Semi-mechanistic pharmacokinetic-pharmacodynamic modeling of tumor size dynamics in advanced breast cancer patients treated with single-agent amcenestrant

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1. INTRODUCTION

- Selective estrogen receptor degraders (SERDs) provide an important therapeutic option for hormone receptor positive breast cancer [1]. SERDs act by fully antagonizing and degrading the estrogen receptor (ER), resulting in inhibition of the ER signaling pathway
- Amcenestrant is an oral SERD in development for the treatment of ER+, HER2- breast cancer [1].
- In two phase 1 studies, AMEERA-1 (NCT03284957 - part A: dose escalation; part B: dose expansion) [2] and AMEERA-2 (NCT03816839) [3], amcenestrant was evaluated in non-Japanese and Japanese patients with ER+ and HER2- advanced breast cancer and efficacy data were available (tumor size [TS], objective response rate [ORR])
- Tumor growth inhibition (TGI) modeling aims to describe the dynamics of TS evolution, anti-tumor drug effect as well as to explore resistance to treatment
- Several approaches have been developed to characterize drug resistance [4] from empirical models, e.g., Claret model [5], to more mechanistic models including intra-tumor heterogeneity [6]

- The objectives of this study were:
  - to characterize the effect of amcenestrant as single agent on TS dynamics in phase 1 study patients with ER+ and HER2- advanced breast cancer
  - to identify baseline covariates impacting tumor response
  - to evaluate the amcenestrant dose-response relationship

2. METHODS

Data

- Of the 81 patients included in the AMEERA-1 and -2 studies, 75 evaluable patients with ≥2 measurements of TS were considered in this analysis.
- TS was defined as the sum of maximum diameter of target lesions
- TS and response data were evaluated by investigator and/or an independent central review (ICR).

Modeling strategy and software

- The evolution of tumor burden was characterized using a TGI model by analyzing the tumor size of the target lesions only (Figure 1)
- Individual treatment exposure over time was introduced using concentrations predicted by a population pharmacokinetic model characterized by two-compartment distribution, linear elimination and four transit compartments to account for absorption delay
- A covariate model was then built using the COSSAC algorithm [7] implemented in Monolix2020R1 to examine the influence of baseline covariates on TS kinetics
- Model selection was based on the corrected Bayesian information criteria (BICc), parameters uncertainty, relevant interpretation of the parameters, and clinical pertinence
- Model evaluation was done through residual- and simulation-based graphical diagnostics

Covariate impact

- Simulations were performed to quantify the impact of each covariate using the population parameters and was visualized in a typical patient
- The effect of covariates was assessed individually by setting others to their median value for continuous covariates and for the most frequent class for the categorical covariate
- The effect of continuous covariates was examined for variations within the 5th to 95th percentiles of the database

Simulation of dose effects

- 100 trials of 1000 patients bootstrapped from the pool of AMEERA-1 and -2 were used in this analysis. To mimic the actual treated population, the set of covariates characterizing each patient was used. Individual parameters were sampled from the distribution of the population parameters.
- Several dosing regimens covering dose range from the escalation part were considered in the simulation, i.e., 100, 200, 400 and 600 mg QD.
- TS kinetics were simulated for each patient/dose every five days for 90 weeks.
- Based on the tumor size dynamics, the target lesions response rate (TLRR) was derived, i.e. the number of patient achieving a 30% decrease from baseline or a complete response (<limit of quantification, e.g. 5mm). Of note, response was also to be confirmed as per protocol 4 weeks after its documentation.

3. RESULTS

Baseline patient characteristics

- Baseline patient characteristics were generally balanced between study parts (Table 1), patients in part B being less severe

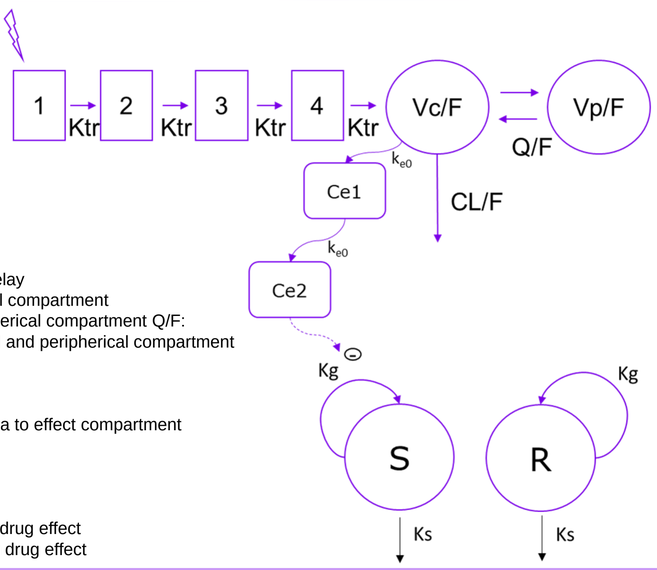
Model development

- 2 compartment accounting for the dynamics of resistant/sensitive cells with inhibition of the tumor proliferation rate (Kg) of the sensitive cells only, driven by amcenestrant effect concentrations after 2 transit compartments.

Covariate impact

- The covariates explained 76% of inter-individual variability (IIV) on tumor shrinkage / tumor proliferation rate ratio while explaining very low IIV on tumor size at baseline (i.e. 8%)
- Patients without liver metastasis and lower number of organs with metastasis (NMET<3) tend to have lower tumor size at baseline.
- Patients tend to have faster tumor regrowth if they have low albumin or presence of lymph node metastasis or have prior CDK4/6 therapy.
- Of note, there was no effect of ESR1 mutation on pR, the proportion of resistant cells at baseline (Figure 2).

Figure 1. Schematic representation of the integrated drug disease model



Ktr: transit rate for absorption delay
Vc/F: apparent volume in central compartment
Vp/F: apparent volume in peripherical compartment Q/F: apparent transit between central and peripherical compartment
CL/F: apparent clearance

Ks: shrinkage rate
ke0: equilibrium rate from plasma to effect compartment
Kg: proliferation rate
PK: pharmacokinetic
S: sensible cells
R: resistant cells
Ce1: 1st transit compartment in drug effect
Ce2: 2nd transit compartment in drug effect

Model evaluation

- The model was able to well describe various tumor size dynamics patterns such as drug effect delay, response to treatment, potential relapse, stable disease.
- VPC plot generated from the longitudinal model and incorporating progression from target lesions (20% and 5 mm increase from nadir) indicates the agreement between model prediction and observation of the tumor size dynamics at the population level (Figure 3).

Simulation of dose effects

- Dose increase is associated with a better TLRR over time (Figure 4), with median TLRR at 12 months of 16.8%, 19.4%, 21.8% and 22.9% for 100, 200, 400, 600 mg QD respectively
- 400 mg QD provides a slightly higher TLRR vs. 200 mg QD (+2.3 % at 12 months), and higher TLRR vs. 100 mg QD (4.8% at 12 months) and a plateau at 600 mg QD is observed with only +1.2% at 12 months when compared to 400 mg QD (Figure 4).

Table 1. Baseline demographic and patient characteristics

Type	Label	Level	AMEERA-1 PART A (n=21)	AMEERA-1 PART B (n=46)	AMEERA-2 (n=8)
Continuous variable			Median (min,max)	Median (min,max)	Median (min,max)
Age (years)	AGE		59 (40-86)	64 (37-88)	66 (48-76)
Normalized albumin /ULN	ALBN		0.74 (0.53-0.86)	0.74 (0.60-0.87)	0.72 (0.60-0.80)
Normalized serum alkaline phosphatase /ULN	ALKN		0.94 (0.29-3.92)	0.89 (0.27-2.72)	0.59 (0.39-2.49)
Categorical variable			n (%)	n (%	n (%)
ESR1 mutation	ESR1	Yes	13 (61.90)	19 (41.30)	4 (50.00)
Number of prior lines	NPRIOR	≥3	15 (71.43)	27 (58.70)	5 (62.50)
Prior CDK4/6	PRIORCDK4/6	Yes	17 (80.95)	27 (58.70)	6 (75.00)
Liver metastasis	LIVMET	Yes	16 (76.19)	25 (54.35)	5 (62.50)
Bone metastasis	BONMET	Yes	16 (76.19)	33 (71.74)	5 (62.50)
Lymph node metastasis	LYMMET	Yes	12 (57.14)	18 (39.13)	4 (50.00)
Number of organs with metastasis	NMET	≥3	11 (52.38)	25 (54.35)	5 (62.50)

*ULN: Upper Limit Normal

Table 2. Parameter estimates (relative standard error %) of tumor size kinetics for the basic model and the best final model with covariate

Population parameters	Estimate	RSE(%)	p-value (wald-test)
Fixed effect			
TS0 (mm)	57.14	10.27	
β1 ~ LIVMET=absence	-0.42	32.76	0.002
β2 ~ NMET <3	-0.36	37.08	0.007
Ks (1/day)	0.09*	Fixed	
RE (=Ks/Kg) (-)	0.991	0.28	
β3 ~LYMMET=presence	-1.22	28.34	0.0004
β4 ~ALBN	6.42	26.66	0.00018
β5 ~PRIORCDK4/6=absence	2.29	21.22	2.44e-06
IC50 (mol/L)	1.73	8.48	
pR (%)	71	9.56	
ke0 (1/day)	0.005**	Fixed	
Interindividual variability			
ωTS0 (%)	57	8.30	
ω RE (%)	89	21.81	
ω pR (%)	141	18.72	
ω ke0 (%)	278	22.75	
Residual variability			
σ additive (mm)	0.47	41.72	
σ proportional (%)	9	12.48	

Abbreviations: β: coefficient of covariate effect; IC50: molar amcenestrant concentration at the effect site inducing 50% of maximum inhibition; pR: percentage of resistant cells at baseline; RE, the ratio between Ks and Kg; RSE: relative standard error; TS0: tumor size at baseline

*the tumor shrinkage rate was fixed to 0.09 day^{-1} consistent with literature value [8]

**ke0, the effect-compartment equilibrium rate constant, was fixed to 0.005 day^{-1} based on sensitivity analysis

Figure 2. Impact of covariate effects on tumor size kinetics

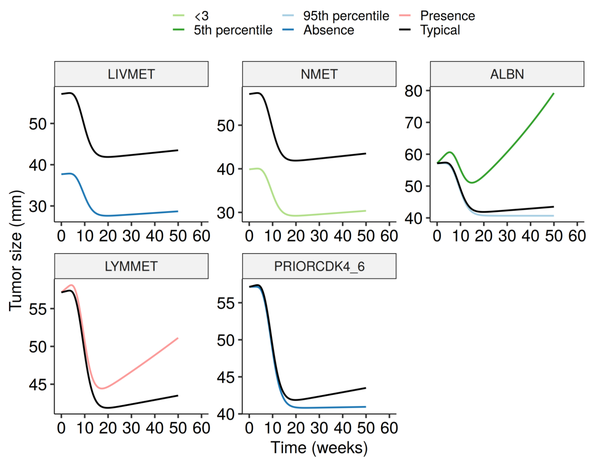


Figure 3. Visual predictive checks (VPC) plot of tumor size of target lesions

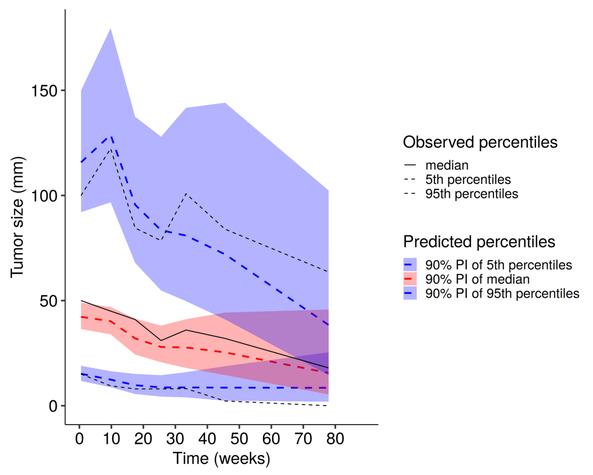


Figure 4. TLRR across dose at 6 and 12 months

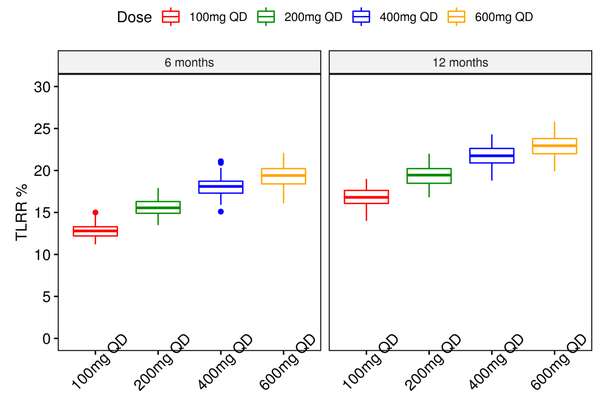
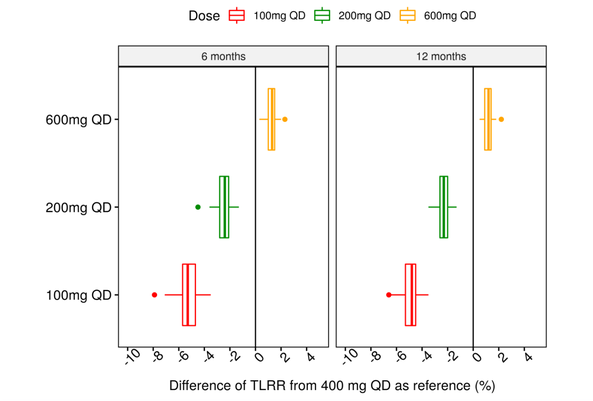


Figure 5. Forest plot of TLRR difference compared to 400 mg QD



4. CONCLUSIONS

- **The present TGI model characterized the tumor size dynamics well on both the individual and population levels.**
- **Based on the simulations, a limited positive dose-response relationship on tumor size of target lesions was predicted in this advanced breast cancer population.**
- **However, other causes of progression (i.e., non-target, new lesions, death) should be considered in future work to allow objective response rate prediction according to RECIST 1.1 criteria and to refine the dose-response assessment.**

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DISCLOSURES:

All authors are employed by Sanofi and may hold shares and/or stock options in the company

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