Semi mechanistic joint modeling of tumor dynamics and PFS in advanced breast cancer: leveraging data from early amcenestrant phase I-II trials

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1. INTRODUCTION

- Amcenestrant is an orally bioavailable selective estrogen receptor (ER) degrader developed for the treatment of ER+/HER2- advanced breast cancer.
- Despite a favorable safety profile and promising activity as monotherapy and in combination with palbociclib in the phase 1/2 AMEERA [AM]-1 (NCT03284957) and AM-2 (NCT03816839) studies [1,2], amcenestrant failed to demonstrate progression-free survival (PFS) superiority over physician's choice endocrine monotherapy in the pivotal phase 2 AM-3 (NCT04059484) study [3].
- A tumor growth inhibition (TGI) model [4] was initially constructed using tumor size (TS) data from 75 Japanese and non-Japanese patients from the AM 1-2 studies who were treated with amcenestrant monotherapy. The model accounted for exposure to amcenestrant at doses ranging from 20 to 600 mg daily and included a resistance process.
- The aims of the present analysis were:
  - to develop a joint model of TS and PFS using phase 1/2 data to further evaluate the exposure-response relationship of amcenestrant, and to identify baseline covariates influencing both TS & PFS
  - to evaluate how the model that has been trained on AM 1-2 studies performs in predicting AM-3 trial
  - to refine the joint model using the pool data of AM 1-2-3.

2. METHODS & DATA

Modeling endpoints

- TS was defined as the sum of longest diameters of the measurable target lesions
- PFS was defined as the time from randomization to progression as per RECIST 1.1 criteria
  - Progression of at least 20% and 5 mm from the lowest observed tumor size of target lesions (nadir)
  - Progression event if death, progression from non-target lesions or appearance of new lesions
- TS and PFS data evaluated by investigator were used

Modeling framework

- A **training** dataset was defined based on the 75 patients of AM 1-2 studies.
- A **validation** dataset was defined from the AM-3 trial, consisting of 98 patients with measurable target lesions at baseline.
- A **calibration** dataset was defined from the pool of AM 1-2-3 studies with a total of 214 patients, including 36 with non-measurable lesions at baseline.
- A classical model building strategy was used to develop the joint model:
  - Step 1: develop a PK/TGI model for TS with covariate selection using COSSAC method [5] and a separate parametric time-to-event (TTE) model for PFS with covariate selection using SCM method
  - Step 2: identify a link function between TS and PFS when fitted simultaneously
  - Step 3: remove non-statistically significant covariates using Wald test step by step.
- Calibration was performed by repeating the covariate model building at each step of the joint model building.
- Model parameters were estimated using the SAEM algorithm implemented in Monolix2020R1, and simulations were performed using Simulx2020R1 and R version 3.6.1
- Model evaluation was done through residual- and simulation-based graphical diagnostics

Covariate impact evaluation

- Simulation 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

3. RESULTS

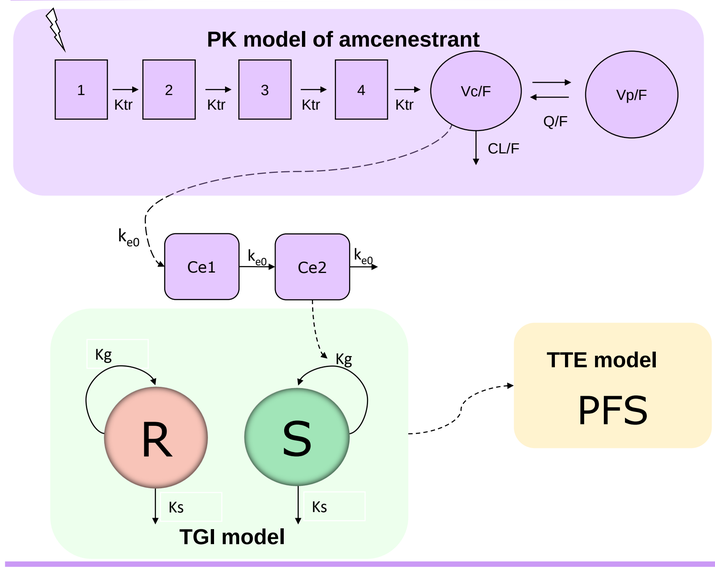
Baseline patient characteristics

- Baseline patient characteristics were generally balanced between study arms (Table 1), with less heavily pre-treated and/or fewer metastases in AM-1 part B patients. Patients in the AM-3 study were less severe, with less prior line, and mainly without prior treatment with mTOR and/or fulvestrant.

Model development

- The joint model (Figure 1) developed on the training dataset was composed of a PK model, a TGI model of sensitive and resistant cells for TS (TS=sum of sensitive and resistant cells), a treatment effect (inhibition of growth rate of sensitive cells) driven by amcenestrant concentration in the effect compartment with delay, and a Weibull proportional hazard model for PFS.
- The link function between TS & PFS was best characterized by the slope of TS.

Figure 1. Schematic representation of the integrated drug disease model



PK parameters:
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

PD parameters:
Ks: shrinkage rate
ke0: equilibrium rate from plasma to effect compartment
Kg: proliferation rate
Ce1: 1st transit compartment in amcenestrant effect
Ce2: 2nd transit compartment in amcenestrant effect
S: sensible cells
R: resistant cells
TS = R + S

Model evaluation

- The joint model from the phase 1/2 data was able to predict the time course of TS and PFS profiles of the amcenestrant in the training dataset (Figure 2A).
- The external evaluation of this model on the validation dataset (AM-3) showed good model performance in overall and in most of the tested subpopulations, except for patients with liver metastasis (Figure 2B).
- Model predicted well the calibration dataset in overall and all tested sub-populations, including liver metastasis (Y/N) (Figure 2C).

Covariate impact

- The significant baseline covariates in the joint model from the calibration dataset were age, menopausal status, number of organs with metastases, aspartate aminotransferase (AST) and liver metastases on tumor size kinetics, and AST and liver metastases on PFS (Figure 3).
- Patients with liver metastases or high AST levels tended to have faster tumor growth and a higher risk of progression.
- Other covariates had a limited impact on PFS.

Table 1. Baseline characteristics of advanced breast cancer patients in AM 1-2-3 (median and range or %)

Covariates (unit)	Training dataset			Validation dataset	Calibration dataset
	AM-1 Part A (n=21)	AM-1 Part B (n=46)	AM-2 (n=8)	AM-3 (n=98)	All (n=214)
Age (years)	59 (40-86)	64 (37-88)	66 (48-76)	58 (29-84)	60 (29-88)
Serum alkaline phosphatase (ALK) (IU/L)	100 (38-412)	95 (47-272)	202.5 (126-801)	90.3 (35-1940)	94 (35-1940)
Aspartate amino transferase (AST) (IU/L)	26 (9-113)	29 (9-95)	24.5 (17-77)	27.5 (7-148)	28.4 (7-180)
Number of patients without measurable target lesions	0 (0)	0 (0)	0 (0)	0 (0)	36 (16.8)
Menopausal status (post)	19 (90)	43 (93)	8 (100)	81 (83)	185 (86)
Number of patients with at least 3 organs with metastasis	11 (52.4)	25 (54.3)	5 (62.5)	44 (44.9)	97 (45.3)
Number of prior lines>=3	12 (57.1)	20 (43.5)	5 (62.5)	3 (3.1)	41 (19.2)
Liver metastasis (LIVMET) (Yes)	16 (76.2)	25 (54.3)	5 (62.5)	46 (46.9)	101 (47.2)
Prior mTOR (Yes)	11 (52.4)	14 (30.4)	0 (0)	1 (1)	26 (12.1)
Prior Fulvestrant (Yes)	14 (66.7)	20 (43.5)	5 (62.5)	10 (10.2)	54 (25.2)
Prior CDK4/6 (Yes)	17 (81)	27 (58.7)	6 (75)	73 (74.5)	160 (74.8)

Figure 2. Kaplan-Meier visual predictive check of PFS based on (A) the **training** dataset, (B) the **validation** dataset, unstratified (left) and stratified by liver met (right, 0: absence, 1: presence), (C) the **calibration** dataset, unstratified (left) and stratified by liver met (right, 0: absence, 1: presence)

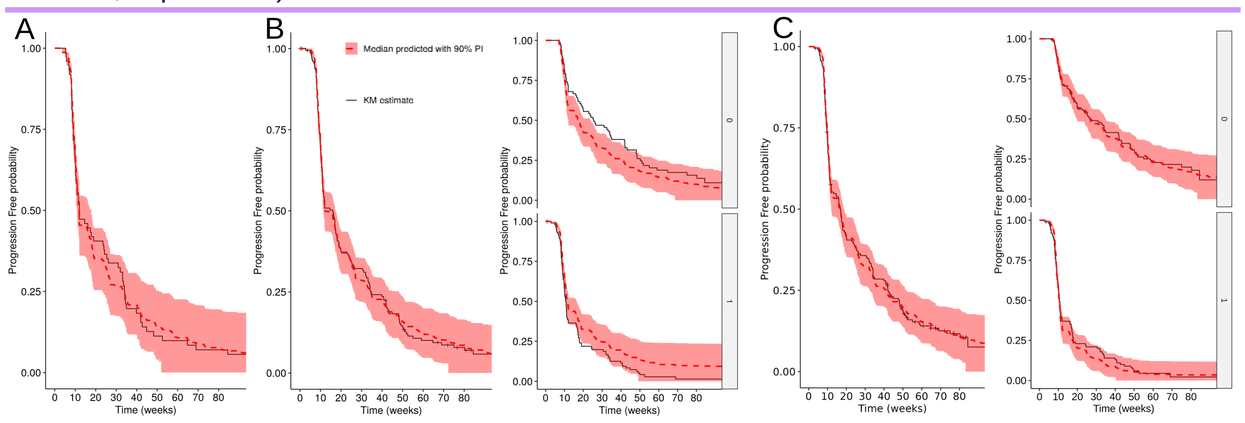


Table 2. Parameter estimates (relative standard error %) of tumor size kinetics for the calibrated model with covariate

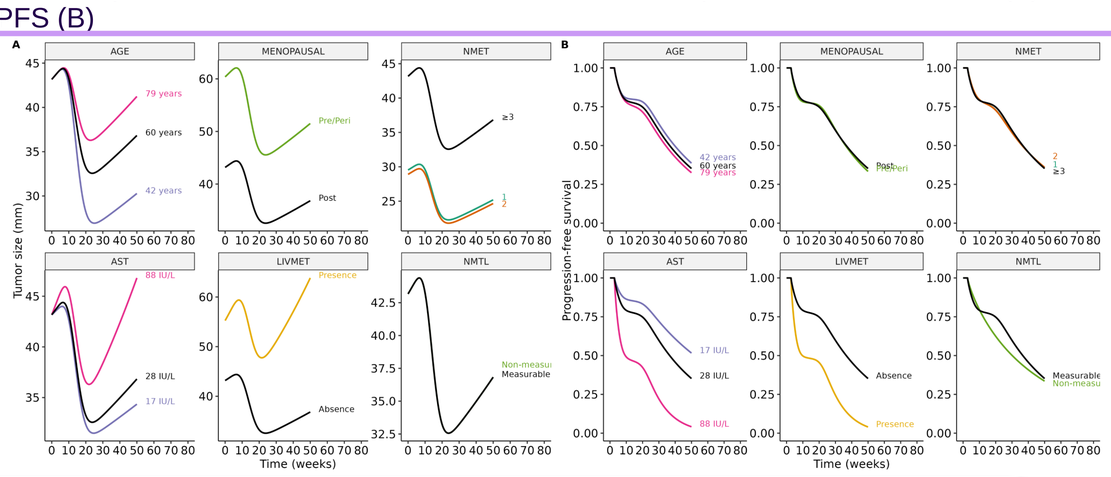
Population parameters	Estimate (RSE %)	p-value (wald-test)
	Fixed effect	
TS0 (mm)	43.17 (8.24)	
$\beta TS0_{LIVMET}yes$	0.25 (35.26)	0.0046
$\beta TS0_{MENOPAUSAL}(\mathrm{pre/peri})$	0.34 (37.93)	0.0084
$\beta TS0_{\mathrm{NMET\ (1)}}$	-0.38 (40.56)	0.0137
$\beta TS0_{\mathrm{NMET\ (2)}}$	-0.4 (22.78)	1.13e-5
RE (-)	0.992 (0.16)	
$\beta RE_{logtASTN}$	-0.57 (44.58)	0.0249
βRE_{LIVMET}	-0.78 (33.88)	0.0032
IC50 (mol/L)	3.74 (28.97)	
pR (%)	66 (4.9)	
$\beta pR_{\mathrm{logtAGE}}$	1.35 (47.93)	0.0370
shape (-)	0.84 (3.91)	
Te (day)	297.73 (12.3)	
$\beta_{slopeTS}$	10.73 (17.85)	2.11e-8
$\beta E_{logtASTN}$	0.68 (43.12)	0.0204
βE_{LIVMET}	0.52 (20.89)	1.7e-6
	Interindividual variability	
ωTS0 (%)	57 (5.42)	
ω RE (%)	125 (9.99)	
ω pR (%)	84 (13.72)	
ω ke0 (%)	351 (17.42)	
	Residual variability	
σ additive (mm)	0.75 (22.24)	
σ proportional (%)	6 (9.4)	

ke0 fixed to 0.005 day^{-1}; Ks fixed to 0.09 day^{-1}; RE=Ks/Kg ratio

TS0 Tumor size at baseline; pR, proportion of resistant cells ;IC50 amcenestrant concentration in the effect compartment needed to reach half of the inhibition of tumor proliferation,

Te scale parameter of log-logistic baseline hazard; shape, shape parameter of the log-logistic time to event model

Figure 3. Impact of covariate effects from the calibration step on tumor size kinetics (A) and PFS (B)



4. CONCLUSIONS

- **In this retrospective analysis, we showed that the joint modelling framework with PK, TS dynamics and PFS, at early oncology development stage (phase 1/2 dose escalation/expansion, N=75) was able to accurately predict the unstratified PFS of the amcenestrant arm of the phase II AM-3 trial.**
- **The use of drug disease modeling to leverage clinical and PK data as early and efficiently as possible in the development program is key to optimize drug dosing in oncology development.**

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DISCLOSURES:

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

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