

Exposure-response analysis of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma

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Rationale

Erdafitinib (Balversa [®]) is a selective pan–fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, approved to treat adult patients with locally advanced or metastatic urothelial carcinoma (mUC) with susceptible FGFR3 genetic alterations. Erdafitinib exposure-response (ER) analyses conducted based on Phase 2 study¹⁾ illustrated how serum phosphate (PO₄) was a better biomarker to describe efficacy and safety than erdafitinib PK-based exposure.

Objective

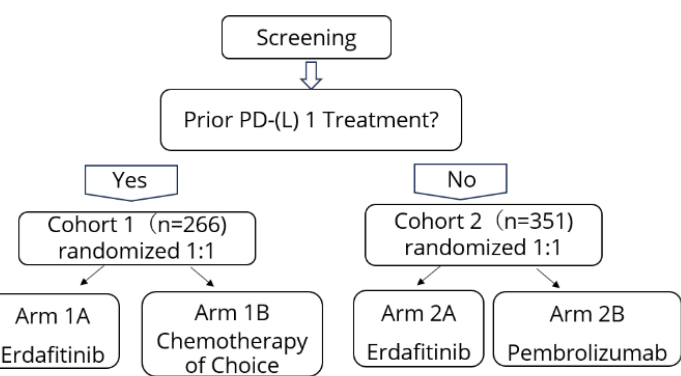
Exposure–response analyses were conducted to

- Confirm the relationship between selected efficacy and safety endpoints and serum PO₄ level.
- Confirm if the proposed erdafitinib dose (starting with 8 mg/day and PO₄-based titration) applied in Phase 3 study (BLC3001) was adequate in terms of efficacy and safety, in locally advanced or metastatic urothelial carcinoma patients with select FGFR alterations treated with erdafitinib.

Data

BLC3001 Study design

Subjects were assigned to Cohort 1 based upon prior treatment with an anti-PD-(L)1 agent and were randomized in a 1:1 ratio to erdafitinib versus chemotherapy. In Cohort 2, subjects who had not received prior treatment with an anti-PD-(L)1 agent were randomized in a 1:1 ratio to erdafitinib versus pembrolizumab, Primary endpoint: overall survival (OS); Key secondary endpoints : progression-free survival (PFS) , objective response rate (ORR).



Data for ER analysis

- Data from BLC3001-Cohort 1 (266 patients; 136 patients receiving erdafitinib and 130 receiving chemotherapy) was used for the exposure-efficacy analysis,
- Data from 3 studies including BLC3001 (814 patients) were used to analyze the exposure-safety analysis.

Methods

Exposure-efficacy/safety analysis

OS and PFS

- A Kaplan-Meier analysis with patients stratified into 4 groups by serum PO₄ concentrations (one group with chemotherapy with baseline PO₄ and three groups with erdafitinib treated subjects stratified by average PO₄ concentrations terciles).
- Univariate and multivariate Cox regression analysis models were conducted to assess the relationship between serum PO₄ and OS, PFS.

ORR

- Univariate and multivariate logistic regression models were applied to assess the relationship between serum PO₄ and ORR.

Safety

- Univariate logistic regression models were applied to assess the relationship between serum PO₄ and the selected safety endpoints.

Results

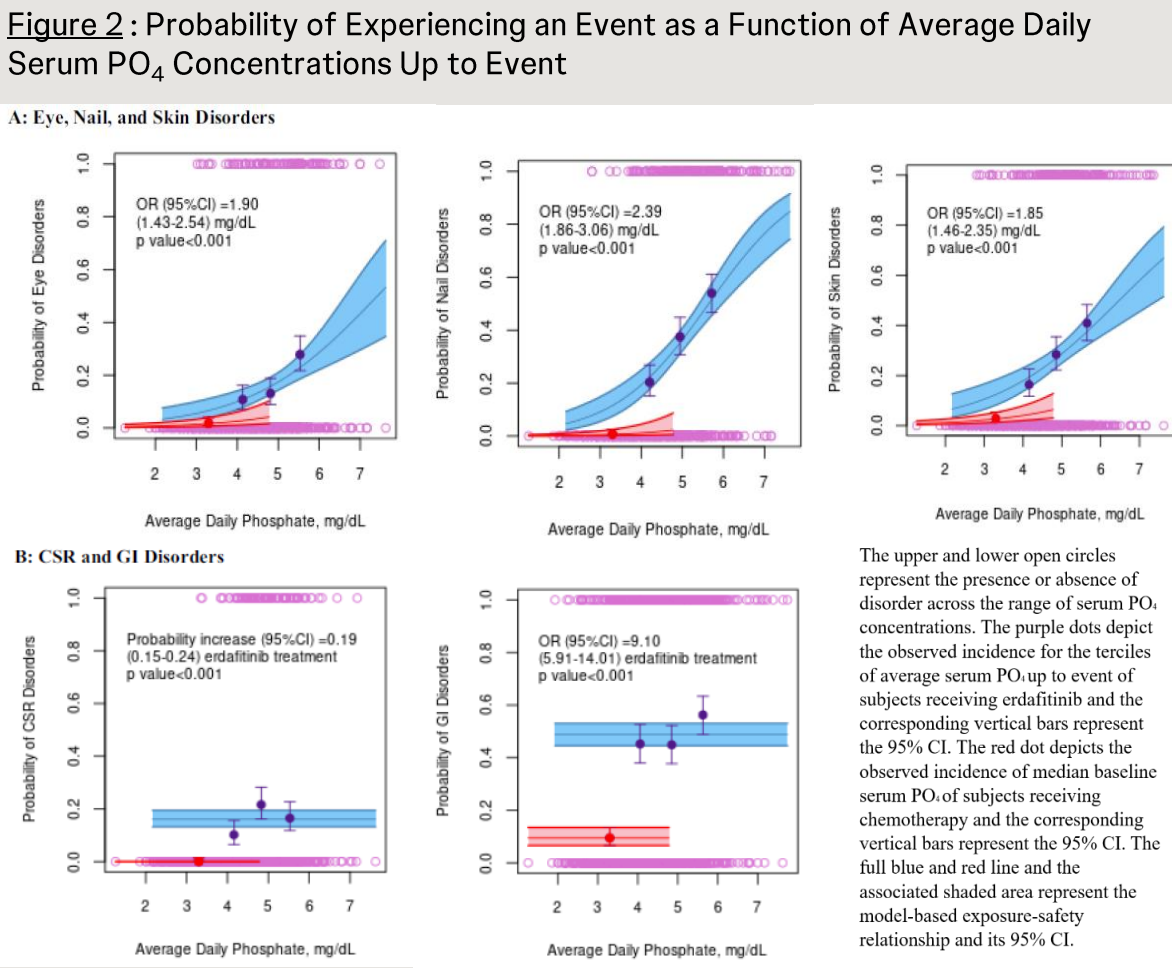
Exposure-efficacy

The Kaplan-Meier and multivariate Cox regression analysis showed that patients with higher average serum PO₄ levels showed better **OS** than subjects with lower average serum PO₄ with correlation between OS and time dependent serum PO₄ (Figure 1, Table 2). Consistent with the relationship with OS, subjects with higher average serum PO₄ over time showed slower disease progression (ie, have longer **PFS**) than subjects with lower average serum PO₄. In addition, an increase in average serum PO₄ concentrations up to 6 weeks was correlated with significantly increase **ORR** as assessed by the investigator.

Table 2: Final PO₄-Efficacy Cox/logistic Regression Models for OS, PFS and ORR

Endpoint	Biomarker/Prognostic	HR/OR ^a (95% CI)	p-value ^b
OS	PO ₄ -Time Dependent (per 1 mg/dL increase)	0.53 (0.44, 0.65)	<0.001
	ECOG>1 (vs 0-1)	1.84 (1.09, 3.11)	0.023
	Hemoglobin ≥ 10 g/dL vs <10 g/dL	0.53 (0.35, 0.78)	0.001
	Race: white (vs non-white)	1.58 (1.14, 2.20)	0.007
PFS	PO ₄ -Time Dependent (per 1 mg/dL increase)	0.69 (0.60, 0.79)	<0.001
ORR	Intercept	0.03 (0.01, 0.09)	<0.001
	PO ₄ -avg6weeks (per 1 mg/dL increase)	1.84 (1.43, 2.37)	<0.001

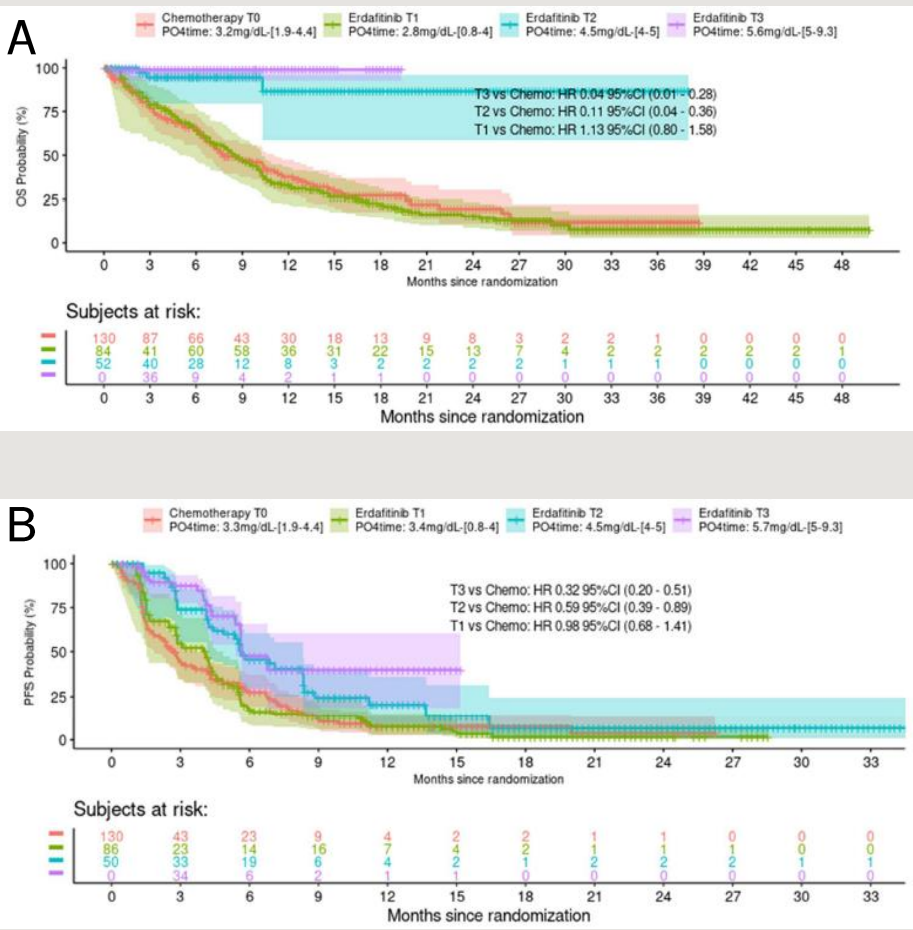
ECOG: Eastern Cooperative Oncology group; HR=hazard ratio; OR=odds ratio; CI=confidence interval
^aHR for OS and PFS, OR for ORR, ^bp-values are rounded to 3 decimals and have 0.001 as lower bound



Key Takeways

The relationship between serum PO₄ levels and efficacy/safety outcomes supported the appropriateness of serum PO₄ concentration as a relevant pharmacodynamic biomarker for dose titration of erdafitinib. The totality of the efficacy data, safety data, and ER analyses showed that the recommended dose regimen with pharmacodynamically-guided uptitration as implemented in BLC3001 showed an overall favorable benefit-risk in patient with mUC.

Figure 1: Time-dependent Kaplan-Meier Plot of OS (A) and PFS (B) of Study BLC3001 Cohort1 as a Function of Erdafitinib Terciles of time dependent PO₄



Exposure-safety

The incidence of Grade ≥2 eye, nail, and skin disorders had a positive and statistically significant relationship with the average serum PO₄ up to the day of event. The magnitude of the association varied across the different disorders and was strongest for nail disorders (OR >2, for an increase of 1 mg/dL of average serum PO₄ up to the day of event). The incidence of Grade ≥1 Central serous retinopathy (CSR) and Grade ≥2 GI Disorders had no association with average serum PO₄ concentration or average erdafitinib concentration up to the day of the event, despite these events being known class effects of FGFR inhibitors (Figure 2).

Erdafitinib was discovered in collaboration with Astex Pharmaceuticals. The authors would like to thank all of the patients and their families who participated in the BLC3001 study, to all medical personnel and institutions that cooperated in the study

Acknowledgments

1. Dosne AG, et al. Exposure-response analyses of erdafitinib in patients with locally advanced or metastatic urothelial carcinoma. Cancer Chemo ther Pharmacol. 2022;89(2):151-64.