Neratinib efficacy in patients with *EGFR* exon 18-mutant non-small-cell lung cancer: findings from the SUMMIT basket trial

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Background

- *EGFR* exon 18 mutations represent 5% of all *EGFR* mutations detected in lung cancer.[1]
- *In vitro* data have shown that *EGFR* exon 18 mutations are highly sensitive to neratinib, an oral, irreversible, tyrosine kinase inhibitor (TKI) of EGFR (ERBB1), HER2 (ERBB2), & HER4 (ERBB4).[2–4]
- Clinical trial data also show that *EGFR* exon 18 mutations are highly sensitive to neratinib:[5,6]
  - The phase 2 SUMMIT basket trial (NCT01953926) demonstrated efficacy of neratinib in a subset of patients with *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC).[6]
- Neratinib also has documented activity in HER2-positive metastatic breast cancer, including patients with central nervous system (CNS) metastases.[7,8]

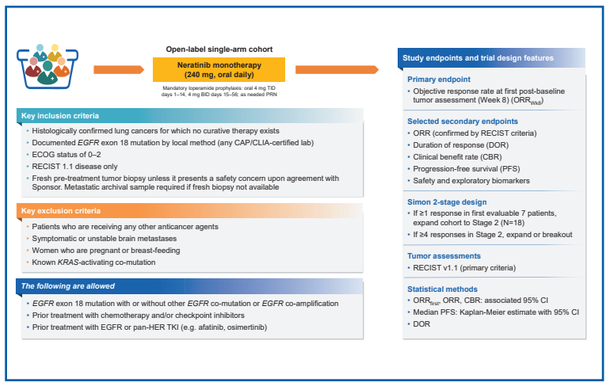
Objectives

- In this poster we report updated data on the efficacy and safety of neratinib in an expanded cohort of patients with *EGFR* exon 18-mutant NSCLC in SUMMIT according to prior EGFR TKI treatment.

Methods

- The overall SUMMIT study design has been presented previously.[6,9]
- The design of the *EGFR* exon 18-mutant lung cancer cohort is shown in detail in Figure 1.

Figure 1. SUMMIT *EGFR* exon 18-mutant lung cancer cohort



Results

Table 1. Baseline demographics and patient characteristics

Patient characteristics	Efficacy evaluable patients (n=29)
Median age (range), years	65 (42–87)
<65 years, n (%)	10 (34.5)
≥65 years, n (%)	19 (65.5)
Gender, n (%)	
Female	17 (58.6)
Male	12 (41.4)
ECOG performance status, n (%)	
0	14 (48.3)
1	11 (37.9)
2	4 (13.8)
Race, n (%)	
White	21 (72.4)
Black or African American	4 (13.8)
Other	4 (13.8)
Prior EGFR tyrosine kinase inhibitor, n (%)	23 (79)
Prior chemotherapy, n (%)	15 (52)
Prior checkpoint inhibitor, n (%)	5 (17)
Number of prior lines in metastatic/locally advanced setting, range	1–6

Data cutoff date: Sep 2022.

Key efficacy findings

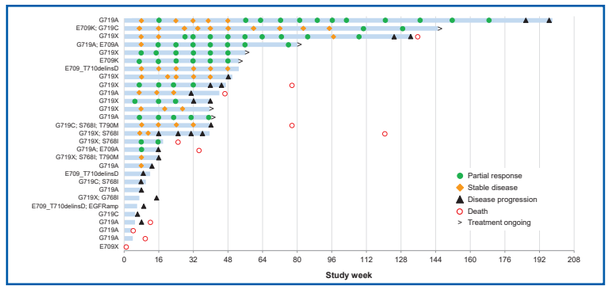
- The confirmed objective response rate (ORR) was 34.5% overall, 30.4% in patients pretreated with TKIs, and 50.0% in patients not pretreated with TKIs (Table 2).
- Response or stable disease lasting for ≥48 weeks was observed in 7 patients (6 PR, 1 SD).
- Two of 7 patients with baseline CNS metastasis had a partial response (PR; median PFS 3.6 months; 95% CI 1.9–9.1 months).
- At data cutoff, treatment was ongoing in 6 patients.

Table 2. *EGFR* exon 18-mutant lung cancer cohort receiving neratinib monotherapy: Efficacy summary

Parameter	All efficacy-evaluable patients (n=29)	TKI pretreated patients (n=23)	Patients with no prior TKI (n=6)	Patients with CNS metastases at baseline (n=7)
Objective response (confirmed),[a] n	10 (34.5)	7 (30.4)	3 (50.0)	2 (28.6)
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	10 (34.5)	7 (30.4)	3 (50.0)	2 (28.6)
Objective response rate, % (95% CI)	34.5 (17.9–54.3)	30.4 (13.2–52.9)	50.0 (11.8–88.2)	28.6 (3.7–71.0)
Best overall response, n	11	8	3	2
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	11 (37.9)	8 (34.8)	3 (50.0)	2 (28.6)
Best overall response rate, % (95% CI)	37.9 (20.7–57.7)	34.8 (16.4–57.3)	50.0 (11.8–88.2)	28.6 (3.7–71.0)
Median DOR,[b] months (95% CI)	NE (NE–NE) Range: 4.0–26.1*	NE (NE–NE) Range: 4.0–26.1*	NE (NE–NE) 6.2, 9.4*, 13.8*	6.8 (6.2–7.5) 6.2, 7.5
Clinical benefit,[c] n	15	11	4	3
CR or PR	10 (34.5)	7 (30.4)	3 (50.0)	2 (28.6)
SD ≥16 weeks	5 (17.2)	4 (17.4)	1 (16.7)	1 (14.3)
Clinical benefit rate, % (95% CI)	51.7 (32.5–70.6)	47.8 (26.8–69.4)	66.7 (22.3–95.7)	42.9 (9.9–81.6)
Median PFS,[b] months (95% CI)	5.8 (2.3–11.0)	3.7 (2.3–9.2)	NE (NE–NE)	3.6 (1.9–9.1)

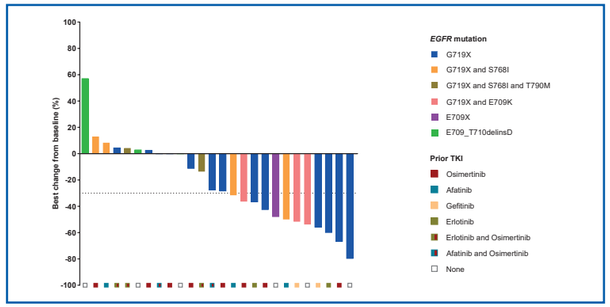
Data cutoff date: Sep 2022. Responses were evaluated as per RECIST v1.1 criteria:
[a]Objective response rate is defined as either a complete or partial response that is confirmed no less than 4 weeks after the criteria for response are initially met; [b]Kaplan-Meier analysis in efficacy population; [c]Clinical benefit rate is defined as confirmed CR or PR or stable disease SD for ≥16 weeks (within ± 7-day visit window); NE = not estimable; *response ongoing; #censored

Figure 2. Treatment duration and best response



Data cutoff date: Sep 2022.

Figure 3. Best change in tumor response[a]



Data cutoff date: Sep 2022.
[a]3 patients were not evaluable for response and are not represented here.

Table 3. *EGFR* exon 18-mutant lung cancer cohort: Most common treatment-emergent adverse events >10%

TEAEs	Safety evaluable patients (n=31)[a]	
	Any grade	Grade ≥3
Diarrhea	16 (51.6)	3 (9.7)
Constipation	12 (38.7)	0
Nausea	11 (35.5)	0
Decreased appetite	10 (32.3)	2 (6.5)
Vomiting	8 (25.8)	1 (3.2)
Fatigue	7 (22.6)	0
Cough	6 (19.4)	0
Anemia	5 (16.1)	3 (9.7)
Arthralgia	5 (16.1)	0
Back pain	5 (16.1)	0
Dyspnea	5 (16.1)	2 (6.5)
Rash	5 (16.1)	0
Weight decreased	5 (16.1)	1 (3.2)
Dizziness	4 (12.9)	0

Data cutoff date: Sep 2022.
[a]Patients who received at least one dose of neratinib.

Key safety findings

- Neratinib with mandatory loperamide prophylaxis (first 2 cycles) was well tolerated.
- The most common adverse events were diarrhea (51.6%), constipation (38.7%), nausea (35.5%) and decreased appetite (32.3%).
- No grade 4 diarrhea was reported. Grade 2 and grade 3 diarrhea were each reported in 10% patients; 1 subject discontinued due to diarrhea.
- The were no notable differences in the safety profiles of patients based on prior TKI use.

Conclusions

- Neratinib monotherapy had meaningful activity in patients with *EGFR* exon 18-mutant NSCLC, most of whom had received prior TKIs:
  - 34.5% of patients had a confirmed PR.
- Treatment with neratinib was well tolerated:
  - Diarrhea, the most common side effect, was manageable with mandatory loperamide prophylaxis given for the first 2 cycles.
  - Rates of diarrhea, including grade 3, were lower than seen in patients with HER2+ breast cancer and compared favorably with rates reported for other TKIs commonly used in lung cancer.
  - Discontinuation due to diarrhea was also lower than reported in other neratinib studies.
- Given the lack of effective therapies for patients with NSCLC and difficult-to-treat uncommon mutations after failure of EGFR TKIs, treatment with neratinib should be considered.
- Enrollment into the SUMMIT trial is now closed, and additional data are forthcoming.

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