

Exposure-response analysis of erdafitinib and pharmacodynamic-guided dose individualization in patients with locally advanced or metastatic urothelial carcinoma

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INTRODUCTION

- Erdafitinib is an oral, pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor recently approved in the US for the treatment of locally advanced or metastatic urothelial carcinoma (mUC) with specific *FGFR 3* or *2* alterations and who progressed after ≥1 lines of platinum-based chemotherapy.
- Serum phosphate (PO4) is a pharmacodynamic (PD) marker of FGFR engagement and proposed to be a biomarker for efficacy and safety.
- Thus, erdafitinib dosing is adapted for each individual based on their PO4 concentrations.

OBJECTIVE

- To characterize the exposure-response (ER) relationship between PO4 and selected efficacy and safety endpoints based on data from study BLC2001 (NCT02365597), to further support PO4 as a biomarker for erdafitinib dose individualization.

METHODS

Study design and patients

- BLC2001 is a multiple-dose, open-label, Phase 2, two-arm multicenter study to determine the efficacy and the safety of different dose regimens of erdafitinib in adults with metastatic or unresectable urothelial cancers with *FGFR* mutations or gene fusion alterations.
- The ER analysis was performed using data from patients randomized to one of two dosing regimens:
 - 6 mg group (6 mg erdafitinib daily with PD-guided up-titration to 8 mg daily, based on PO4 at Day 28);
 - 8 mg group (8 mg erdafitinib up-titrated to 9 mg based on PO4 at Day 14).
- Dose interruptions and/or reductions were mandated based on serum PO4 and selected AEs.

Exposure metrics

- Individual average PO4 values were derived based on post hoc pharmacokinetic (PK) and PK-PD parameter estimates, which were used as the exposure metrics for ER analysis.
- Average PO4 values up to the first response assessment (planned at 6 weeks) were used in the exposure-efficacy analysis, and average PO4 values up to the first highest grade AE were used in the exposure-safety analysis.
- Average PO4 values up to 2 weeks (before any dose changes) were also investigated in both analyses.
- A longitudinal analysis using weekly PO4 was also performed for PFS.

Efficacy endpoints

- Objective response rate (ORR; complete [CR] and partial [PR] response) based on best response:
 - Assessment of responses for solid tumors was performed according to Response Evaluation Criteria In Solid Tumors (RECIST) (version 1.1)³;
 - Subjects had response assessments performed by radiographic image assessments (computed tomography or magnetic resonance imaging).
- Disease control rate (DCR; CR, PR, or stable disease), based on best response
- Progression-free survival (PFS):
 - For subjects experiencing progression or death: PFS was defined as duration from the date of the first dose of study drug until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever came first;
 - For subjects not experiencing progression or death or with unknown status: PFS was censored at the last tumor assessment available in absence of progression or death.

Safety endpoints

- The key safety endpoints included in the exposure-safety analyses were selected based on their clinical relevance, occurrence (>10%), or presence of high degree of severity (Grade ≥3).
- The safety endpoints included in the analysis were: incidence of eye disorders, central serous retinopathy (CSR), nail disorders, palmar-plantar erythrodysaesthesia (PPES) and skin disorders.

Statistical analyses

- ER relationship between average PO4 and ORR or adverse events was evaluated using logistic regression models, and between PO4 and PFS using Cox proportional-hazards models.
- For the efficacy endpoints, the impact of selected baseline potential prognostic factors (hemoglobin, Eastern Cooperative Oncology Group [ECOG] status, presence of visceral metastases) and type of FGFR alteration were also investigated using multivariate analyses.
- Model selection was based on Akaike's Information Criterion (AIC), and magnitude and statistical significance of the drug effect.
- All analyses were carried out using the R Project for Statistical Computing, version 3.4.1 or higher [2], except for the derivation of post hoc PK-PD parameter estimates which was performed in NONMEM 7.3.

RESULTS

Patients

- For the efficacy ER analysis, data from 156 patients (n=68 and n=88 in the 6 mg and 8 mg groups, respectively) with chemotherapy-relapsed/refractory mUC were available.
 - 79.5% of the subjects had visceral metastases, 77.6% had hemoglobin levels >10 g/L, 7.7% had ECOG > 1 and 80.8% had *FGFR* mutations and 19.2% had gene fusions.
- Safety ER analysis included data from 177 patients (n=78 and n=99 in the 6 mg and 8 mg group, respectively).

Efficacy

Overall response rate

- The ORR was 40.3% (n=63/156), with responses generally achieved by 2 months.
- Differences in ORR between the terciles of average daily phosphate up to 6 weeks were borderline statistically significant. (**Table 1**)
- Higher average daily PO4 up to 6 weeks (ie > 4.8 mg/dL) was associated with higher ORR (odds ratio [OR]: 1.38; 95% CI: 1.02, 1.86; Model D, *P*=0.04); average daily PO4 up to Day 14 was not significantly associated with ORR.
- The type of *FGFR* alterations was included as a significant covariate. (**Table 2, Figure 1**)

Table 1. Efficacy measures according to terciles for average daily PO4 up to 6 weeks

Tercile Range (n)	ORR		DCR		PFS	
	n (%)	<i>P</i> -value	n (%)	<i>P</i> -value	Median PFS (95% CI), months	<i>P</i> -value
2.4-4.8 (49)	13 (26.5%)	0.050	29 (59.2%)	<0.001	4.3 (1.5-5.4)	0.044
4.8-5.6 (53)	26 (49.1%)		45 (84.9%)		5.4 (4.0-5.7)	
5.6-10.4 (54)	24 (44.4%)		51 (94.4%)		5.6 (5.5-8.3)	

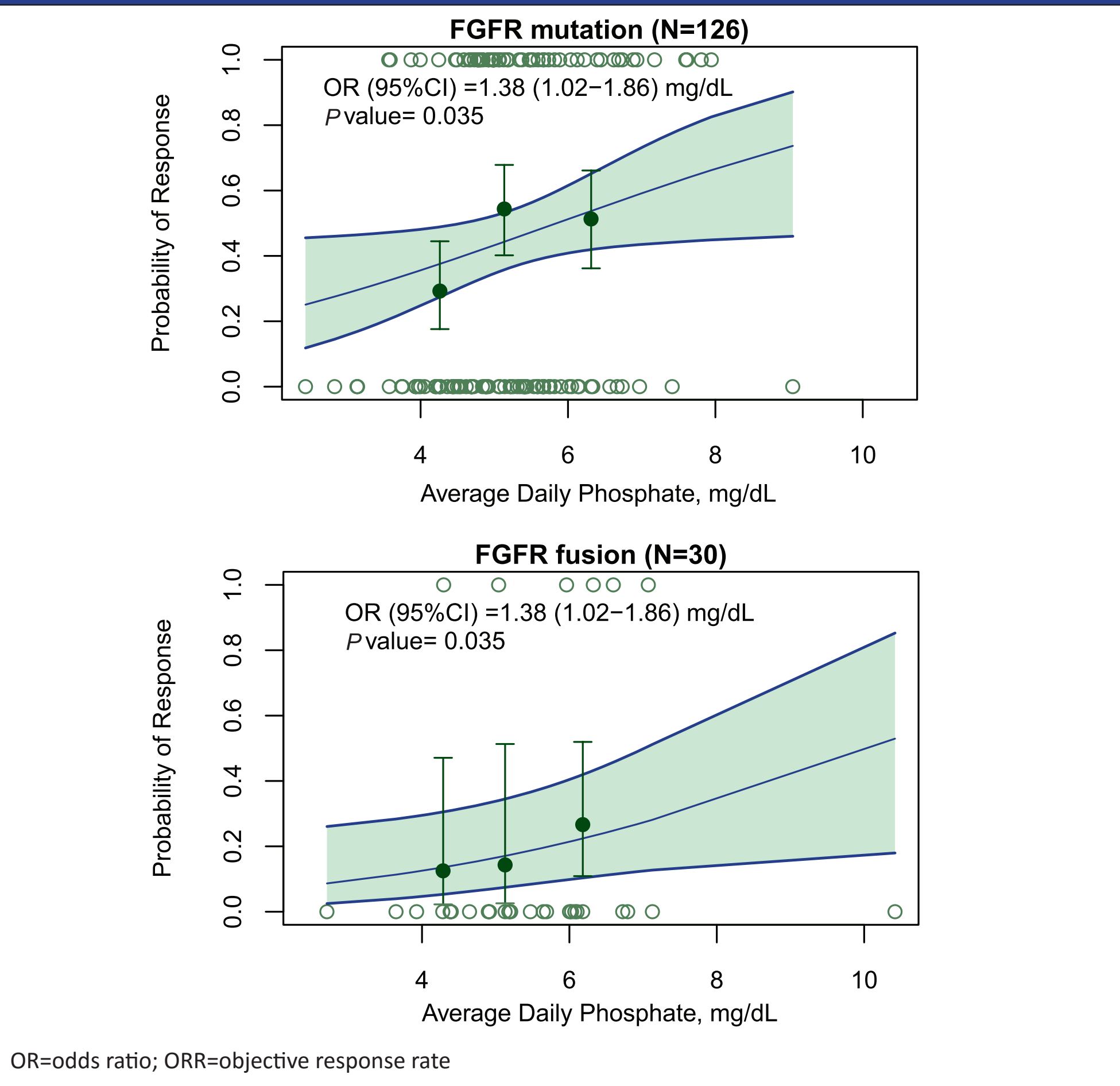
ORR=objective response rate; DCR=disease control rate; PFS=progression-free survival. For ORR and DCR, *P*-values correspond to a Pearson's chi-squared test for difference in proportions. For PFS, the *P*-value corresponds to a log-rank test.

Table 2. Results of the univariate and multivariate logistic regression analyses for ORR based on investigator's response in patients with chemotherapy relapse-refractory mUC (n=156)

Model	-2LL	AIC	OR (95%CI)	<i>P</i> -value
Model A PO4 up to Day 14 (mg/dL)	209.7	213.7	1.15 (0.84-1.58)	0.39
Model B PO4 up to ≈6 weeks (mg/dL)	207.3	211.3	1.29 (0.97-1.72)	0.08
Model C PO4 up to ≈6 weeks (mg/dL) Hemoglobin (≤ 10 vs >10 g/L) ECOG (> 1 vs ≤ 1) Visceral metastases (yes vs no) <i>FGFR</i> alteration (fusion vs mutation)	195.5	207.5	1.31 (0.96-1.78) 0.84 (0.37-1.92) 0.47 (0.12-1.89) 0.58 (0.25-1.35) 0.24 (0.09-0.67)	0.09 0.68 0.29 0.21 0.01
Model D (final model) PO4 up to ≈6 weeks (mg/dL) <i>FGFR</i> alteration (fusion vs mutation)	198.9	204.9	1.38 (1.02-1.86) 0.26 (0.10-0.70)	0.04 0.01

AIC= Akaike's Information Criterion; ECOG= Eastern Cooperative Oncology Group; *FGFR*=fibroblast growth factor receptor gene; -2 LL=-2 log-likelihood; OR=odds ratio.

Figure 1. Probability of ORR stratified by FGFR genetic alteration (Model D)



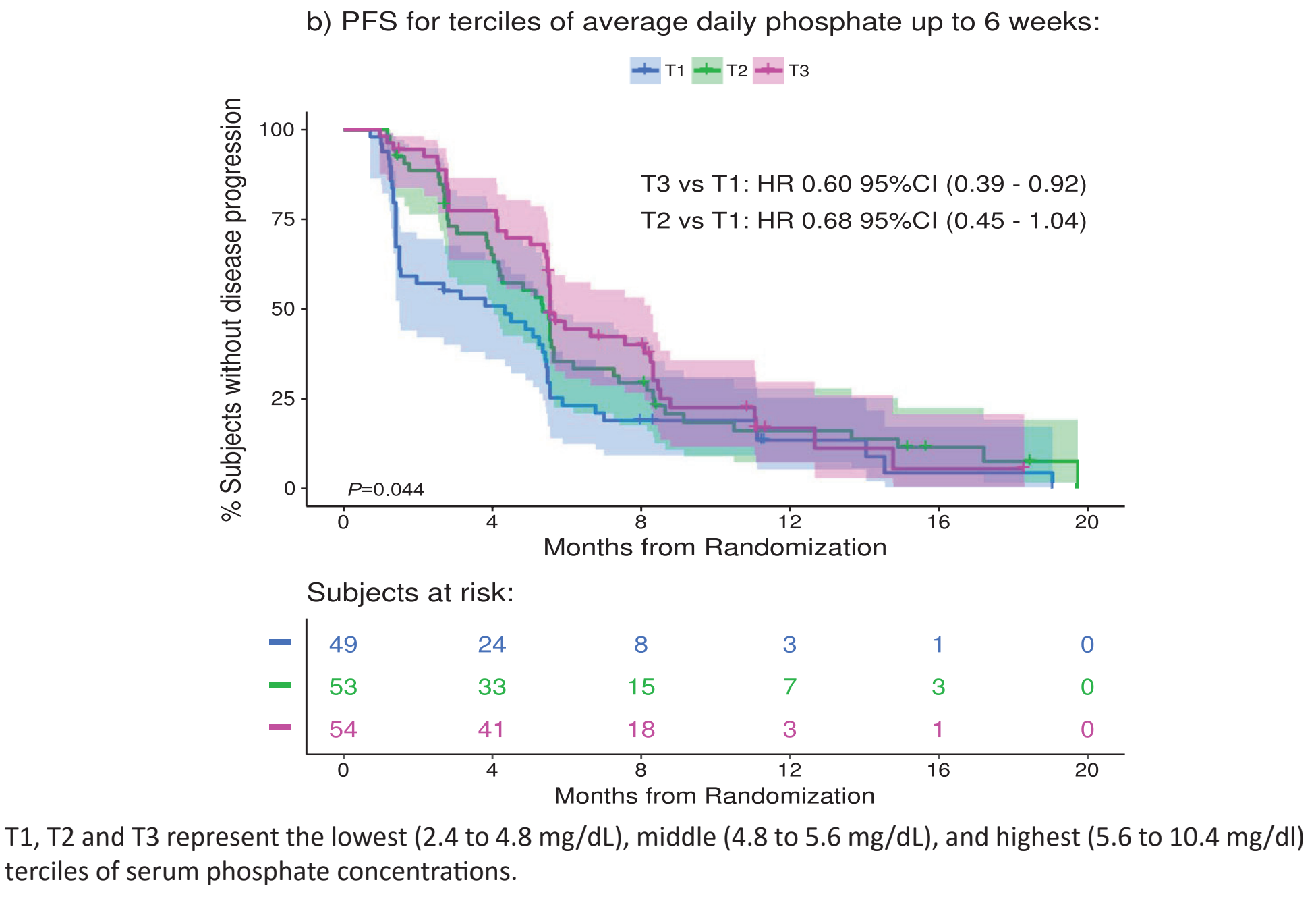
Disease Control Rate

- DCR for investigator's response was 80.1% (n=125/156)
- Higher serum PO4 concentrations, when PO4 concentrations were categorized by terciles, were significantly associated with greater DCR (*P*<0.001; Table 1.)

Progression-free survival

- Median PFS by investigator assessment was 5.5 months (95% CI: 4.8, 5.6). Median PFS significantly increased with increasing terciles of average daily phosphate up to 6 weeks. (**Table 1, Figure 2**) Cox regression analysis showed that a 1 mg/dL increase in serum phosphate significantly decreased the risk of disease progression or death by 20% (hazard ratio [HR]: 0.80; 95% CI: 0.67, 0.94). (**Table 3**) Average daily PO4 up to Day 14 was not significant.
- Including PO4 as time-dependent covariate entails similar HR estimate but poorer fit to the data, showing that average PO4 up to 6 weeks is a better predictor of PFS compared to current PO4.
- This finding suggests that earlier increases in PO4 levels are critical to achieve efficacy, justifying the early up-titration. It also hypothesizes that the observed decreasing PO4 levels over time do not compromise efficacy.

Figure 2. Kaplan-Meier Plot for PFS as a function of serum PO4 terciles



T1, T2 and T3 represent the lowest (2.4 to 4.8 mg/dL), middle (4.8 to 5.6 mg/dL), and highest (5.6 to 10.4 mg/dl) terciles of serum phosphate concentrations.

Table 3. Results of the Univariate and Multivariate Cox Regression Analyses for Investigator's PFS

Model	-2LL	AIC	HR (95%CI)	<i>P</i> -value
Model A PO4 up to Day 14 (mg/dL)	1108.3	1110.3	0.89 (0.79-1.07)	0.20
Model B (final model) PO4 up to ≈6 weeks (mg/dL)	1103.2	1105.2	0.8 (0.67-0.94)	0.01
Model C PO4 up to ≈6 weeks (mg/dL) Hemoglobin (≤ 10 vs >10 g/L) ECOG (> 1 vs ≤ 1) Visceral metastases (yes vs no) <i>FGFR</i> alteration (fusion vs mutation)	1099.3	1109.3	0.84 (0.70-1.01) 0.92 (0.60-1.42) 1.56 (0.81-3.01) 1.36 (0.86-2.15) 1.11 (0.71-1.73)	0.06 0.71 0.18 0.19 0.65
Model E Time-dependent phosphate (mg/dL)*	1107.5	1109.5	0.85 (0.70; 1.03)	0.10

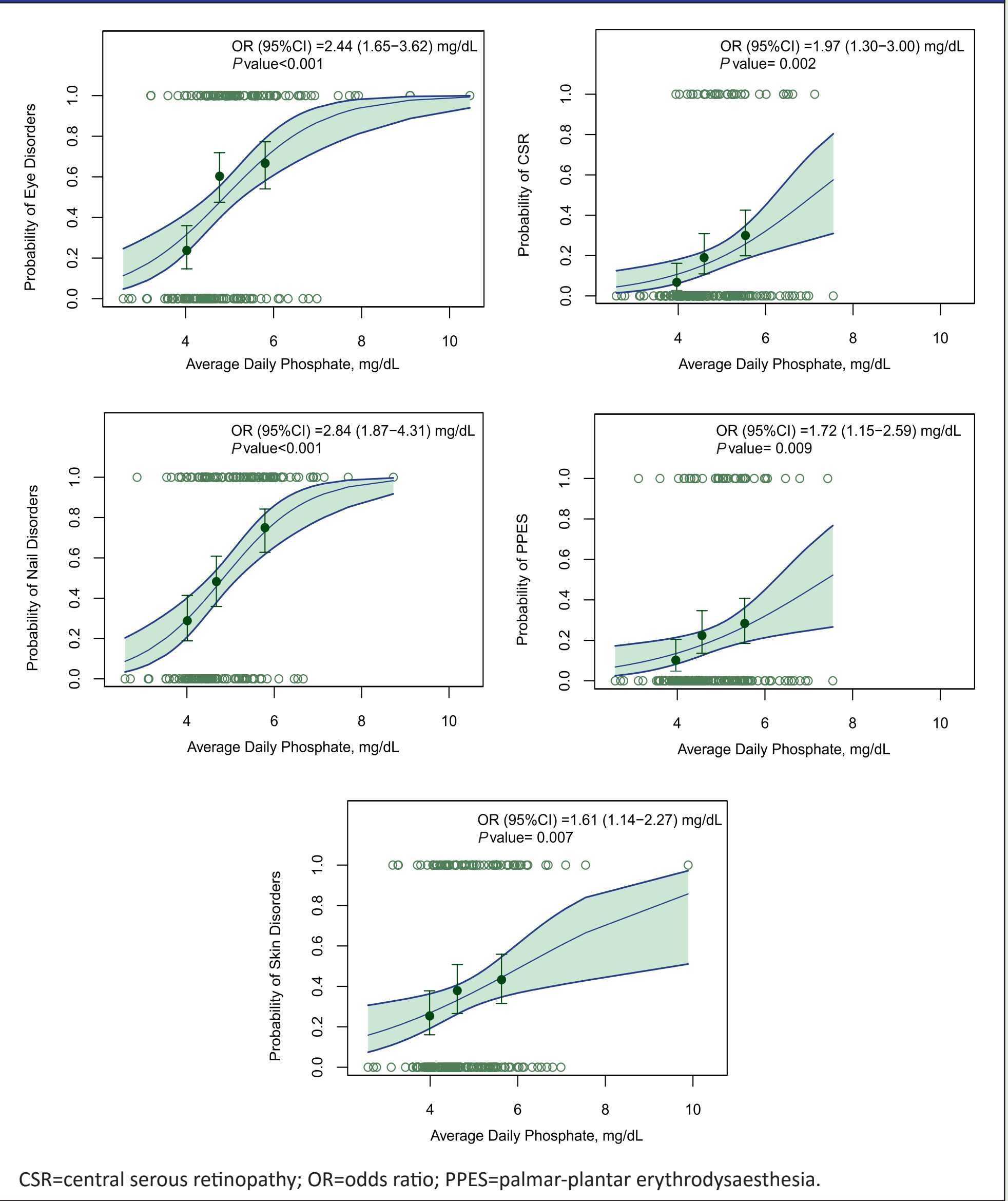
AIC= Akaike's Information Criterion; ECOG= Eastern Cooperative Oncology Group; *FGFR*=fibroblast growth factor receptor gene; -2 LL=-2 log-likelihood; OR=odds ratio

*Time-dependent phosphate approximated by weekly phosphate for each patient estimated based on the PK/PD model; Model E assumes a direct effect of current phosphate on PFS hazard.

Safety

- Incidence of eye disorders, CSR, nail disorders, PPES, and skin disorders of any severity, was positively and statistically significantly associated with average daily serum PO4 concentrations up to the day the disorder appeared (range, 2.6 to 10.5 mg/dL). (**Figure 3**) Average daily PO4 up to Day 14 was not significantly associated with the incidence of four of these AEs (all but eye and nail disorders).
- Magnitude of the association between PO4 concentrations and specific disorders varied:
 - Association with nail and eye disorders being the strongest (OR>2 for a 1 mg/dL increase in daily serum PO4 concentrations up to the day of event).
- Safety analyses using free AUC were also investigated:
 - No model improvement was seen when including AUCfree_{0,24} instead of serum phosphate concentration up to the time of event.

Figure 3. Probability of experiencing eye, CSR, nail, PPES or skin disorders in mUC patients treated with erdafitinib



CONCLUSIONS

- Average daily serum PO4 concentrations from the start of erdafitinib up to the first response assessment (planned at 6 weeks) were associated with significantly better ORR, DCR and PFS in patients with chemotherapy-relapsed/refractory mUC
- Incidence of eye disorders, CSR, nail disorders, PPES, and skin disorders, at any grade, had a positive and statistically significant relationship with average daily serum PO4 up to the day of AE occurrence
- The relationship between PO4 and efficacy/safety as characterized in the ER analysis further supports the erdafitinib dose individualization (up-titration, dose interruptions and reductions) to maximize the benefit/risk ratio of erdafitinib treatment

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DISCLOSURES

All authors were employees of Janssen R&D at the time the work was done.