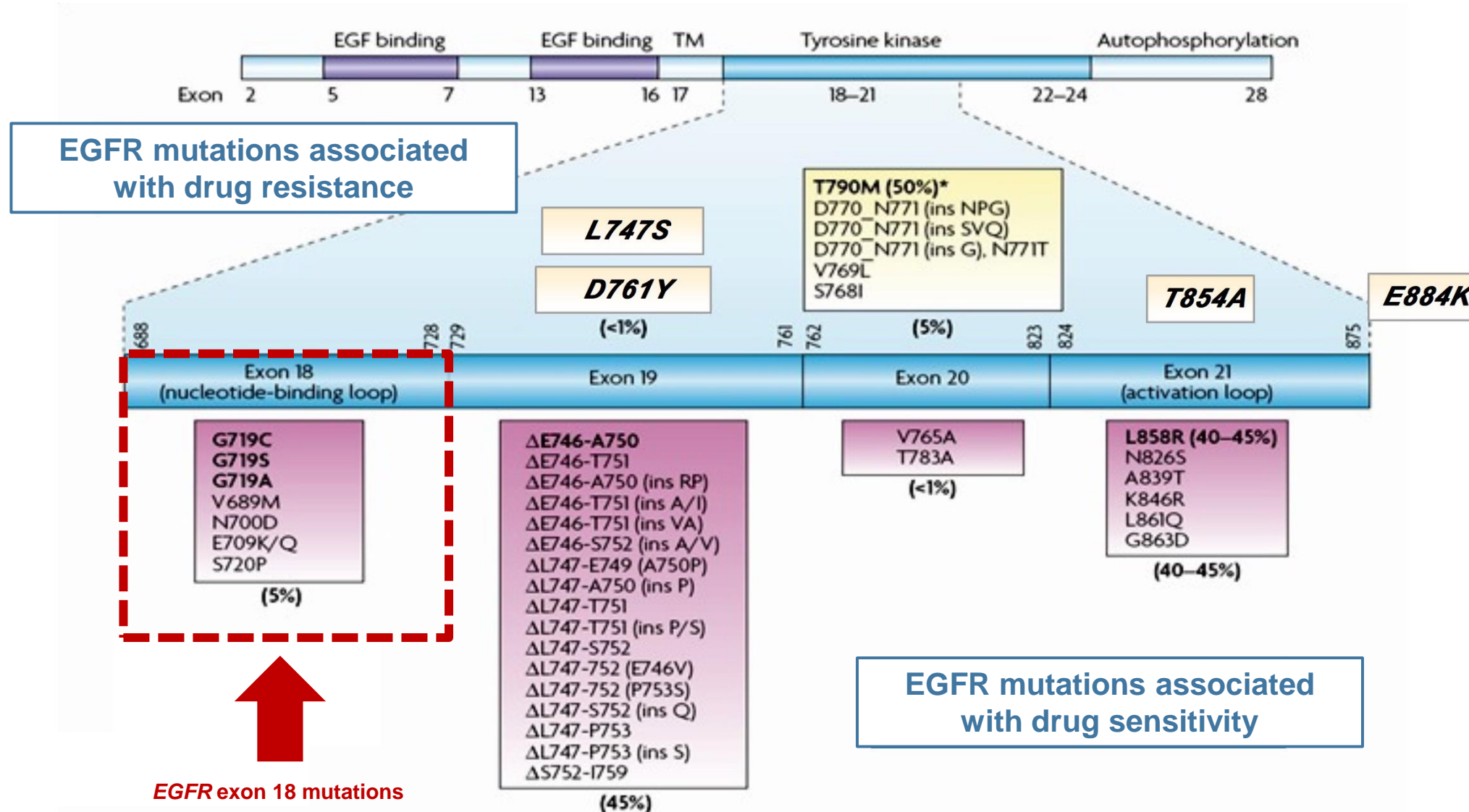


# **SUMMIT (PUMA-NER-5201) Basket Trial**

*EGFR* exon 18 lung cancer cohort update

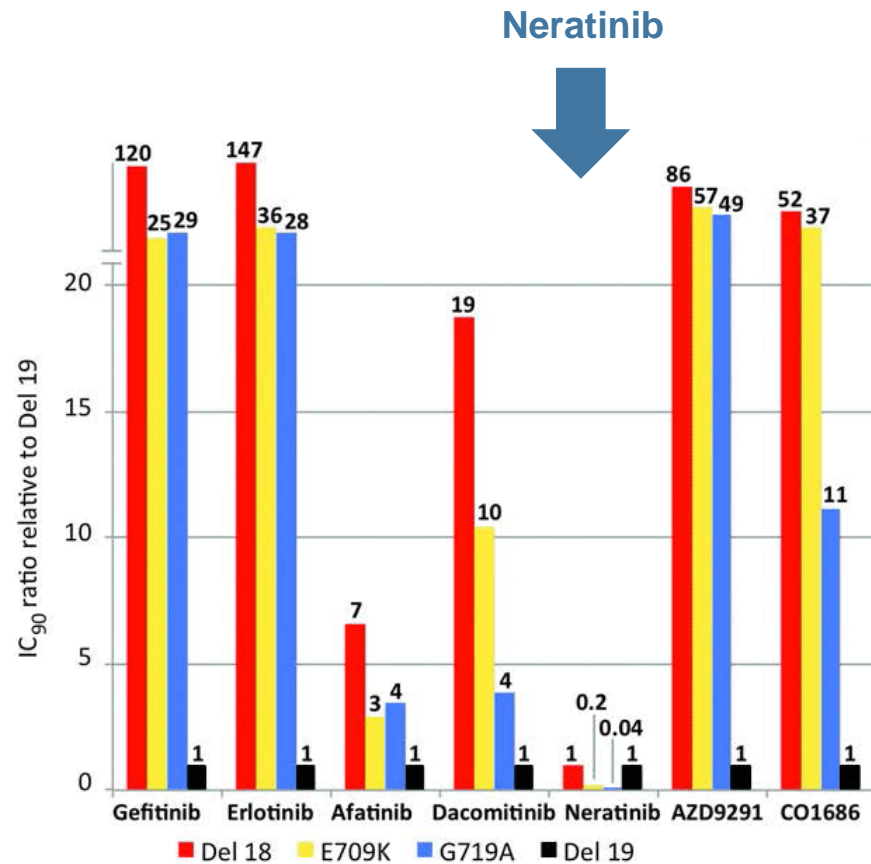


# EGFR exon 18 mutations are rare in NSCLC adenocarcinomas: represents only 5% of all EGFR mutations detected in lung cancer

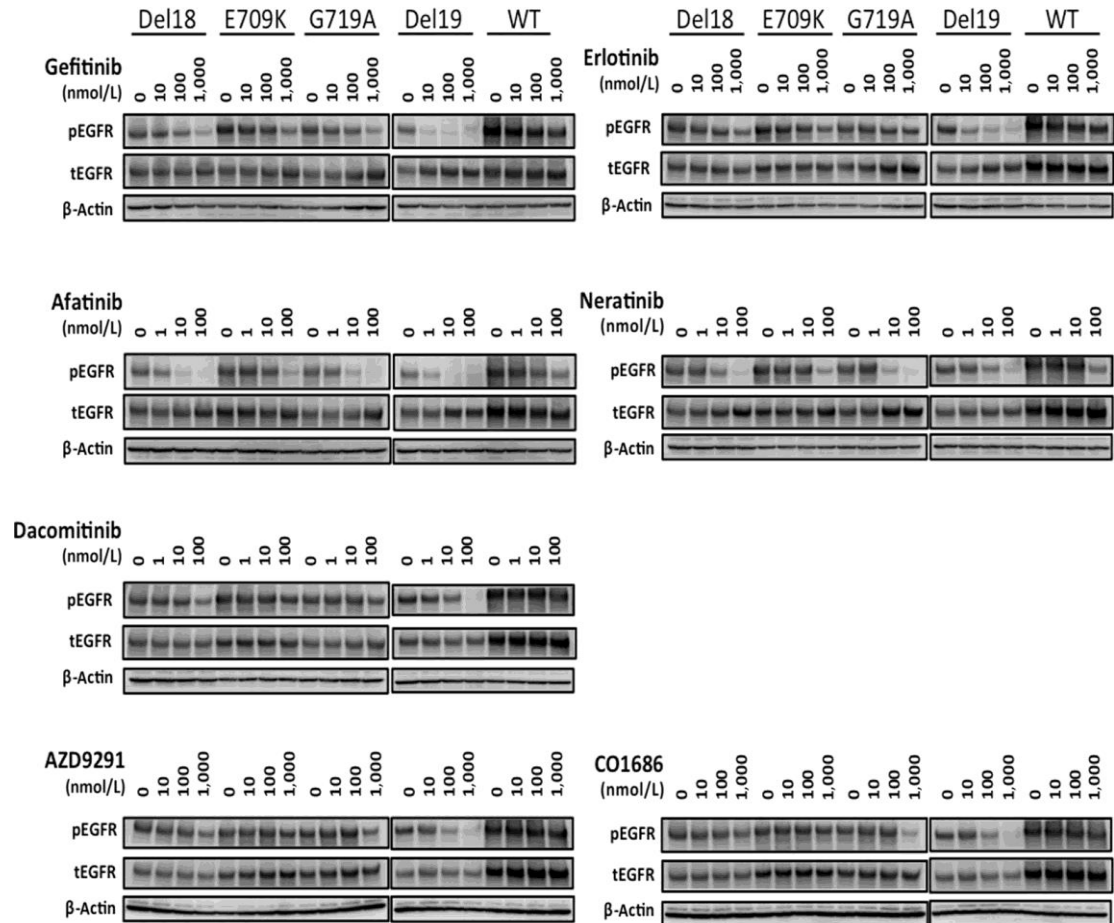


# EGFR exon 18 mutations are highly sensitive to neratinib (irreversible pan-HER TKIs) *in vitro* studies

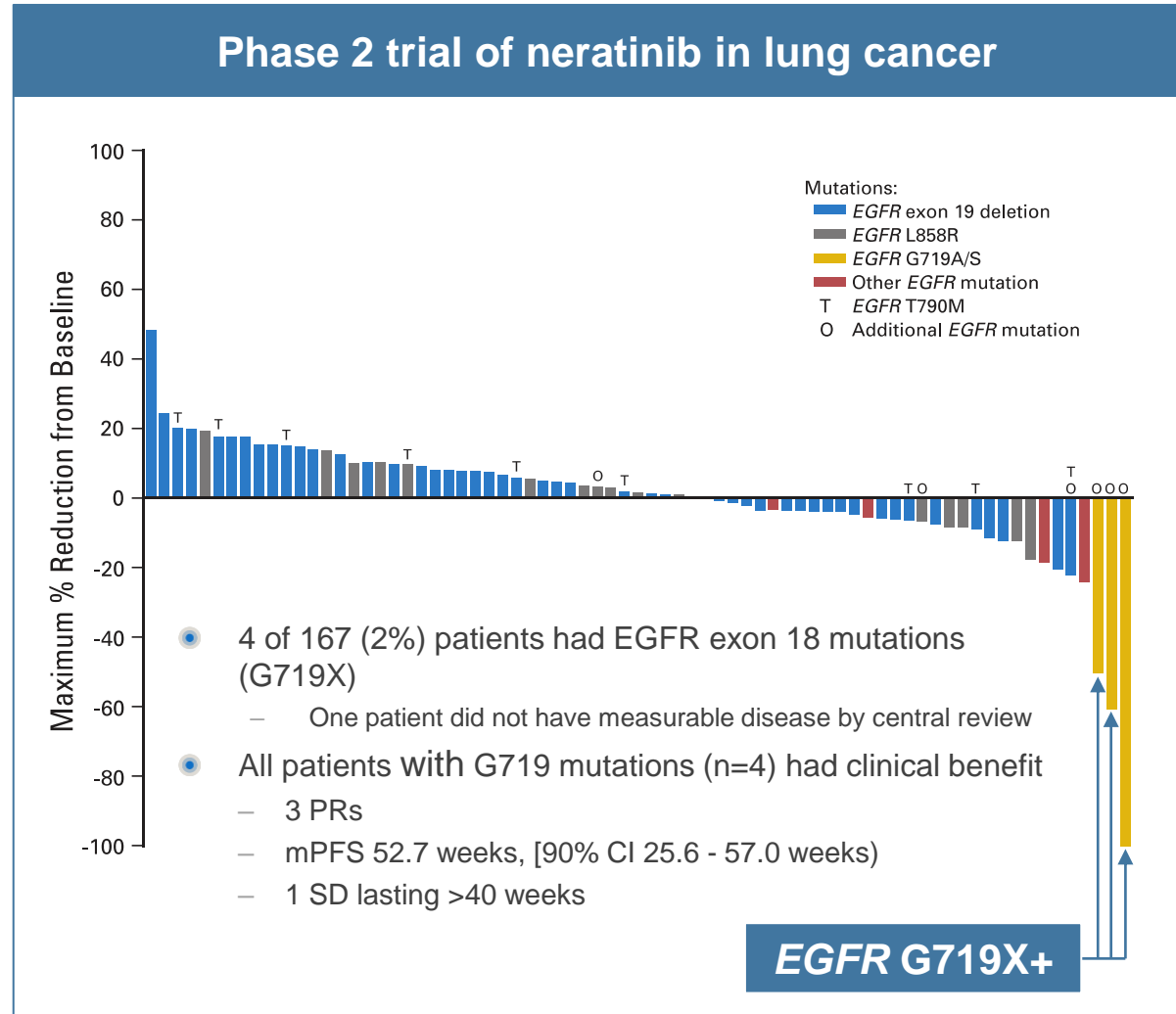
## Comparative TKI affects in EGFR exon 18+ cells



## Western blot analyses of transfected HEK293 cells



# EGFR exon 18 mutations are highly sensitive to neratinib in NSCLC patients from POC trial



Source: L. Sequist et al (2010) *J. Clin. Oncol.* 28:3076-3083..

# SUMMIT study design for *EGFR* exon 18 mutant lung cancer cohort



## *EGFR* exon 18-positive Lung Cancer

Open label single arm cohort

### Neratinib monotherapy (240 mg, oral daily)

Mandatory Loperamide prophylaxis: oral 4 mg TID days 1–14, 4 mg BID days 15–46; as needed PRN

## Study Endpoints and Trial Design Features

### Primary endpoint

- Objective response rate at first post-baseline tumor assessment (Week 8) ( $ORR_{Wk8}$ )

### Secondary endpoints

- ORR (confirmed by RECIST criteria)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

### Simon 2-stage design

- If  $\geq 1$  response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If  $\geq 4$  responses in Stage 2, expand or breakout

### Tumor assessments

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

### Statistical methods

- $ORR_{first}$ , ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI
- DOR

### Key inclusion criteria

- Histologically confirmed lung cancers for which no curative therapy exists
- Documented *EGFR* exon 18 mutation by local method (any CAP/CLIA-certified lab)
- Prior treatment with *EGFR* or pan-HER TKI allowed (afatinib, dacomitinib, osimertinib etc)
- ECOG status of 0 to 2
- RECIST 1.1 disease only

### Key exclusion criteria

- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding
- Known *KRAS* activating co-mutation

# EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Baseline demographics and patient characteristics

Patient characteristics	Safety/Efficacy evaluable patients (n=11)
Median (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 checkpoint inhibitor, n (%)	3 (27)
Prior chemotherapy, n (%)	6 (55)
<b>Prior tyrosine kinase inhibitor, n (%)</b>	<b>10 (91)</b>
gefitinib/erlotinib (reversible 1 <sup>st</sup> gen EGFR TKI)	7 (58)
osimertinib (irreversible EGFR T790M TKI)	3 (25)
afatinib (irreversible pan-HER TKI)	2 (17)

# EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Efficacy summary

Parameter	Efficacy evaluable patients (n=11)	TKI Pre-Treated (n=10)
Objective response (confirmed), <sup>a</sup> n	<b>4</b>	<b>4</b>
CR	0	0
PR	4	4
Objective response rate, % (95% CI)	<b>36 (11–69)</b>	<b>40 (12–74)</b>
Best overall response, n	<b>6</b>	<b>6</b>
CR	0	0
PR	6	6
Best overall response rate, % (95% CI)	<b>54 (23–83)</b>	<b>60 (26–88)</b>
Median DOR, <sup>b</sup> months (95% CI)	<b>7.5 (4.0–NE)</b> <b>(1.9*, 4.0, 7.5, 9.2*)</b>	<b>7.5 (4.0–NE)</b> <b>(1.9*, 4.0, 7.5, 9.2*)</b>
Clinical benefit, <sup>c</sup> n	<b>8</b>	<b>8</b>
CR or PR	4	4
SD ≥16 weeks	4	4
Clinical benefit rate, % (95% CI)	<b>73 (39–94)</b>	<b>80 (44–97)</b>
Median PFS time to event, months (95% CI)	<b>6.9<sup>b</sup> (2.1–NA)</b>	<b>9.1 (3.7–NA)</b>

<sup>a</sup> 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

<sup>b</sup> Kaplan-Meier analysis in safety population. <sup>c</sup> 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, \* response ongoing



# **EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Most common treatment emergent adverse events >10%**

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

# EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Characteristics of treatment emergent diarrhea

	Lung EGFR (N) (N = 11)
<b>Incidence of diarrhea, n (%)<sup>a</sup></b>	
Any grade	5 (45.5)
Grade 1	4 (36.4)
Grade 2	1 (9.1)
<b>Grade 3</b>	<b>0</b>
<b>Action taken with neratinib, n (%)</b>	
Leading to temporary hold	0
Leading to dose reduction	0
Leading to permanent discontinuation	0
<b>Diarrhea leading to hospitalization, n (%)</b>	0
<b>Time to first diarrhea, median (range) in days</b>	15 (3 – 253)
<b>Time to first grade 2 diarrhea, median (range) in days</b>	8 (8 – 8)
<b>Duration of grade 2 diarrhea per episode, median (range) in days</b>	2 (1 – 2)

# Historical response rates of afatinib in NSCLC patients with *EGFR* exon 18 mutations (G719X)

**Table 3. Response Rates With Afatinib in Patients With NSCLC Harboring Uncommon Mutations**

Mutation Type		CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DCR, n (%)	ORR, n (%)	DoR, Mo (95% CI)
<b>EGFR TKI-naïve patients</b>								
TKI-naïve patients →	Major uncommon mutation (n = 110)	5 (4.5)	61 (55.5)	35 (31.8)	9 (8.2)	101 (91.8)	66 (60.0)	17.1 (11.0-20.8)
	G719X (n = 55)	4 (7.3)	31 (56.4)	16 (29.1)	4 (7.3)	51 (92.7)	35 (63.4)	17.1 (10.3-22.0)
	L861Q (n = 47)	0 (0.0)	28 (59.6)	14 (29.8)	5 (10.6)	42 (89.4)	28 (59.6)	13.8 (7.4-20.6)
	S768I (n = 8)	1 (12.5)	4 (50.0)	3 (37.5)	0 (0.0)	8 (100.0)	5 (62.5)	NR (15.9-NR)
	Compound (n = 35)	0 (0.0)	27 (77.1)	5 (14.3)	3 (8.6)	32 (91.4)	27 (77.1)	16.6 (13.8-18.7)
	With major uncommon mutation (n = 23)	0 (0.0)	18 (78.3)	4 (17.4)	1 (4.3)	22 (95.7)	18 (78.3)	17.1 (14.7-NR)
	Exon 20 insertion (n = 70)	2 (2.9)	15 (21.4)	41 (58.6)	12 (17.1)	58 (82.9)	17 (24.3)	11.9 (5.4-26.7)
	T790M (n = 25)	0 (0.0)	6 (24.0)	13 (52.0)	6 (24.0)	19 (76.0)	6 (24.0)	4.7 (3.8-11.0)
	Others (n = 23)	0 (0.0)	15 (65.2)	5 (21.7)	3 (13.0)	20 (87.0)	15 (65.2)	9.0 (3.5-11.9)
<b>EGFR TKI-pretreated patients</b>								
TKI-pre-treated patients →	Major uncommon mutation (n = 32)	0 (0.0)	8 (25.0)	14 (43.8)	10 (31.3)	22 (68.8)	8 (25.0)	4.9 (2.0-18.0)
	G719X (n = 19)	0 (0.0)	2 (10.5)	10 (52.6)	7 (36.8)	12 (63.2)	2 (10.5)	10.0 (2.0-18.0)
	L861Q (n = 11)	0 (0.0)	5 (45.5)	3 (27.3)	3 (27.3)	8 (72.7)	5 (45.5)	4.4 (4.3-8.4)
	S768I (n = 2)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)	1 (50.0)	NR
	Compound (n = 21)	0 (0.0)	6 (28.6)	10 (47.6)	5 (23.9)	16 (76.2)	6 (28.6)	16.7 (9.9-21.8)
	With major uncommon mutation (n = 8)	0 (0.0)	3 (37.5)	3 (37.5)	2 (25.0)	6 (75.0)	3 (37.5)	16.7 (9.9-16.7)
	Exon 20 insertion (n = 21)	0 (0.0)	3 (14.3)	9 (42.9)	9 (42.9)	12 (57.1)	3 (14.3)	3.7 (2.7-10.1)
	T790M (n = 64)	0 (0.0)	12 (18.8)	31 (48.4)	21 (32.8)	43 (67.2)	12 (18.8)	6.1 (2.6-7.9)
Others (n = 25)	0 (0.0)	9 (36.0)	8 (32.0)	8 (32.0)	17 (68.0)	9 (36.0)	6.3 (0.8-11.3)	

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; PD, progressive disease; ORR, overall response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; NR, not reported.

## Milestones for neratinib in EGFR exon 18 mutant lung cancer cohort in SUMMIT study

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- The success criteria for the 1<sup>st</sup> stage and 2<sup>nd</sup> stage of the Simon's 2-stage design has been met
  - Enrollment in the 2<sup>nd</sup> stage is continuing up to a total of 30 patients
- Anticipate presentation of additional data from SUMMIT in patients with EGFR exon 18 mutant lung cancer in H1 2021
- Anticipate scheduling meeting with FDA to discuss potential accelerated approval strategy for patients with EGFR exon 18 mutant lung cancer who have been treated with a prior EGFR TKI in 2021