

A novel drug disease model in oncology to evaluate benefit-risk balance of tusamitamab ravtansine monotherapy

Poster I-056

Marc Cerou (1), Sophie Fliscounakis-Huynh (2), Clemence Pouzin (3), Nathalie Fagniez (3), Frano Mihaljevic (4), Emmanuelle Comets (5), Mustapha Chadjaa (6), Hoai-Thu Thai (1)

(1) Translational Disease Modelling Oncology, Sanofi, France. (2) IT&M Stats, France (3) Pharmacokinetics Dynamics and Metabolism, Sanofi, France (4) Simulations Plus, Lixoft division, France (5) Université Paris Cité, Université Sorbonne Paris Nord, IAME, Inserm; Univ Rennes, Inserm, EHESP, Irset - UMR_S 1085, France (6) Lung Cancer Oncology Dev, Sanofi, France



INTRODUCTION

- Tusamitamab ravtansine (Tusa Rav) is a novel antibody-drug conjugate that targets carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) in tumor cells, delivering the cytotoxic agent DM4.
- In a phase 1 FIH study (NCT02187848), Tusa Rav monotherapy demonstrated encouraging antitumor activity and a favorable safety profile in non-squamous (NsQ) non-small cell lung cancer (NSCLC) patients with CEACAM5 expression ≥ 2+ intensity. The observed adverse events (AE), in particular corneal events, were manageable by dose modifications (e.g., dose delay /reduction/ discontinuation).
- Evaluation of the benefit-risk balance for dose optimization is necessary but challenging due to the impact of AE-related dose modifications.

OBJECTIVES

- develop a Drug-Disease Model (DDM) characterizing the relationship between exposure, progression-free survival (PFS) and adverse events (AEs) (corneal vs non-corneal AEs) using Tusa Rav phase 1 data,
- evaluate the impact of dose modifications and the benefit-risk of different dosing regimens of interest by iterative simulations.

METHODS

Modeling endpoints

- Efficacy endpoint: PFS, defined as the time from randomization to disease progression, or death, as per RECIST 1.1 criteria, evaluated by investigator.
- Safety endpoints: dose-altering AEs, categorized as corneal vs. non-corneal events
 - Corneal events: clinical grades (grade 2 or grade 3)
 - Non-corneal events: grade 1 (dose delay), grade 2 (dose delay + dose reduction)

Modeling framework

- Population pharmacokinetic (PK) model: previously developed [2].
 - Exposure parameters of the ADC: time-varying Cmax/AUC/Ctrough.
- Efficacy endpoint:
 - Parametric TTE model approach used to predict PFS.
 - Underlying baseline hazard distribution characterized using Exponential, Weibull, and log-logistic models.
- Safety endpoints:
 - Time to AE, AE grade, and AE duration described by parametric repeated time-to-event (RTTE), mixed effects categorical, and linear mixed-effects models, respectively.
- Classical structural model building strategy was used with the corrected BIC as selection criteria. Covariate modeling was performed separately for each submodel with the COSSAC approach [3] for safety model and SCM for PFS model.

Iterative simulation process

- Needed to evaluate the models and simulate clinical trials
- Simulation steps:
 - Generate simulated doses using toxicity models
 - Estimate time-varying exposure parameters
 - Input simulated doses and/or associated exposure parameters into the PFS model

Simulation of different dosing regimens

- Different Tusa Rav dosing regimens for benefit-risk evaluation: 80, 100 & 120 mg/m² every 2 weeks (Q2W)
- Patient population: patients with Nsq NSCLC and high CEACAM5 expression (≥2+ intensity in ≥50% tumor cells) (N=64).

Software

- Model fitting and simulations were performed using MonolixSuite version 2023R1.

RESULTS

Baseline patient characteristics

- Baseline patient characteristics were generally balanced between study subgroup (Table 1).

Model development

- The integrated DDM developed to evaluate the impact of doses on safety and clinical endpoints is shown in Figure 1.
- Exposure/PFS Analysis:
 - The log-logistic proportional hazards model best described the data (see Table 2 for parameter estimates).
 - Higher Ctrough (time-varying) was found to be associated with a decreased risk of disease progression
 - Larger baseline tumor size, higher alkaline phosphatase levels, and longer time from diagnosis to first dose corresponded to an increased risk of progression
 - Model evaluation in Figure 2 showed that this model accurately predicted the PFS profile of the Tusa Rav Phase 1 data.
- Exposure/Safety Analysis:
 - The best PK/safety model (see Table 2 for parameter estimates) consists of:
 - An exponential model for the risk of both corneal and noncorneal events with inter-individual variability (iiv)
 - A binary logistic regression for both corneal and noncorneal event grades, with and without iiv respectively
 - A linear model without slope for the duration of corneal and noncorneal events, with and without iiv respectively
 - Time-varying Cmax, up to the currently administered dose, was found to be the best predictor of the risk of corneal events

Trial simulation

- In a simulation study using virtual patients with Nsq NSCLC and ≥ 50% CEACAM5 expression:
 - No significant difference in median PFS was found between doses (3.1, 3.3, and 3.5 months for 80, 100, and 120 mg/m² Q2W, respectively) (Figure 3).
 - For corneal events, a lower proportion of patients experiencing at least grade 2 requiring dose modification was predicted with the 80 mg/m² Q2W dose (6, 16 and 32% for 80, 100 and 120 mg/m² Q2W, respectively).
 - For noncorneal events, similar proportions of patients with at least grade 2 (dose delay and reduction) were predicted.

Table 1: Baseline characteristics of phase 1 patients

Median (min-max) for continuous variable and N (%) for categorical variable

		Dose escalation N=74	Dose Expansion		Overall N=254
			All (N=180)	Nsq NSCLC high (≥50%) (N=64)	
Age (years)		59 (34-74)	63 (31-91)	61.5 (41-91)	62 (31-91)
Body Mass Index (kg/m2) (BMI)		24.89 (15.06-40.76)	23.76 (14.61-36.59)	23.08 (16-34.48)	24.1 (14.61-40.76)
Alkaline phosphatase (IU/L) (ALK)		125.5 (47-834)	98.5 (38-1142)	89 (48-619)	103.5 (38-1142)
Aspartate Amino-Transferase (IU/L) (AST)		27,5 (12-122)	24 (10-208)	23 (10-144)	25 (10-208)
Tumor size at baseline (mm) (TSBASE)		86 (16-339)	82.5 (11-320)	76.5 (11-320)	84 (11-339)
Time from diagnosis to 1st dose (months) (DURATION)		2.65 (0.49-16.99)	2.22 (0.33-13.17)	2.13 (0.57-10.51)	2.33 (0.33-16.99)
Nprior	<3	1 (1.4)	13 (7.2)	2 (3.1)	14 (5.5)
	≥3	73 (98.6)	167 (92.8)	62 (96.9)	240 (94.5)
CEACAM5	< 50%	23 (34.8)	49 (27.5)	0	72 (29.5)
expression	50% to 80%	14 (21.2)	57 (32)	30 (46.9)	71 (29.1)
(Intensity 2+/3+)	≥ 80%	29 (43.9)	72 (40.5)	34 (53.1)	101 (41.4)

Figure 1: Schematic representation of the integrated drug disease model

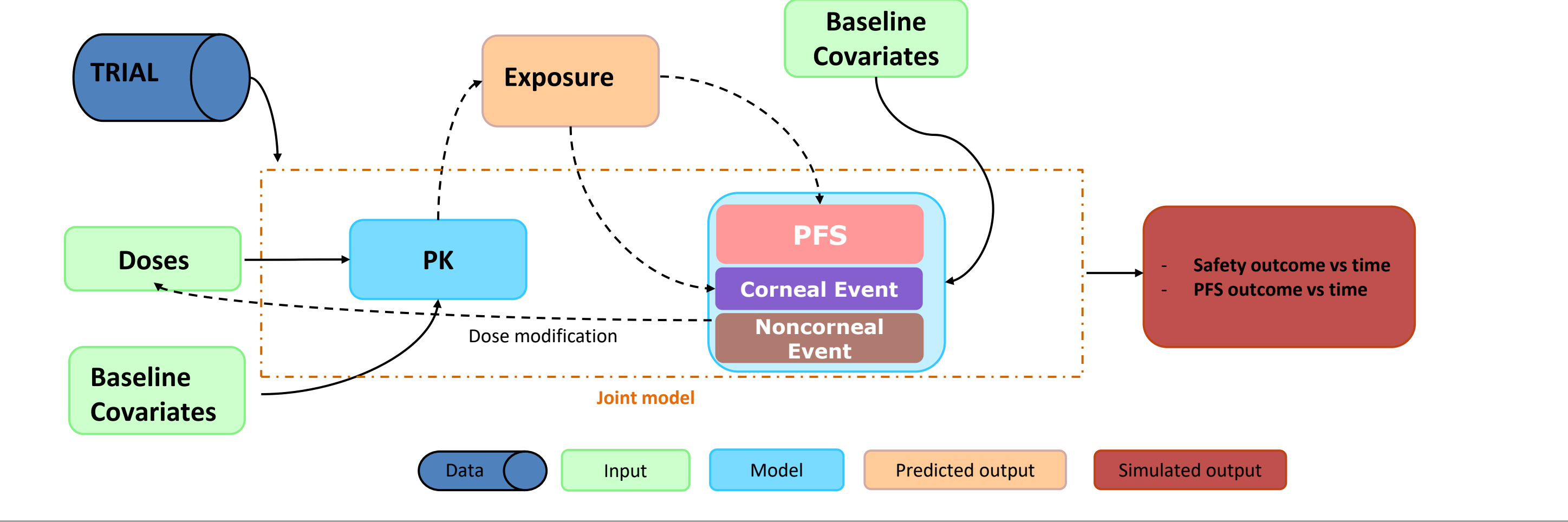


Table 2: Best models estimate (and RSE%) fitted on the overall population (N=254)

Exposure-PFS model			Exposure-safety mode		
Population parameters	Estimate	RSE %	Population parameters	Estimate	RSE %
Fixed effect			Fixed effect		
Te	69.84	2.89	rate_corneal	0.00006	37.43
S	2.4	NaN	h_corneal	1	Fixed
h_cov	1.0	Fixed	β:logtAGE*	-2.27	33.01
β:LungCohort (Yes)	-0.63	24.7	β:Cmax-h	7.6	8.41
β:logtALKN*	0.32	36.8	th1_corneal	2.23	23.53
β:logtDURATION*	-0.27	36.8	intercept_duration_corneal	15.29	5.43
β:logtTSBASE*	0.32	34.9	rate_non-corneal	0.0017	18.23
β:NPRIOR (≥3)	0.75	21.1	h_non-corneal	1	Fixed
β:Ctrough	-6.51	29.9	β:logtASTN*	0.88	28.18
			β:logtBMI*	2.61	27.42
			th1_non-corneal	1.74	18.05
			duration_non-corneal	13.31	6.84
			Interindividual variability		
			ω:h_corneal	0.86	22.36
			ω:th1_corneal	2.45	21.92
			ω:duration_corneal	0.27	35.9
			ω:h_non-corneal	0.65	23.87
			Residual variability		
			Additive (duration_corneal)	0.39	11.62
			Additive (duration_non-corneal)	0.62	7.86

- Te & s: scale and shape parameters of log-logistic distribution
- th1: logit probability of grade 1/2 event
- rate: constant hazard parameter
- h / h_cov: dummy parameter for hazard model
- duration: time duration between event and next dose
- *Continuous variable were centered (median) and log-transformed: $tCov = \log(Cov/median)$

Figure 2: Internal evaluation (N=254) of the exposure/PFS and exposure/safety models

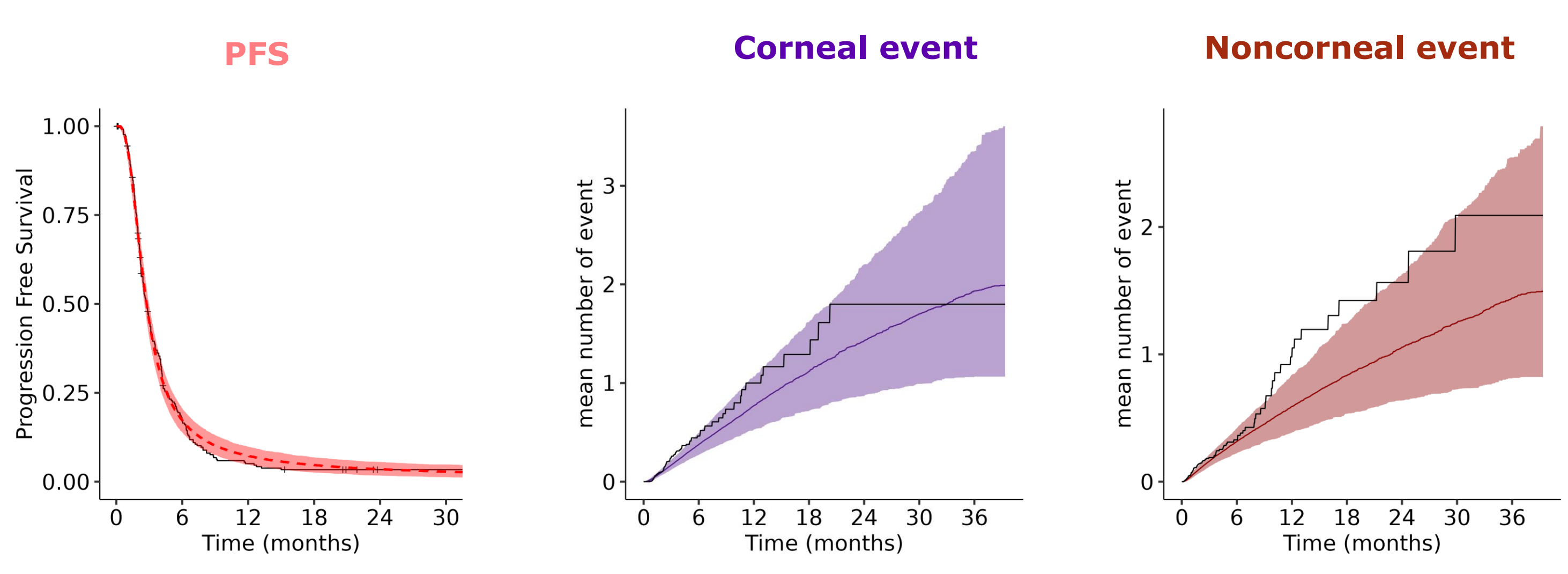
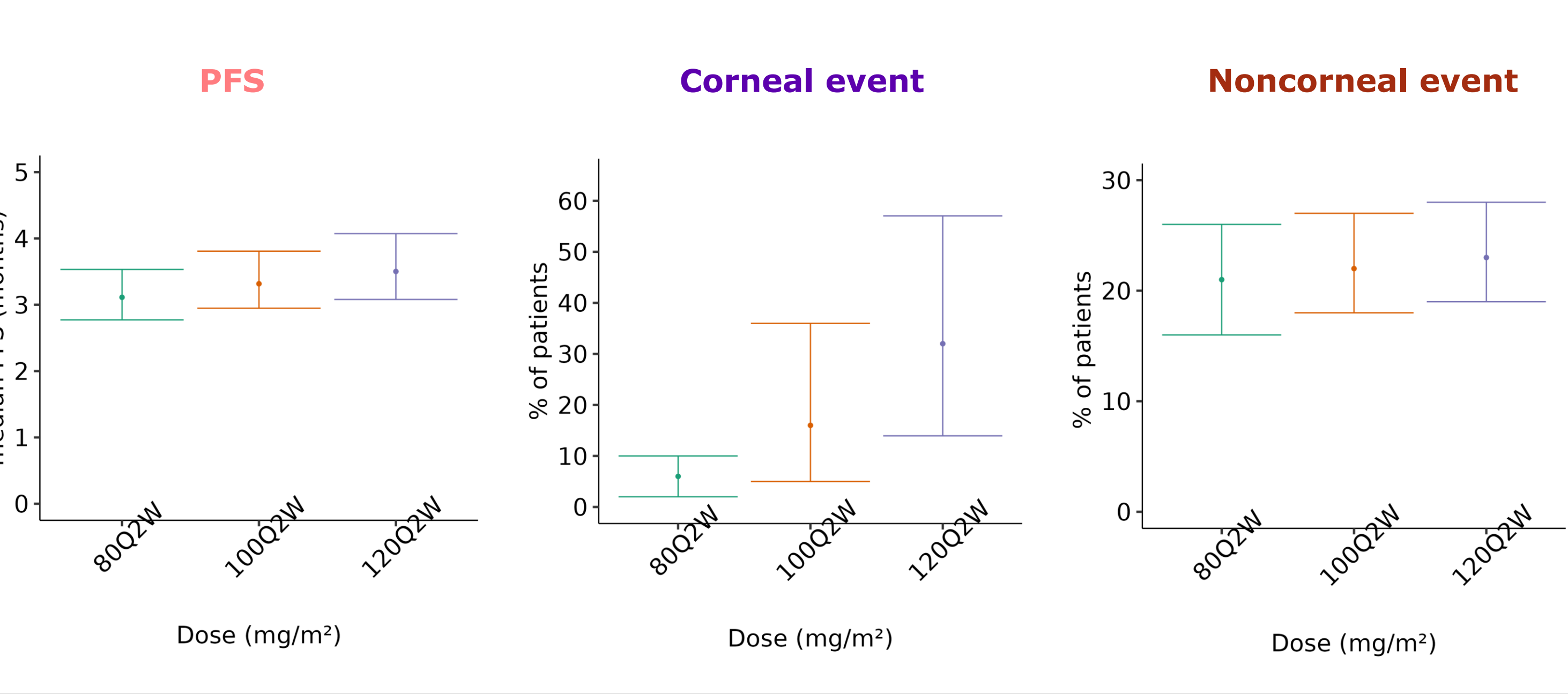


Figure 3: Comparison of dosing regimens (80-100-120 mg/m² Q2W) in term of median PFS, % of patients having at least grade 2 corneal events inducing dose modification and noncorneal events (dose delay) – Based on patients with Nsq NSCLC and ≥50% CEACAM expression (N=64)



CONCLUSIONS

- This novel drug-disease model accurately predicted both the observed efficacy and safety endpoints of Tusa Rav phase 1 (N=254).
- This model considered the AE-related dose modifications and allowed to evaluate the benefit-risk of different dosing regimens of Tusa Rav.

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M.Ce., H-T.T., C.P, N.F. and M.C. are employees of Sanofi and may hold stock/stock options. All other authors declared no competing interests for this work. E.C. and F.M. were hired by Sanofi as experts for this project.

