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Predictive value of KL-6 and SP-D in patients with *EGFR* exon 20 insertion–positive metastatic NSCLC receiving mobocertinib therapy

Paul Hofman,[1] Matthias Scheffler,[2] Zhenqiang Su,[3] Xin Tong,[3] Veronica Bunn,[3] Sampurna Chatterjee,[3] Shu Jin,[3] Sylvie Vincent[3]

[1]University Côte d'Azur, Nice, France; [2]University Hospital of Cologne, Cologne, Germany; [3]Takeda Development Center Americas, Inc., Lexington, MA, USA

Introduction

- Epidermal growth factor receptor gene (*EGFR*) exon 20 insertion (ex20ins) mutations account for up to 12% of *EGFR*-mutated non–small cell lung cancer (NSCLC) tumors[1]
- Mobocertinib, a first-in-class oral tyrosine kinase inhibitor (TKI) designed to target *EGFR* ex20ins mutations,[2,3] is approved in multiple countries for *EGFR* ex20ins–positive patients with advanced or metastatic NSCLC (mNSCLC) who have received prior platinum chemotherapy[4-7]
- Mobocertinib treatment resulted in a 28% confirmed objective response rate per independent review committee (IRC), median duration of response of 17.5 months per IRC, and median progression-free survival of 7.3 months in platinum-pretreated patients with mNSCLC (N=114; November 1, 2020 data cutoff)[3]
- Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D) are biomarkers of inflammation in lung tissue and have been shown to predict lung injury with anticancer therapies[8-11]
  - Elevated levels of KL-6 are observed in lung cancer patients with and without interstitial lung disease[12]
  - Lower expression of SP-D has been observed in lung cancer cells compared with normal tissue and has been associated with progression of bronchial dysplasia in patients who smoke[13,14]

Objectives

- To characterize the association of circulating KL-6 and SP-D with treatment emergent pulmonary AEs (ie, pneumonitis or interstitial lung disease [ILD])
- To characterize the association of circulating KL-6 and SP-D with clinical response to mobocertinib

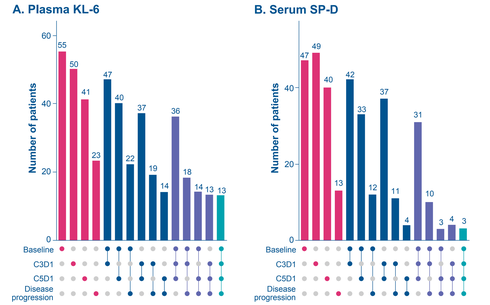
Methods

- Plasma and serum samples were collected at baseline, after 2 cycles (Cycle 3, Day 1 [C3D1]), after 4 cycles (Cycle 5, Day 1 [C5D1]), and at disease progression from previously treated patients with *EGFR* ex20ins–positive mNSCLC who received once-daily mobocertinib 160 mg orally (28-day cycles) in a phase 1/2 study (NCT02716116)
  - KL-6 concentrations were measured in K2 EDTA plasma using the Nanopia® KL-6 assay (Sekisui Medical Co, Ltd.)
  - SP-D concentrations were measured in serum using the Quantkine™ human SP-D ELISA kit (R&D Systems, Inc.)
- Clinical response was evaluated according to RECIST criteria and was confirmed by IRC (data cutoff: November 1, 2020)
- Ratios of KL-6 concentrations at C3D1 and C5D1 to KL-6 concentrations at baseline were evaluated by best change in tumor target lesions at these time points
  - Statistical correlations of biomarker levels at baseline with pulmonary AEs were performed using the Wilcoxon signed-rank test
  - Statistical correlations of biomarker levels at baseline with IRC-confirmed best objective response were performed using the Kruskal-Wallis H test

Results

- The numbers of patients assessed for KL-6 and SP-D at each time point are shown in **Figure 1**

Figure 1. Number of patients with plasma KL-6 and serum SP-D assessments at each timepoint



Data cutoff date: November 1, 2020
Circles with connecting lines indicate patients with samples at 2 or more of the specified time points.
The population shown in purple is a subset of the population shown in blue.

- Pulmonary AEs of pneumonitis or ILD were observed in 5 of the 92 patients assessed for KL-6 expression and in only 1 of the 74 patients assessed for SP-D **(Table 1)**
- The numbers of patients with baseline KL-6 and SP-D assessments by response categories are shown in **Table 1**

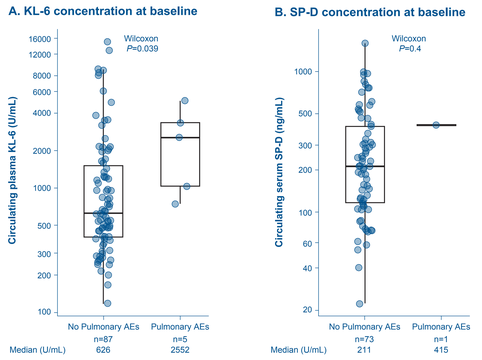
Table 1. Pulmonary AEs and response in patients with baseline KL-6 and SP-D assessments

Biomarker	Pulmonary AE	n (%)	Confirmed Objective Response (IRC)	n (%)
KL-6 (n=92)[a]	None	87 (95)	PR	18 (33)
			SD	28 (51)
	Pneumonitis/ILD	5 (5)	PD	9 (16)
SP-D (n=74)[a]	None	73 (99)	PR	16 (34)
			SD	22 (47)
	Pneumonitis/ILD	1 (1)	PD	9 (19)

Data cutoff date: November 1, 2020
[a]Patients with baseline KL-6 (n=92) and SP-D (n=74) included 90 patients who received mobocertinib 160 mg/day, 1 patient who received mobocertinib 120 mg/day, and 2 patients who did not receive mobocertinib.

- Baseline KL-6 levels were higher in patients with pneumonitis, but the distribution of values overlapped with those in patients without any pulmonary AEs **(Figure 2A)**
- Baseline SP-D values were widely distributed in patients without pulmonary AEs; only 1 patient with pneumonitis had a baseline SP-D value **(Figure 2B)**

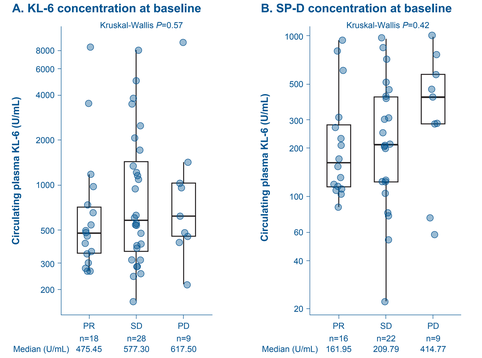
Figure 2. KL-6 and SP-D concentrations at baseline relative to the incidence of pulmonary AEs



Data cutoff date: November 1, 2020

- Baseline concentrations of KL-6 and SP-D do not appear to predict response to mobocertinib **(Figure 3)**

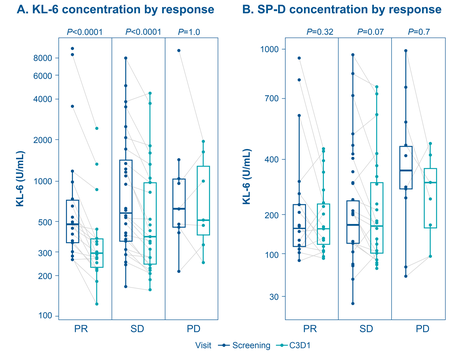
Figure 3. Baseline KL-6 and SP-D concentrations by confirmed objective response (per IRC)

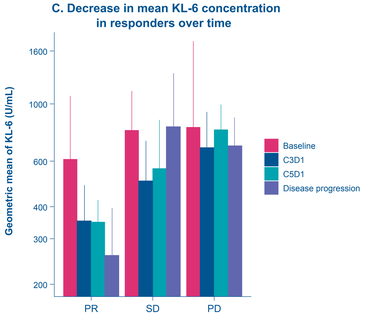


Data cutoff date: November 1, 2020

- Significant decreases in KL-6 concentrations were observed in patients with IRC-confirmed PR or SD but not in patients with PD **(Figure 4A)**
- No significant changes in SP-D concentration were observed regardless of response **(Figure 4B)**
- The geometric mean KL-6 concentration declined to a greater extent in patients who achieved PR compared with those with SD or PD **(Figure 4C)**

Figure 4. Change in KL-6 and SP-D concentration by response (per IRC) over time

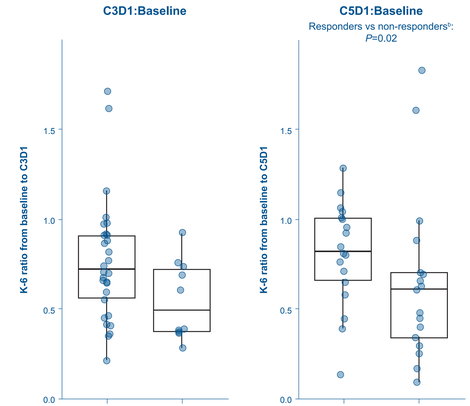




P values are from paired Wilcoxon test.
Data cutoff date: November 1, 2020

- Low KL-6 ratios (C3D1/baseline and C5D1/baseline) were associated with response to mobocertinib **(Figure 5)**
- After adjustment for time point using a mixed effects model, the KL-6 ratio in responders was lower (0.31) than that in non-responders (*P*=0.02)

Figure 5. KL-6 ratios by best overall response[a] (per IRC) at C3D1 and C5D1



Data cutoff date: November 1, 2020
[a]Per RECIST v1.1
[b]After adjustment for time point using a mixed effects model

Conclusions

- Baseline KL-6 and SP-D concentrations are not predictive of response outcomes or occurrence of pulmonary AEs in patients with mNSCLC treated with mobocertinib
- Decrease in plasma KL-6 concentration is significantly associated with achievement of PR or SD in patients receiving mobocertinib
- No correlation was observed between change in SP-D concentration and response to mobocertinib
- Circulating levels of KL-6 are a potential indicator of response in patients with mNSCLC receiving mobocertinib therapy

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Abbreviations

AE, adverse event; C3D1, cycle 3 day 1; C5D1, cycle 5 day 1; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion; ILD, interstitial lung disease; IRC, independent review committee; KL-6, Krebs von den Lungen-6; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; SP-D; surfactant protein D; TKI, tyrosine kinase inhibitor

Disclosures

PH: No conflicts to report; **MS:** Advisory roles or paid lectures (Takeda, Janssen, Boehringer Ingelheim); research award (Takeda); **ZS:** Employment (Takeda); **XT:** Employment (Takeda); **VB:** Employment (Takeda); **SC:** Employment (Takeda); **SJ:** Employment (Takeda); **SV:** Employment (Takeda)

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Email for questions or comments: Paul Hofman, hofman.p@chu-nice.fr