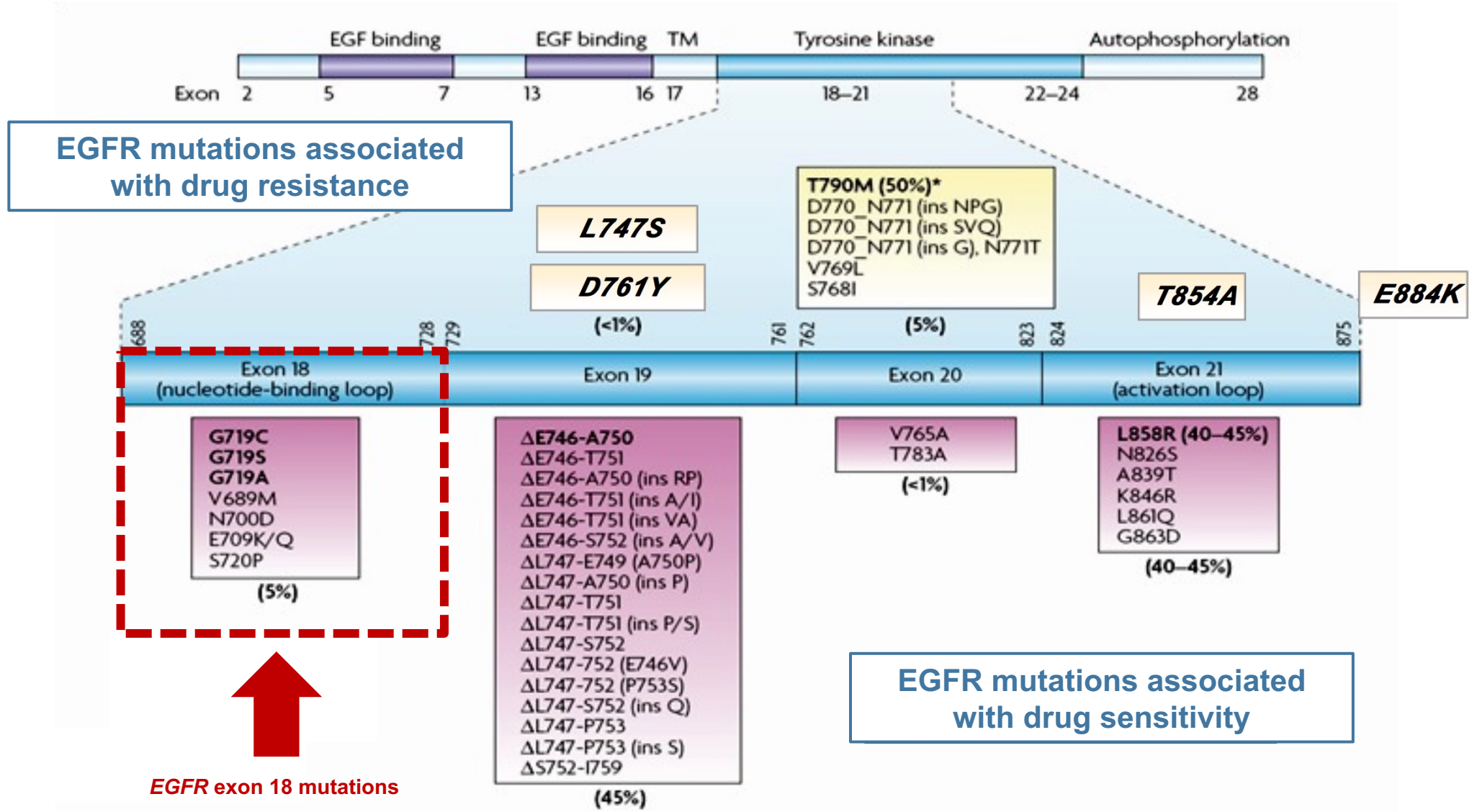
SUMMIT (PUMA-NER-5201) Basket Trial

EGFR exon 18 lung cancer cohort update

Puma Biotechnology

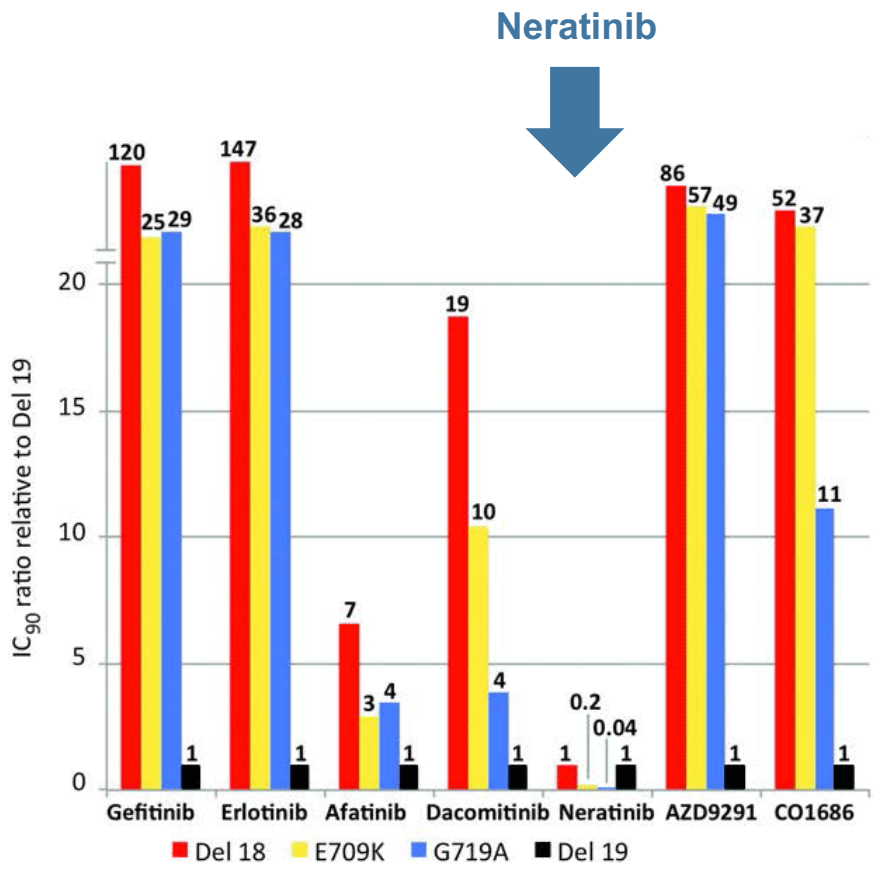
EGFR exon 18 mutations are rare in NSCLC adenocarcinomas: represents only 5% of all *EGFR* mutations detected in lung cancer



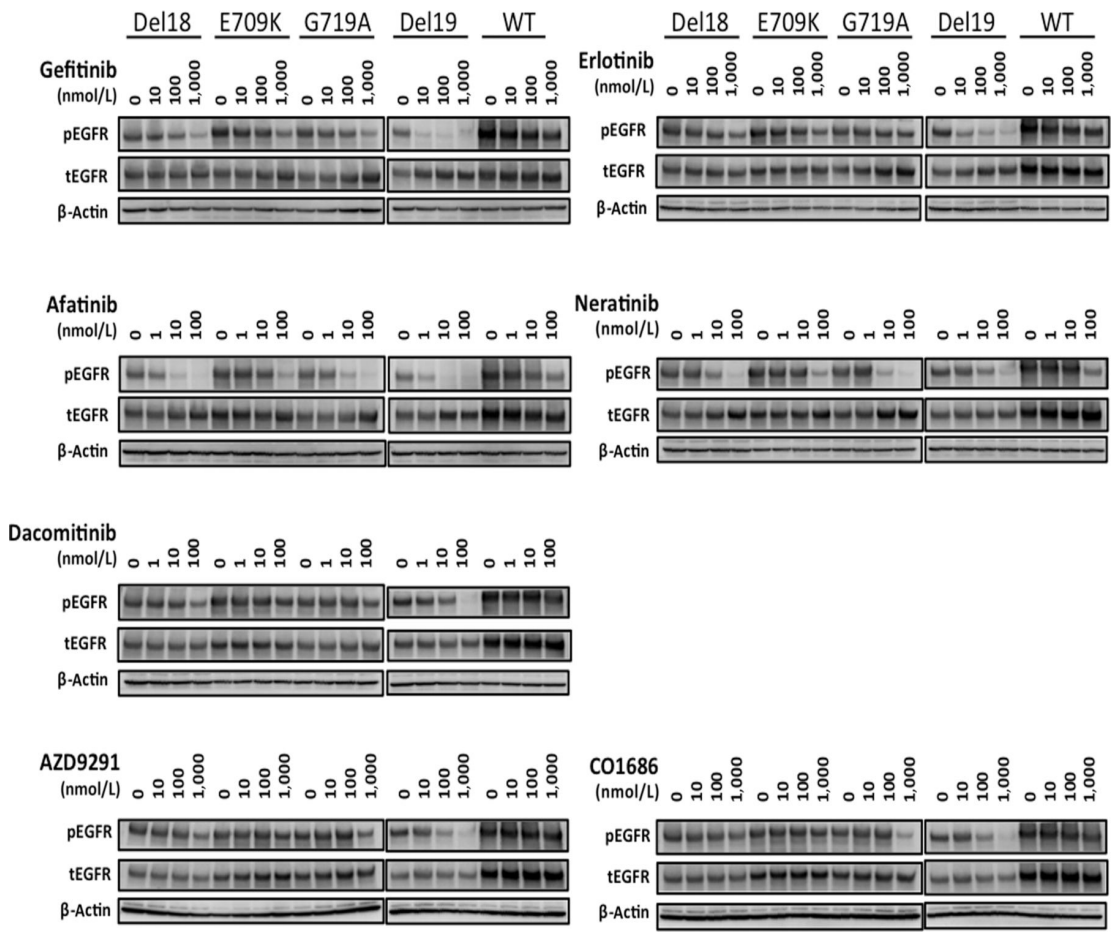
S.V. Sharma et al (2007) *Nature Rev. Cancer*. 7:169–181

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

Comparative TKI affects in *EGFR* exon 18+ cells



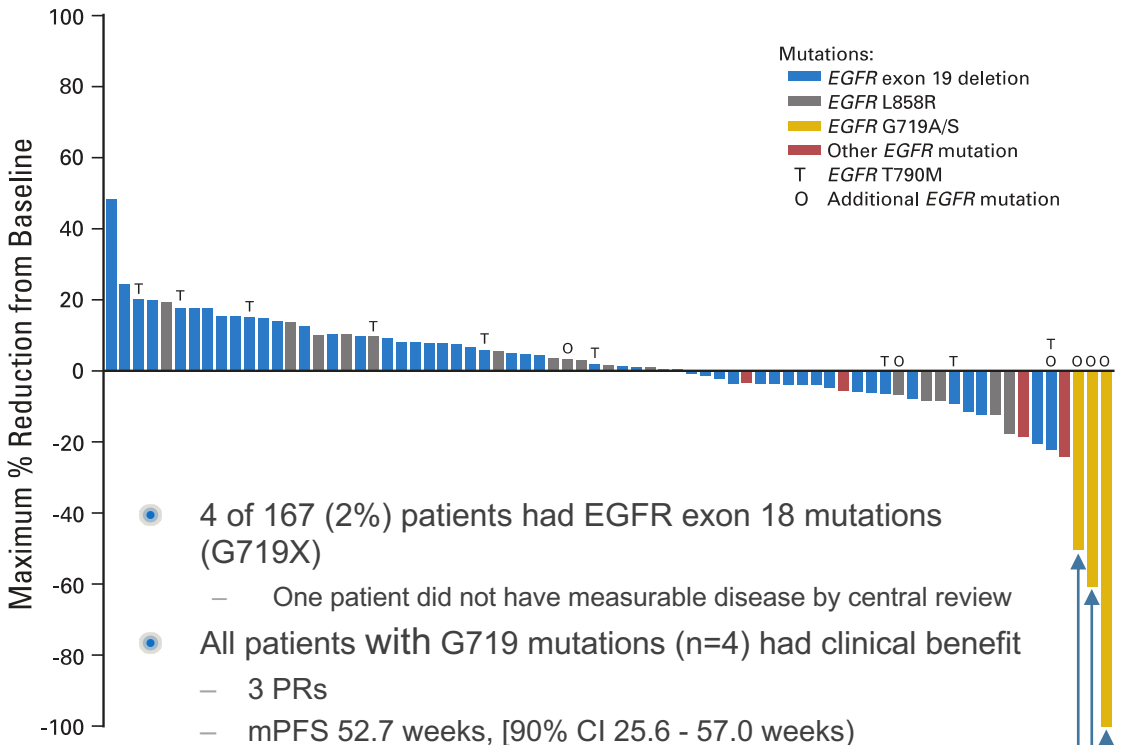
Western blot analyses of transfected HEK293 cells



Source: Kobayashi et al. Clin Cancer Res 2015;21:5305-5313.

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

Phase 2 trial of neratinib in lung cancer



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

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

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 ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥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

Clinical Trials.gov Identifier NCT01953926.

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)
Prior tyrosine kinase inhibitor, n (%)	**10 (91)**
gefitinib/erlotinib (reversible 1st gen EGFR TKI)	7 (58)
osimertinib (irreversible EGFR T790M TKI)	3 (25)
afatinib (irreversible pan-HER TKI)	2 (17)

Data cut-off: 21-Aug-2020

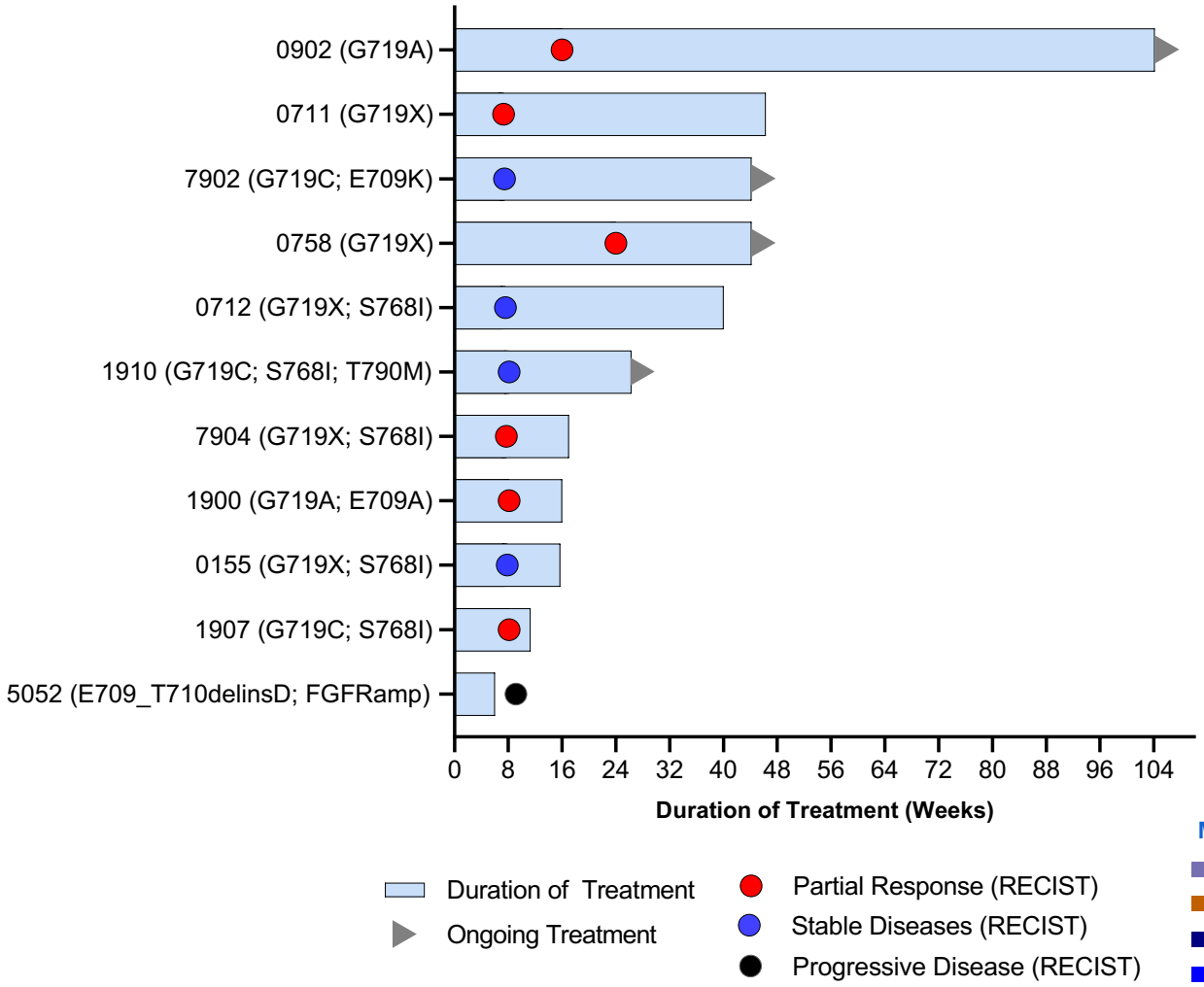
EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Efficacy summary

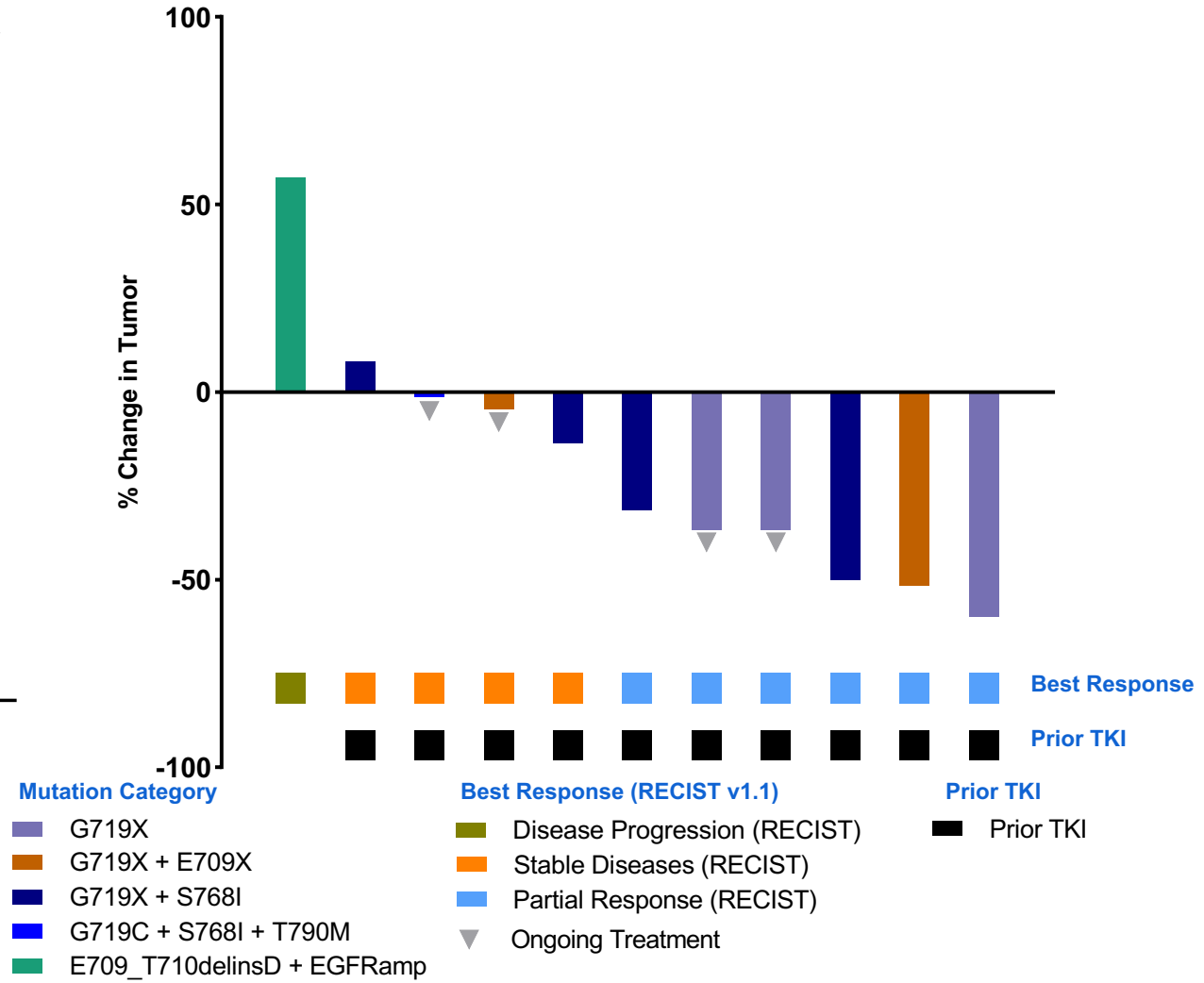
Parameter	Efficacy evaluable patients (n=11)	TKI Pre-Treated (n=10)
Objective response (confirmed),[a] n CR PR Objective response rate, % (95% CI)	**4** 0 4 **36** (11–69)	**4** 0 4 **40** (12–74)
Best overall response, n CR PR Best overall response rate, % (95% CI)	**6** 0 6 **54** (23–83)	**6** 0 6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

[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, * response ongoing

Data cut-off: 21-Aug-2020

EGFR exon 18 mutant lung cancer cohort receiving neratinib monotherapy: Treatment duration, best response and best change in tumor





Data cut-off: 21-Aug-2020

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

TEAE	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 cut-off: 21-Aug-2020

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

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

Data cut-off: 21-Aug-2020

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

TKI-naïve patients

TKI-pre-treated patients

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)
EGFR TKI-naive 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)
EGFR TKI-pretreated 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.

Yang *et al*. Journal of Thoracic Oncology (2020) 15(5): 803-815

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

- The success criteria for the 1st stage and 2nd stage of the Simon's 2-stage design has been met
  - Enrollment in the 2nd 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