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Phase 1 study of CKD-702, an EGFR-cMET bispecific antibody, in advanced or metastatic non-small cell lung cancer (NSCLC)

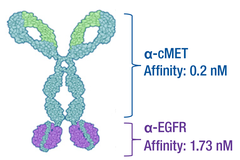
Dong-Wan Kim[1], Se-Hoon Lee[2], In-Jin Jang[3], Kyujin Park[4] and Dae Ho Lee[5]

[1]Department of Internal Medicine, Seoul National University College of Medicine and Seoul National University Hospital, Seoul, Republic of Korea; [2]Department of Medicine, Samsung Medical Center and Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Clinical Pharmacology & Therapeutics, Seoul National University Hospital, Seoul, Republic of Korea; [4]Bio Drug Discovery, CKD - Chong Kun Dang Research Institute (Hyojong), Yongin, Republic of Korea; [5]Department of Oncology, Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea

Introduction

- Aberrant activations of both EGFR and cMET signaling pathways have been implicated in driving tumor cell growth and proliferation in lung cancer. Mutual synergism between EGFR and cMET is known to promote acquired drug resistance. Because of this crosstalk between cMET and EGFR pathways, dual inhibition of these targets holds promise as a treatment for NSCLC patients.
- CKD-702 is a bispecific antibody designed to neutralize, internalize and degrade EGFR and cMET receptors, leading to disruption of downstream signaling (Figure 1). In preclinical studies, CKD-702 demonstrates efficacy in tumor models that have primary/secondary activating EGFR mutations as well as EGFR exon 20 insertion mutations. In addition, CKD-702 is highly effective in models with cMET amplification, exon 14 skipping mutation or cMET TKI-resistance. This preclinical profile supports the clinical trial of CKD-702 as monotherapy in selected lung cancer patients with aberrant cMET and EGFR signaling.

Figure 1. **Structure of CKD-702**

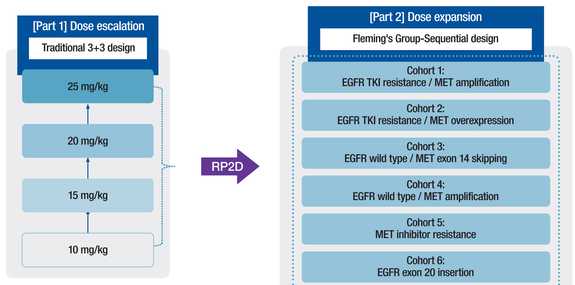


- In this report we present data concerning the safety, pharmacokinetics (PK), pharmacodynamic (PD) and preliminary efficacy of CKD-702 from a dose escalation phase 1 study in patients with advanced/metastatic NSCLC.

Methods

- Patients received intravenous (IV) CKD-702 once every 2 weeks (q2w) using a 3+3 design in 4 escalating doses from 10 mg/kg to 25 mg/kg until progression or unacceptable toxicity (Figure 2).
- Molecular changes were investigated during the screening period using ctDNA and/or tumor tissue.

Figure 2. Study design



Results

Patients

- At data cut-off (3 Feb 2022), 24 patients were enrolled and received CKD-702.
- Of these patients, 6 (25%) were identified with MET exon 14 skipping mutation and 7 (29%) were identified with MET amplification. Among 17 (71%) patients with EGFR mutation, Exon 19 deletion and Exon 21 L858R were most commonly identified (Table 1).
- All 24 response-evaluable patients received prior treatment for advanced or metastatic disease. Among them, 6 (25%) had received 1 course of prior therapy, 4 (17%) had received 2 previous courses of therapy and 14 (58%) had received more than 3 courses of prior therapy.

Table 1. Baseline patient characteristics

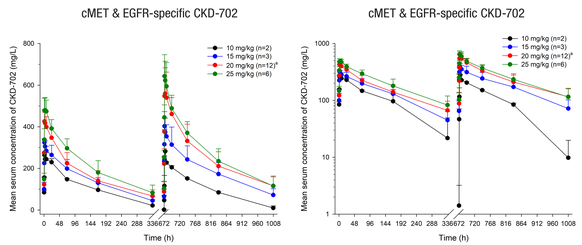
Characteristics	Total (n=24)
Median age, years (range)	67 (48-80)
Male / Female, n (%)	11 (46) / 13 (54)
Smoking history, n (%)	
Never / Former / Current	12 (50) / 12 (50) / 0
ECOG PS, n (%)	
0	3 (13)
1	21 (88)
Median time from diagnosis of metastatic disease, months (range)	2 (0-7)
Histological subtype, n (%)	
Adenocarcinoma	21 (88)
Squamous cell carcinoma	2 (8)
Other (Sarcomatoid carcinoma)	1 (4)
Brain metastases, n (%)	15 (63)
Previous lines of therapies, n (%)	
1	6 (25)
2	4 (17)
≥3	14 (58)
MET exon 14 skipping†, n (%)	6 (25)
MET amplification†‡, n (%)	7 (29)
EGFR mutation†, n (%)	17 (71)
Exon 19 deletion	4 (17)
Exon 19 deletion + T790M	2 (8)
Exon 19 deletion + T790M + C797S	2 (8)
Exon 21 L858R	6 (25)
Exon 21 L858R + T790M	1 (4)
Exon 21 L858R + Exon 20 insertion	1 (4)
Exon 20 insertion	1 (4)

† Patients' information for genetic alterations were determined by local or central test results.
‡ MET GCN ≥5 or MET to CEP7 ratio ≥2

Pharmacokinetics & Pharmacodynamics

- CKD-702 exposure and half-life increased in a dose-related manner; accumulation (~1.3×) was confirmed upon repeat-dosing (Figure 3).
- EGFR-extracellular domain (ECD) tended to increase ~2-fold regardless of CKD-702 dose; cMET-ECD increased dose-dependently to 20 mg/kg with estimated saturation >20 mg/kg.

Figure 3. Mean plasma concentration-time profiles of CKD-702 after single and multiple intravenous infusions of CKD-702



[a]The number of subjects for multiple intravenous infusion was 10.

Safety

- No DLTs were reported; ≥ 1 treatment-emergent AEs (TEAEs) occurred in all 24 patients (Table 2).
- Common (≥20%) all-grade (Gr) TEAEs were rash, paronychia, stomatitis, nausea, and hypoalbuminemia. Infusion related reactions (21%) were all Gr 1–2.
- TEAEs ≥ Gr 3 occurred in 42% of patients; 3 patients reported Gr 3 rash (2 maculopapular, 1 acneiform) (Table 3).

Table 2. Adverse events summary

Adverse Events, n (%)	Total (n=24)
Treatment-Emergent Adverse Events (TEAEs)	24 (100)
Treatment-related AEs	24 (100)
Grade ≥ 3 TEAEs	10 (42)
Grade ≥3 Treatment-related AEs	6 (25)
Serious TEAEs	22 (92)
Treatment-related SAEs[a]	4 (17)
TEAE leading to death[b]	1 (4)
TEAEs leading to discontinuation[c]	4 (17)

[a]One case each of generalised oedema, pyrexia, duodenal ulcer, and pneumonitis. [b]One case of pneumonitis (4%) which was considered treatment-related. [c]Two cases of rash (8%), and one each of pneumonia (4%), and pneumonitis (4%); these correspond to treatment-related AEs (except 1 case of pneumonia).

Table 3. TEAEs ≥15% by dose level (All grade / Grade ≥3)

Preferred term	Total (n=24)		Level 1 (10 mg/kg) (n=3)		Level 2 (15 mg/kg) (n=3)		Level 3 (20 mg/kg) (n=12)		Level 4 (25 mg/kg) (n=6)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Rash	19 (79)	3 (13)	2 (67)	–	2 (67)	–	10 (83)	1 (8)	5 (83)	2 (33)
Paronychia	7 (29)		–		–		3 (25)		4 (67)	
Stomatitis	6 (25)	1 (4)	1 (33)	–	1 (33)	–	2 (17)	1 (8)	2 (33)	–
Hypoalbuminaemia	5 (21)	1 (4)	–	–	–	–	3 (25)	1 (8)	2 (33)	–
Nausea	5 (21)		–		1 (33)		2 (17)		2 (33)	
Pneumonia	4 (17)	1 (4)	–	–	–	–	2 (17)	–	2 (33)	1 (17)
Pruritus	4 (17)		1 (33)		–		2 (17)		1 (17)	

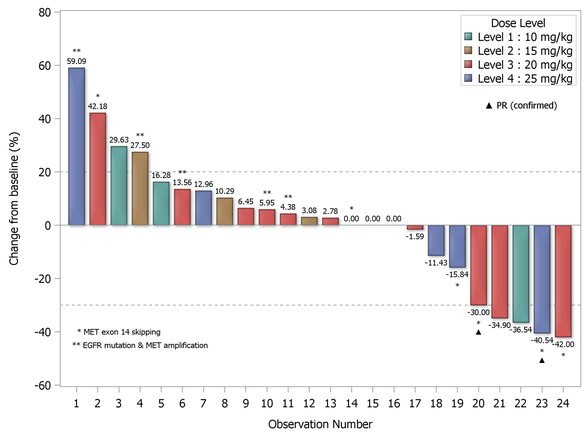
*Grade 1–2 infusion-related reactions for CKD-702 occurred in 5 patients (21%) and included urticaria (n=2), pruritus, rash, dysaesthesia, headache, pyrexia, and myalgia (n=1 for each of these) and multiple symptoms occurred in some patients.

- The recommended phase 2 dose was determined to be 20 mg/kg based on safety, PK, and PD review.

Anti-tumor effects

- Among 24 response-evaluable patients, 5 achieved a best time point response of partial response (PR) including 2 confirmed PR: 3 MET exon 14 skipping, 1 MET IHC 3+ with EGFR exon 19 deletion, and 1 EGFR L858R with no identified MET-alteration.
- Among 6 patients with MET exon 14 skipping (4 cMET TKI-naïve and 2 cMET TKI-resistant), 3 (all of cMET TKI-naïve) had a best time point result of PR including 2 confirmed (Figure 4).

Figure 4. Best % change from baseline in sum of target lesion diameters



Conclusion

CKD-702 has a manageable safety profile related to EGFR and cMET inhibition, and produced a preliminary response in patients with MET exon 14 skipping. In a follow-up dose expansion study, a dosage of CKD-702 20 mg/kg IV q2w will be investigated, and the planned cohort will include patients with MET-alteration NSCLC. ClinicalTrials.gov identifier: NCT04667975

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Presenting author: Dong-Wan Kim (kimdw@snu.ac.kr)