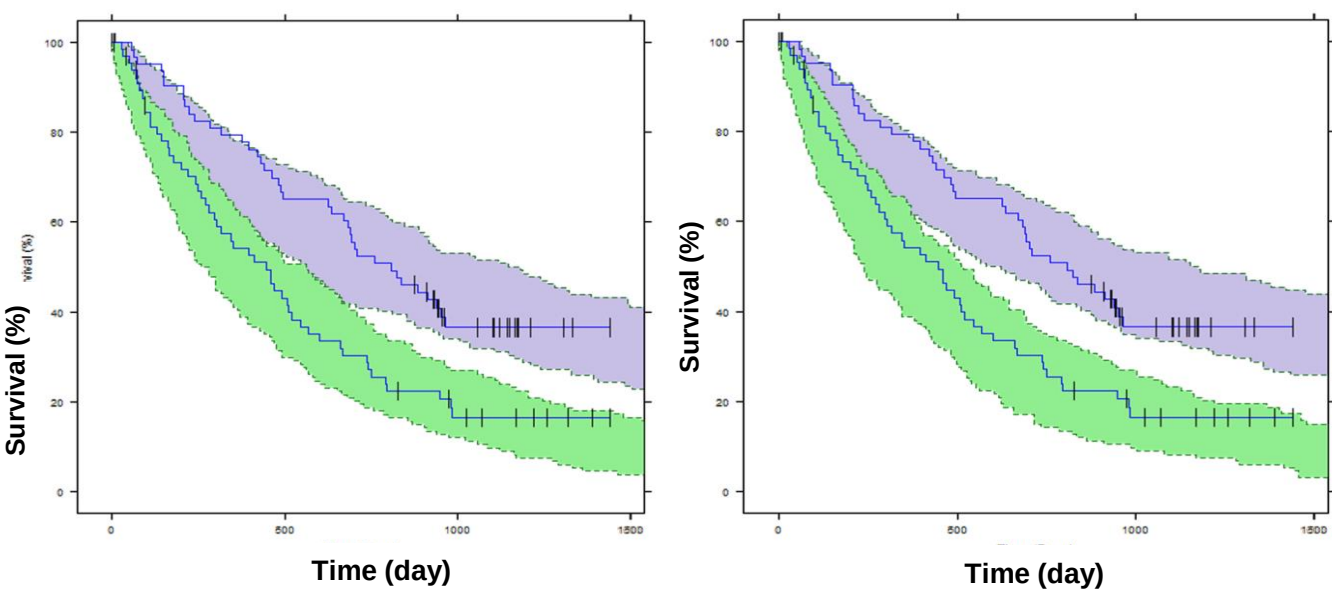
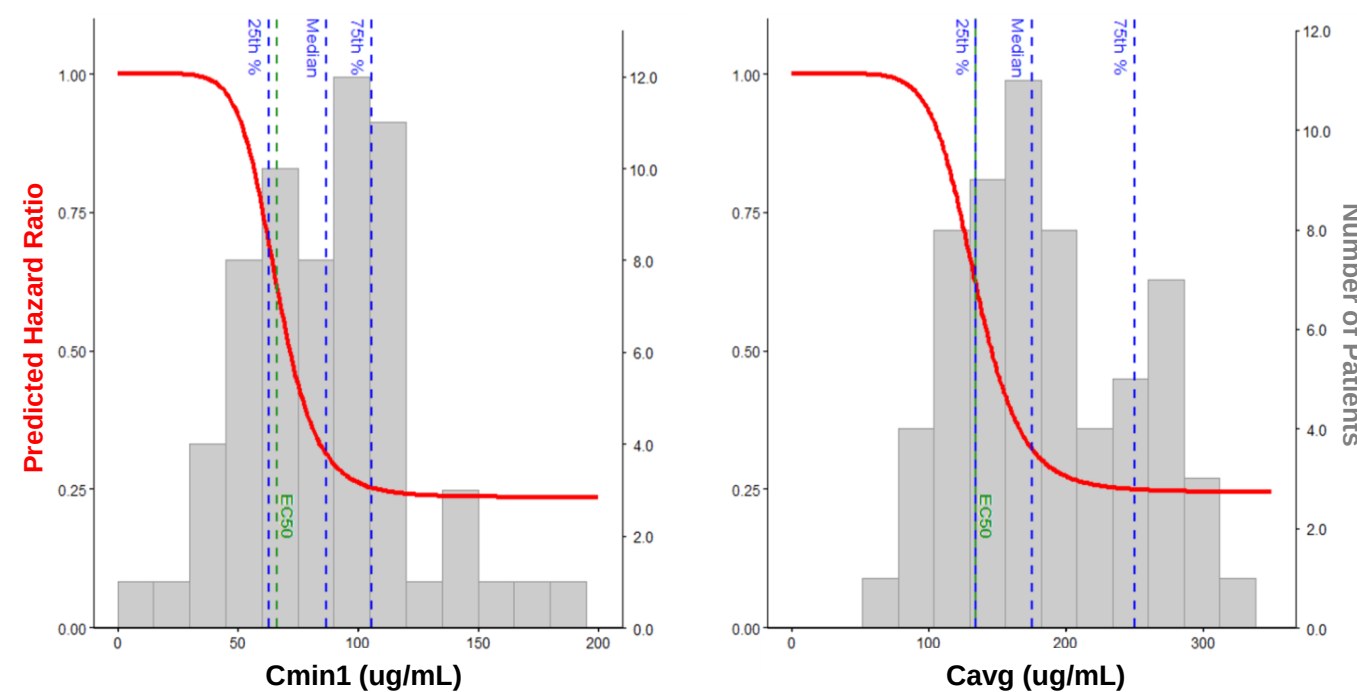


Figure 3. Predicted effect of Olara on the HR for OS as a function of Cmin1 (left panel) or Cavg (right panel). The histograms describe the distribution of Cmin1 and Cavg in the study together with their quartiles (dashed blue lines) and the model-predicted EC50 (dashed green line)



CONCLUSIONS

- OS and PFS in the STS Phase 2 study where patients received Dox alone or combined with Olara were successfully described by survival models with a constant hazard.
- Olara Cmin1 and Cavg showed a similar predictive role for Olara effect on PFS/OS.
- The survival models are consistent with a greater effect of Olara on OS than PFS.
- Maximum improvement in the OS HR was predicted to occur within the range of Olara serum levels achieved at the dose of 15 mg/kg (Days 1 and 8 of a 21-day cycle) used in the study.

References:

- Tap et al., J Clin Oncol 33, 2015 (suppl; abstr 10501)
- Tap et al., CTOS 2015, Abstract 020