#II-48

A framework for prediction of progression-free survival based on modelling of sub-endpoints

Sreenath M. Krishnan,[1] Lena E. Friberg,[1,2] Joakim Nyberg,[1] Céline Sarr,[1]*
Ronald Niebecker,[3] Shaonan Wang,[3] Alejandro Perez Pitarch[3]

[1]Pharmetheus AB, Uppsala, Sweden; [2]Department of Pharmacy, Uppsala University, Uppsala, Sweden; [3]Boehringer Ingelheim Pharma GmbH & Co.KG, Biberach, Germany

*Corresponding author email address: celine.sarr.ext@boehringer-ingelheim.com

Introduction

- The assessment of PFS in solid tumours is based on RECIST, which evaluates certain sub-endpoints:
  - Change in the sum of longest diameter of target lesions **(SLD)**
  - Appearance of new lesion **(NL)**
  - Progression of non-target lesion **(NTR)**
- TTE models have been used to describe PFS. However, TTE models may not be discriminant, especially in small trials
- An alternative method that jointly models PFS as target lesion progression and non-target progression has been proposed by Yu *et al*.[1] Using this methodology, target lesion progression is derived from tumour growth dynamics, and risk of non-target progression is correlated to target lesion tumour size with respect to time. This approach has the potential to predict PFS based on data collected in the early stages of drug development[1]

Objectives

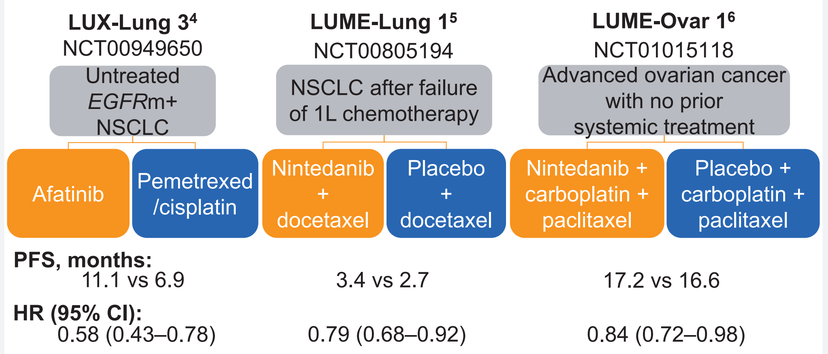
- The aim of the current study was to develop a modelling and simulation framework, based on sub-endpoints, that predicts long-term typical clinical readouts such as PFS, ORR, DOR and BOR

BOR, best overall response; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TTE, time-to-event

Methods

- Data from Phase III trials were used to develop the modelling framework (Figure 1; Table 1)
- For longitudinal SLD data, two TGI models were considered; one assumed acquired resistance[2] and the other assumed the presence of resistant and sensitive populations at treatment initiation[3]
- Binary NTR and NL data collected at each tumour scan were modelled using a logistic regression model estimating the probability of an event at the time of the scan
- In case of estimation issues with logistic regression models, a TTE model was considered for modelling NTR and NL

Figure 1. Overview of the three Phase III trials used in the population model



1L, first-line; CI, confidence interval; *EGFR*m+; epidermal growth factor receptor mutation-positive; HR, hazard ratio; NSCLC, non-small cell lung cancer; TGI, tumour growth inhibition

Methods (cont'd)

- Death prior to progression and dropout from study due to other reasons than progression could happen at any time; hence, a TTE model was used
- In the joint modelling framework, the clinical endpoints including PFS were simulated based on the events in the sub-endpoints' models
- The model evaluations of sub-endpoints as well as the joint model were based on VPCs. NONMEM® 7.4 software was used for model development[7]

Table 1. Data for population model (N=2049 patients)

	LUX-Lung 3		LUME-Lung 1		LUME-Ovar 1	
	Afatinib (n=225)	Chemo (n=107)	Nintedanib + docetaxel (n=607)	Placebo + docetaxel (n=605)	Nintedanib + chemo (n=332)	Placebo + chemo (n=173)
Median age, years (range)	61 (28–86)	62 (31–83)	60 (29–84)	60 (30–80)	59 (23–84)	59 (25–79)
Median SLD, mm (range)	55 (10–760)	52 (10–234)	85 (10–410)	84 (10–394)	49 (10–330)	48 (10–457)
Observed NTR*, n (median TTE, wks)	58 (35)	25 (17)	144 (13)	175 (13)	181 (48)	72 (46)
Observed NL*, n (median TTE, wks)	111 (38)	44 (23)	334 (12)	356 (12)	556 (61)	288 (60)
Deaths before progression, n (median TTE, wks)	8 (13)	2 (8)	87 (10)	62 (10)	19 (15)	8 (12)
Dropouts before progression, n (median TTE, wks)	30 (146)	20 (23)	82 (12)	67 (12)	254 (120)	115 (120)

*Data incomplete for LUME-Ovar 1.
Chemo, chemotherapy; NONMEM, nonlinear mixed effects modelling; VPCs, visual predictive checks; wks, weeks

Key findings and conclusions

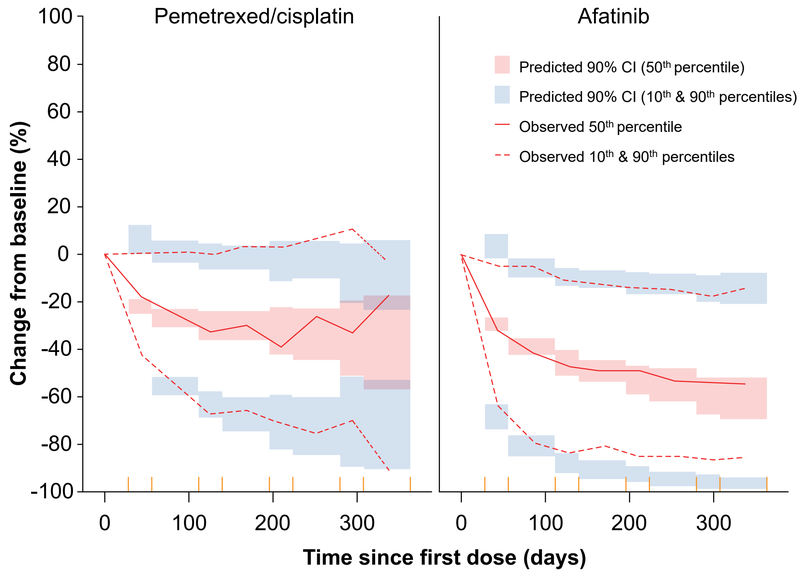
- **Population models for individual metrics were developed that jointly described PFS**
- **Despite the diversity of responses observed in the Phase III trials, the model framework could also predict other long-term clinical readouts, such as ORR, DOR and BOR**

- **The model framework may be used for predicting PFS before PFS data are mature**
- **This approach may therefore provide support for early decision making in indications for which PFS is an important clinical endpoint**

Results

- Models for individual metrics are shown in the supplementary content
- VPCs based on 200 simulations showed acceptable predictive performance of the tumour size model (Figure 2)

Figure 2. VPC of SLD of target lesions in LUX-Lung 3

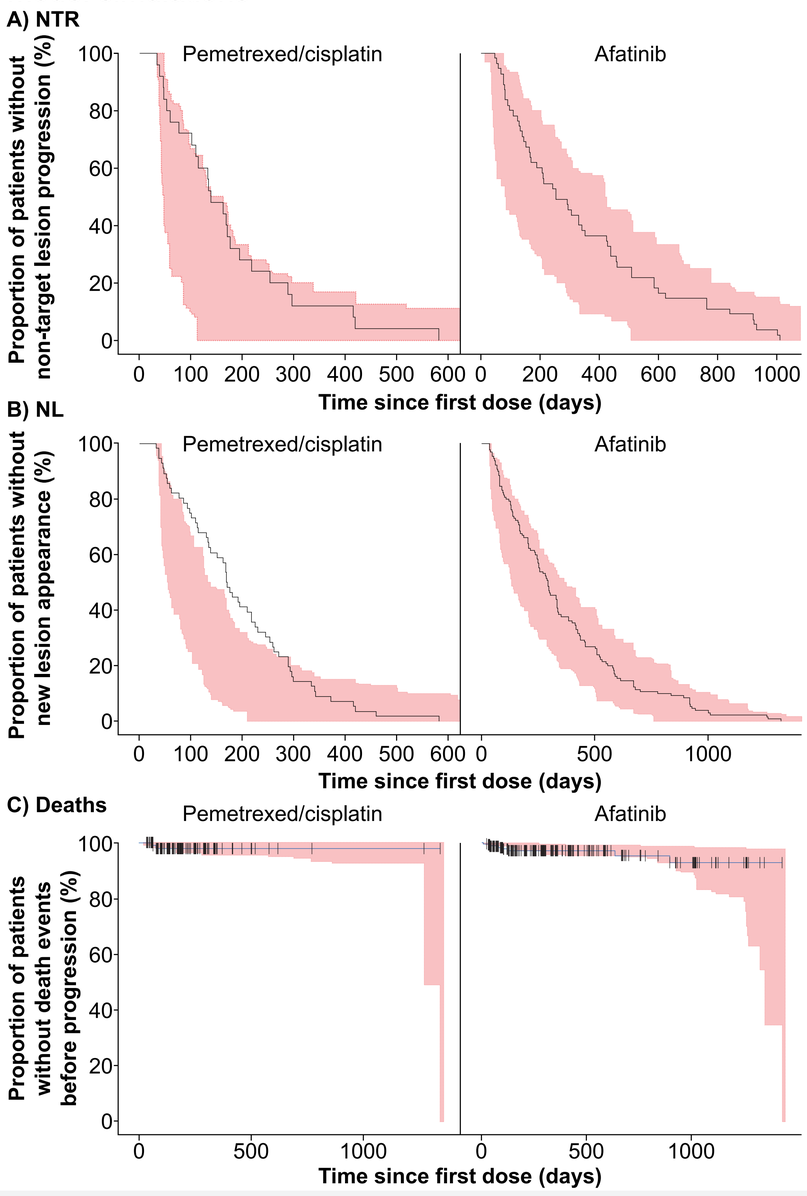


- K–M VPCs showed acceptable predictive performance of the logistic regression models for NTR, NL and for death events (Figure 3)
- K–M VPCs showed acceptable predictive performance with regard to PFS across studies (Figure 4)
- The model framework could also predict long-term clinical readouts other than PFS, such as ORR, DOR and BOR, despite the diversity of response observed in the three Phase III trials (see supplementary content)

K–M, Kaplan–Meier

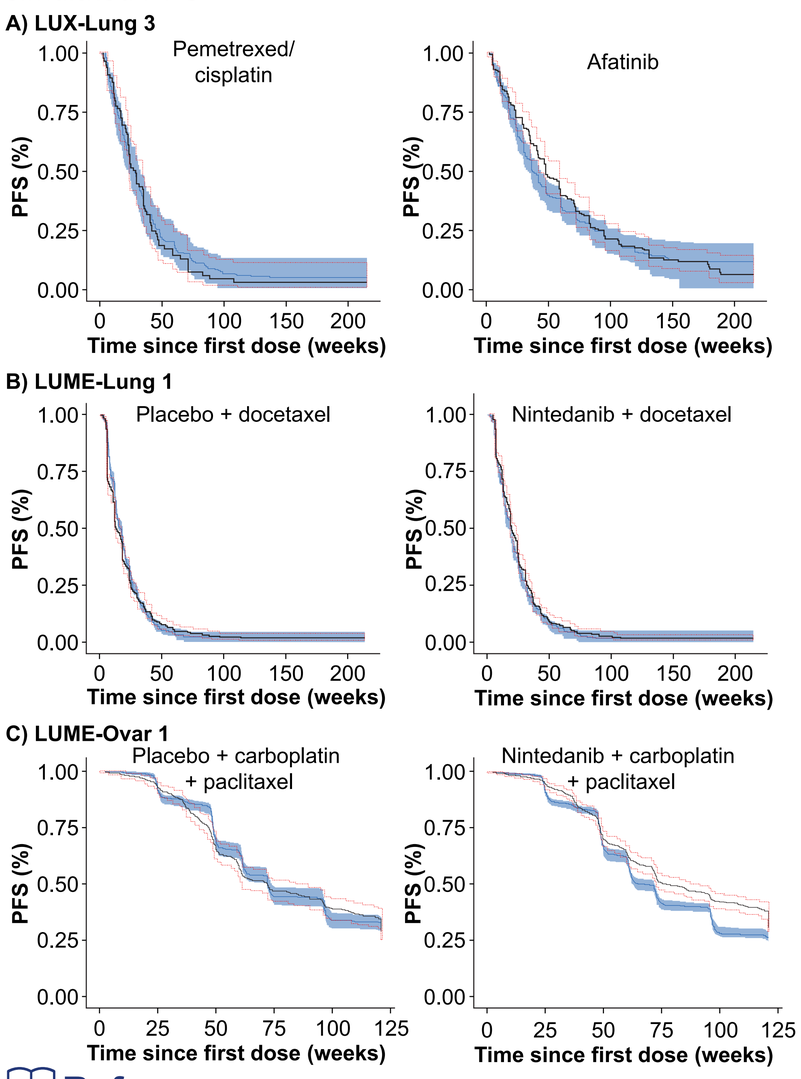
Results (cont'd)

Figure 3. K–M VPCs of death events in LUX-Lung 3
Solid line: observed data. Shaded area: 95% CI from 200 model simulations



Results (cont'd)

Figure 4. PFS simulations based on individual metrics
Observed PFS (solid line) vs 95% CI (shaded area) of the simulated PFS



References

1. Yu J, et al. CPT Pharm Syst Pharmacol 2020;9:177–84; 2. Claret L, et al. J Clin Oncol 2009;27:4103–8; 3. Stein WD, et al. Oncologist 2008;13:1046–54; 4. Sequist LV, et al. J Clin Oncol 2013;31:3327–34; 5. Reck M, et al. Lancet Oncol 2014;5:143–55; 6. du Bois A, et al. Lancet Oncol 2016;17:78–89; 7. NONMEM Users Guides, (1989-2018). Icon Development Solutions, Ellicott City, MD, USA

Presented at the Population Approach Group in Europe (PAGE) Meeting, Ljubljana, Slovenia, 28 June–1 July 2022

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Jim Sinclair, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim