Neratinib efficacy in a subgroup of patients with *EGFR* exon 18-mutant non-small cell lung cancer and central nervous system involvement: findings from the SUMMIT basket trial

Jonathan W. Goldman,[1] Santiago Viteri Ramirez,[2] Amit Mahipal,[3] Jennifer Marie Suga,[4] Lisa D. Eli,[5] Alshad S. Lalani,[5] Richard Bryce,[6] Feng Xu,[6] Naisargee Shah,[6] Fairooz Kabbinavar,[6] Valentina Boni,[7] Barbara B. Haley[8]

[1]University of California, Los Angeles, Los Angeles, CA, USA; [2]Instituto Oncologico Dr Rosell, Hospital Universitario Dexeus, Grupo Quiron Salud, Barcelona, Spain; [3]Mayo Clinic, Rochester, MN; [4]Kaiser Permanente Cancer Research Center, Vallejo, CA; [5]Puma Biotechnology Inc., San Francisco, CA; [6]Puma Biotechnology Inc, Los Angeles, CA; [7]START Madrid-CIOCC, Hospital Universitario, Madrid Sanchinarro, Madrid, Spain; [8]UT Southwestern Medical Center, Dallas, TX

#9068

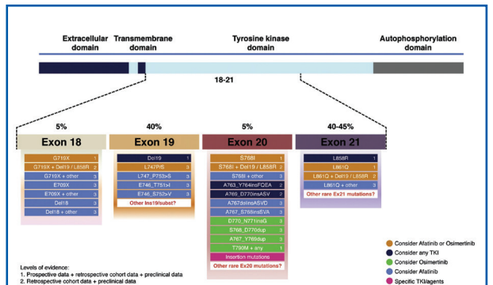
Background

- The phase 2 SUMMIT basket trial (NCT01953926) demonstrated efficacy of neratinib in patients with *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC).[1]
- Neratinib also has documented activity in HER2-positive metastatic breast cancer, including patients with central nervous system (CNS) metastases.[2,3]

Objectives

- To report neratinib single-agent efficacy in a cohort of patients with *EGFR* exon 18-mutant NSCLC from SUMMIT, including patients with CNS involvement.

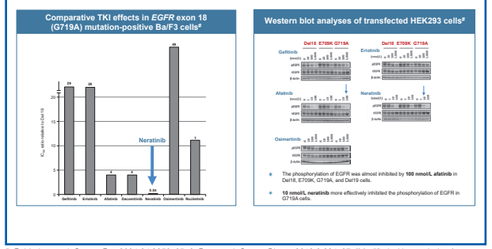
Figure 1. *EGFR* exon 18 mutations represent 5% of all *EGFR* mutations detected in lung cancer



Reproduced from [4]Passaro A, et al. J Thoracic Oncol 2020; Dec 14:S1556-0864(20)31102-3

Figure 2. *EGFR* exon 18 mutations are highly sensitive to neratinib *in vitro*

Neratinib: oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), & HER4 (ERBB4)[5,6]

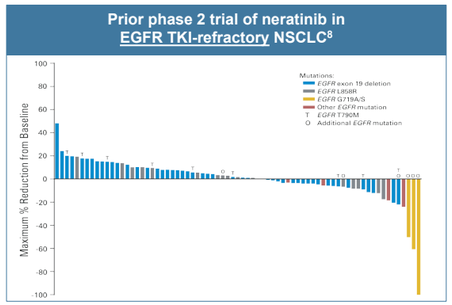


5. Rabindran et al. Cancer Res 2004:64:3958–65; 6. Bose et al. Cancer Discov 2013;3:224–37; #Modified with permission from 7. Kobayashi et al. Clin Cancer Res 2015;21:5305–13

Methods

- The overall SUMMIT study design has been presented previously.[1,9]
- The design of the *EGFR* exon 18-mutant lung cancer cohort is shown in detail in Figure 4.

Figure 3. *EGFR* exon 18 mutations are highly sensitive to neratinib: a POC trial



Yellow bars represent patients whose tumors have *EGFR* G719A/S mutations

- 4/167 (2%) patients had *EGFR* exon 18 mutations (*G719X*); 1 patient did not have measurable disease by central review.
- All patients with *G719* mutations (n=4) had clinical benefit: 3 PRs and 1 SD lasting >40 weeks:
  - Median PFS 52.7 weeks (90% CI 25.6–57.0 weeks).

8. Reproduced with permission from Sequist L, et al. J Clin Oncol 2010;28:3076-83.

Figure 4. SUMMIT (A7) study design for *EGFR* exon 18-mutant lung cancer cohort

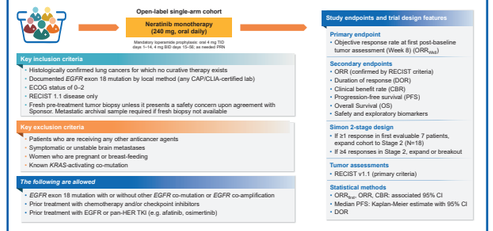


Table 1. Baseline demographics and patient characteristics

Patient characteristics	Safety/Efficacy evaluable patients (n=11)
Median age (range), years	**67** (56–83)
<65 years, n (%)	4 (36)
≥65 years, n (%)	7 (64)
Gender, n (%)	
Female	5 (45)
Male	6 (55)
ECOG performance status, n (%)	
0	5 (45)
1	6 (55)
Race, n (%)	
Black or African American	1 (9)
White	10 (91)
Median number of prior therapies in metastatic/locally advanced setting (range)	2 (1–3)
Prior EGFR tyrosine kinase inhibitor, n (%)	**10 (91)**
Prior chemotherapy, n (%)	6 (55)
Prior checkpoint inhibitor, n (%)	3 (27)

Data cutoff date: 21 August 2020

Key efficacy findings

Efficacy in TKI-pretreated patients

- Among 10 TKI-pretreated patients, 60% (n=6) had a PR, and 40% (n=4) had a confirmed PR.
- SD lasting ≥16 weeks was seen in 4 additional patients, giving a CBR of 80%.
- The median DOR with neratinib was 7.5 months.
- The median PFS with neratinib was 9.1 months.
- The median OS with neratinib was 17.9 months.

Efficacy in TKI-pretreated patients with CNS involvement

- 2 patients had PR and 1 patient had SD as best response by RECIST 1.1.
- Individual PFS times were 1.9 (censored), 6.9, and 9.1 months.
- Individual OS times were 2.6 (censored), 17.7 (censored), and 17.9 months.

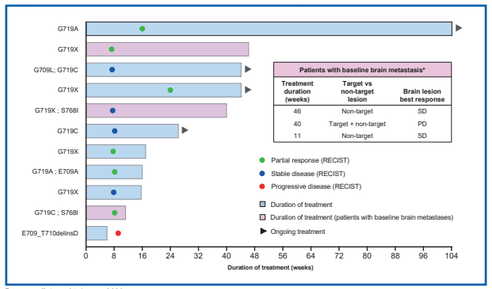
Table 2. *EGFR* exon 18-mutant lung cancer cohort receiving neratinib monotherapy: Efficacy summary

Parameter	Efficacy-evaluable patients (n=11)	TKI pretreated (n=10)
Objective response (confirmed),[a] n	**4**	**4**
CR	0	0
PR	4	4
Objective response rate, % (95% CI)	**36** (11–69)	**40** (12–74)
Best overall response, n	**6**	**6**
CR	0	0
PR	6	6
Best overall response rate, % (95% CI)	**54** (23–83)	**60** (26–88)
Median DOR,[b] months (95% CI)	**7.5 (4.0–NE) (1.9*, 4.0, 7.5, 9.2*)**	**7.5 (4.0–NE) (1.9*, 4.0, 7.5, 9.2*)**
Clinical benefit,[c] n	**8**	**8**
CR or PR	4	4
SD ≥16 weeks	4	4
Clinical benefit rate, % (95% CI)	**73** (39–94)	**80** (44–97)
Median PFS,[b] months (95% CI)	**6.9** (2.1–NA)	**9.1** (3.7–NA)
PFS in patients with CNS metastases, months	See TKI pretreated	**1.9[f], 6.9, 9.1**
Median OS,[b] months (95% CI)	**17.9** (5.8–NE)	**17.9** (5.7–NE)
OS in patients with CNS metastases, months	See TKI pretreated	**2.6[f], 17.7[f], 17.9**

Data cutoff date: 21 August 2020

[a]Objective response rate (ORR) 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 safety population; [c]Clinical benefit rate (CBR) is defined as confirmed CR or PR or stable disease (SD) for ≥16 weeks (within ± 7-day visit window); DOR, duration of response; PFS, progression-free survival, [f]response ongoing

Figure 5. Treatment duration and best response



Data cutoff date: 21 August 2020

*All patients received palliative radiation to the brain prior to study entry.

Key safety findings

- Neratinib was well tolerated with mandatory loperamide prophylaxis (first 2 cycles).
- Four patients reported grade 1 and one patient reported grade 2 diarrhea (the most common side effect of neratinib).
- There was no evidence of grade 3 diarrhea, interstitial lung disease (ILD), or skin rashes.
- No patients required a dose hold, dose reduction, hospitalization or permanently discontinued neratinib due to diarrhea.

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

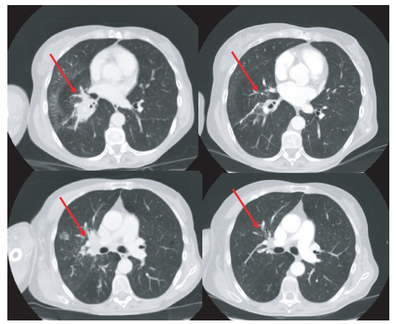
TEAEs	Safety evaluable patients (n=11)	
	Any grade	Grade ≥3
Diarrhea	5 (45.5)	0
Vomiting	4 (36.4)	0
Constipation	3 (27.3)	0
Nausea	3 (27.3)	0
Decreased appetite	3 (27.3)	1 (9.1)
Dizziness	2 (18.2)	0
Hypertension	2 (18.2)	0
Dry mouth	2 (18.2)	0
Fatigue	2 (18.2)	0

Data cutoff date: 21 August 2020

Case study

- Female, 61 years, former smoker.
- December 2016: stage IV lung adenocarcinoma with lung, lymph nodes, bone and brain metastasis and *EGFR* (G719X) mutation.
- December 2016: SBRT on brain; 1st-line erlotinib achieving SD as best response and clinical benefit.
- November 2018: asymptomatic brain/lung progression; 2nd-line neratinib (duration of treatment 46 weeks).
- **January 2019: PR (60% reduction in tumor burden by RECIST 1.1) and stable brain mets on neratinib.**
- September 2019: lung PD; 3rd-line osimertinib.

Baseline Nov 2018 **Jan 2019**



Conclusions

- Activity of single-agent neratinib was observed in prior TKI-exposed patients with *EGFR* exon 18-mutant NSCLC.
- Despite the small sample size of only 3 patients with baseline CNS metastases, the current findings suggest a potential role for neratinib as a systemic treatment option for patients with NSCLC and difficult-to-treat uncommon mutations with CNS involvement:
  - These data are consistent with the CNS activity of neratinib in HER2-overexpressing breast cancer.
- Neratinib single-agent treatment was well tolerated in *EGFR* exon 18-mutant NSCLC patients, with no evidence of grade ≥3 diarrhea.
- In addition, no ILD or skin rash was noted.
- The SUMMIT trial continues to enroll patients with *EGFR* exon 18-mutant NSCLC, with or without prior TKI.

References

1. Boni V, et al. WCLC 2020 (OA04).
2. Saura C, et al. SABCS 2020 (PD13-09).
3. Saura C, et al. J Clin Oncol 2020;38:3138–49.
4. Passaro A, et al. J Thoracic Oncol 2020; Dec 14:S1556-0864(20)31102-3.
5. Rabindran SK, et al. Cancer Res 2004:64:3958–65.
6. Bose R, et al. Cancer Discov 2013;3:224–37.
7. Kobayashi Y, et al. Clin Cancer Res 2015;21:5305–13.
8. Sequist L, et al. J Clin Oncol 2010;28:3076–83.
9. Hyman DM, et al. Nature 2018;554:189–94.

Acknowledgements

- The authors would like to thank all patients and their families for participating in the SUMMIT trial.
- SUMMIT was sponsored by Puma Biotechnology Inc.
- Puma Biotechnology Inc. funded medical writing/editing assistance for this poster, which was provided by Miller Medical Communications Ltd.

Conflict of interest disclosures: Jonathan W. Goldman

Financial interests

- *Consulting or advisory role:* Amgen, AstraZeneca, Bristol-Myers Squibb, Genentech/Roche, Lilly.
- *Speakers' bureau:* Merck.
- *Travel, accommodation, expenses:* AstraZeneca.
- *Research funding:* Abbvie, Advaxis, Array BioPharma, AstraZeneca/MedImmune, Bristol-Myers Squibb, Corvus Pharmaceuticals, Genentech/Roche, Lilly, Puma Biotechnology, Spectrum Pharmaceuticals.

Presented at the 2021 ASCO Annual Meeting, June 4–8, 2021 (virtual)