Activity of afatinib/cetuximab in patients with *EGFR* mutant non-small cell lung cancer and acquired resistance to EGFR inhibitors

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Disclosures

- **Presenter, Yelena Y. Janjigian:**
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Afatinib*

- **Afatinib is an oral, irreversible ErbB Family Blocker that blocks signalling from EGFR (ErbB1), HER2 (ErbB2) and ErbB4 receptors, and phosphorylation of ErbB3[1]**
- **LUX-Lung 1: Afatinib after failure of prior chemotherapy and erlotinib or gefitinib[2]**
  - **Median PFS: 3.3 months**
  - **Response rate: 7%**
- **LUX-Lung 5: Afatinib in treatment-refractory NSCLC patients[3]**
  - **Median PFS: 3.3 months**
  - **Response rate: 8%**

EGFR = epidermal growth factor receptor;
HER = human epidermal growth factor receptor;
PFS = progression-free survival; NSCLC = non-small cell lung cancer.

1. Solca F, et al. *J Pharmacol Exp Ther* 2012; Epub ahead of print;
2. Miller VA, et al. *Lancet Oncol* 2012;13:528–38;
3. Schuler MH, et al. *J Clin Oncol* 2012;30(Suppl.): Abstract 7557.

*Afatinib is an investigational compound. Its safety and efficacy have not yet been fully established.

Study background

- **Acquired resistance to erlotinib/gefitinib is associated with an EGFR T790M mutation in ~50% of cases[1]**
- **Dual inhibition of EGFR by afatinib and cetuximab induces near-complete regression in T790M transgenic murine lung tumour models[2]**
- **Afatinib 40 mg daily + cetuximab 500 mg/m^2 every 2 weeks, is tolerable, with encouraging activity in patients with acquired resistance[3]**

1. Sequist LV, et al. *Ann Rev Med* 2008;59:429–92;
2. Regales L, et al. *J Clin Invest* 2009;119:3000–10;
3. Janjigian Y. *J Clin Oncol* 2011;29(Suppl.): Abstract 7525.

Trials to overcome acquired resistance

Treatment	RR (%)	Reference
EGFR TKI + everolimus	0	Riely, et al. *CCR* 2007
XL647	4	Pietanza, et al. *JTO* 2012
Everolimus	2	Soria, et al. *Ann Oncol* 2009
Neratinib	3	Sequist, et al. *JCO* 2010
IPI-504	4	Sequist, et al. *JCO* 2010
PF00299804	5	Campbell, et al. *PASCO* 2010
PF00299804	15* (only two patients with EGFR mutation)	Park, et al. *PASCO* 2010
Erlotinib + XL184	8* (only one patient with EGFR mutation)	Pietanza, et al. *JTO* 2012
Erlotinib + cetuximab	**0**	**Janjigian, et al. *CCR* 2011**
Dasatinib/erlotinib vs. dasatinib	0	Johnson, et al. *JTO* 2011
Afatinib/placebo	**7**	**Miller, et al. *Lancet Oncol* 2012**

*The number of patients enrolled into the trial with acquired resistance to EGFR TKIs was low.
RR = relative risk; TKIs = tyrosine kinase inhibitors.

Hypothesis

We hypothesized that the combination of afatinib and cetuximab would overcome acquired resistance to erlotinib or gefitinib in patients with NSCLC

Methods: Study design

- **Phase Ib, open-label, multicentre trial in the USA and The Netherlands**
- **Primary endpoints: RECIST 1.1 response and PFS, with imaging at Weeks 4, 8 and 12, and every 8 weeks thereafter**
- **Key eligibility criteria:**

Inclusion

- Pathologically confirmed NSCLC
- Presence of EGFR drug-sensitizing mutations or RECIST response, or SD ≥6 months on prior EGFR TKI
- Gefitinib/erlotinib as last systemic treatment
- Disease progression on treatment with erlotinib or gefitinib within 30 days
- Biopsy (available) at time of acquired resistance
- ECOG performance status 0–2

Exclusion

- Prior treatment with EGFR-targeting antibodies
- Symptomatic brain metastases or disease progression only in CNS

RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease;
ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system.

Baseline patient characteristics

	T790M mutation status*		
	T790M+	T790M–	Total†*
n	53	42	100
Median age, years (range)	57 (31 to 82)	60 (43 to 79)	59 (31 to 82)
Women, n (%)	40 (76)	29 (69)	72 (72)
Ethnicity, Asian/non-Asian, %	19/81	17/83	17/83
Baseline ECOG, 0/1/2, %	24/74/2	21/67/12	22/72/6
Time since diagnosis (*years*), median (range)	2.2 (0.4 to 10.5)	2.4 (0.6 to 6.6)	2.3 (0.4 to 10.5)
Time on prior erlotinib/gefitinib (*years*), median (range)	1.6 (0.2 to 6.8)	1.5 (0.5 to 5.8)	1.6 (0.2 to 6.8)
Prior chemotherapy, n (%)	41 (77)	30 (71)	75 (75)
EGFR mutation			
Del 19, n (%)	33 (62)	30 (71)	63 (63)
L858R, n (%)	18 (34)	12 (29)	32 (32)
Other,‡ n (%)	2 (4)	–	2 (2)

*Five patients not classified: Two with uninformative biopsy for T790M, two EGFR wild type (WT) and one whose EGFR mutation was untested;
†This study is ongoing: 100 eligible patients who have initiated treatment for at least 6 months are reported here;
‡EGFR exon 18 mutation and exon 19 insertion.

Safety and tolerability in all patients

- **Data reported on the first 100 patients treated:**
  - **Median duration: 4.7 months; range: 3 days to 21+ months**

Patients with adverse event*	n=100		
	Grade 1–2	Grade ≥3	All grades
Rash/acne,† n	79	18	97
Diarrhea, n	64	7	71
Fatigue,† n	52	9	61
Nausea, n	50	3	53
Xerosis, n	49	3	52
Stomatitis,† n	50	1	51
Nail effect,† n	48	0	48
Discontinuations			
Disease progression, n	63		
Adverse events‡, n	19		
Other, n	5		

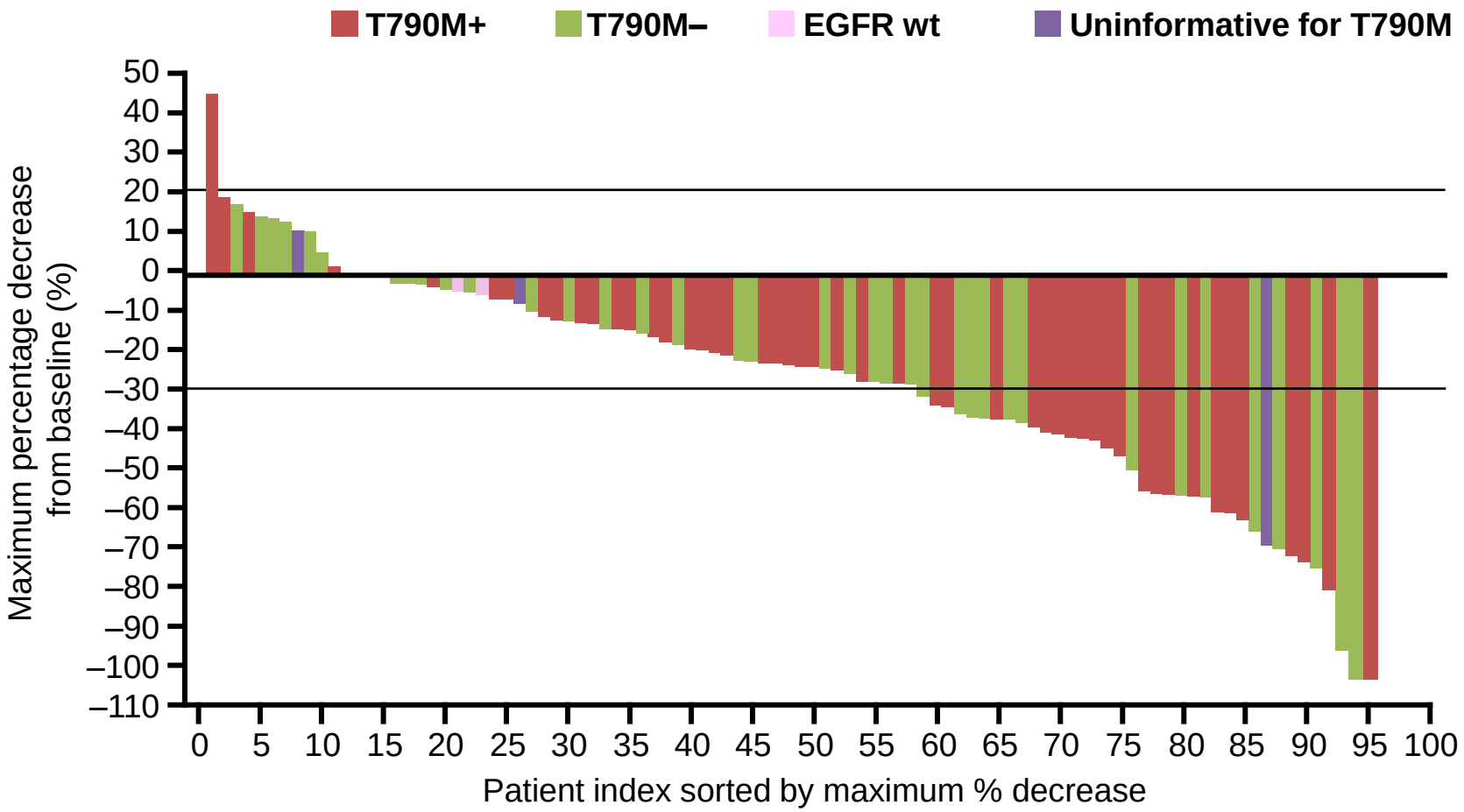
*Adverse event by grouped term and remaining preferred terms; †Grouped terms.
‡All Adverse Events – regardless of drug relationship. 13 patients still on study.

Responses at MTD

	T790M mutation status*		
	T790M+	T790M–	Total*
Total treated, n	53	39	96
Confirmed PR, n (%)	17 (32)	11 (28)	29 (30)
Duration of confirmed response (months), median (range)	6.4 (2.5 to 15.6)	9 (3.7 to 15.6)	8 (2.5 to 15.6)
SD	26 (49)	14 (36)	43 (45)
Clinical benefit (any PR + SD)	43 (81)	25 (64)	72 (75)
Progression of disease	7 (13)	8 (21)	15 (16)
Non-evaluable for confirmed response†	3 (6)	6 (15)	9 (9)

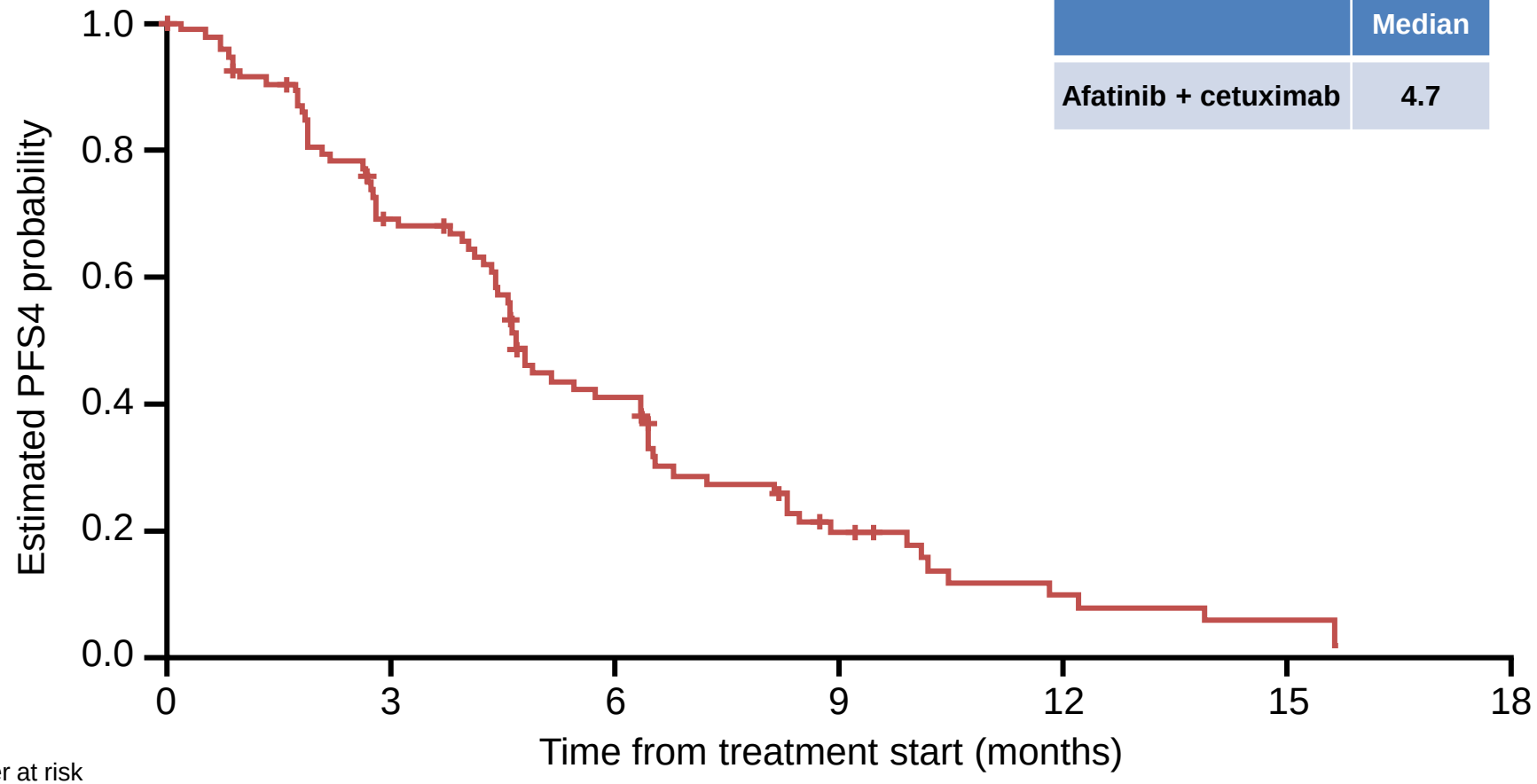
***Four patients EGFR WT or T790M status unknown. Total treated at MTD (n=96).** Data were evaluated up to 6 August 2012.
†Non-evaluable or missing for best overall response.
PR = partial response.

Afatinib + cetuximab at MTD: Responses by T790M mutation



PFS at MTD

	Median
Afatinib + cetuximab	4.7



Number at risk

Afatinib + cetuximab	96	59	32	12	5	3	0

MTD: Afatinib 40 mg daily + cetuximab 500 mg/m^2 every 2 weeks

MTD = maximum tolerated dose; PSF4 = progression-free survival at 4 months.

Conclusions

- **Confirmed response rate 30% in heavily pre-treated population with T790M-positive and T790M-negative tumors**
- **75% of study participants with PR+SD, with a median duration of response of 8 months**
- **Efforts are ongoing to elucidate the mechanisms underlying the tumors regressions and eventual progression on the combination**
- **Afatinib + cetuximab should be further explored**

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    - **University Medical Center Groningen, The Netherlands**
    - **VU University Medical Center, The Netherlands**
  - **Boehringer Ingelheim (study sponsor)**

Additional slides

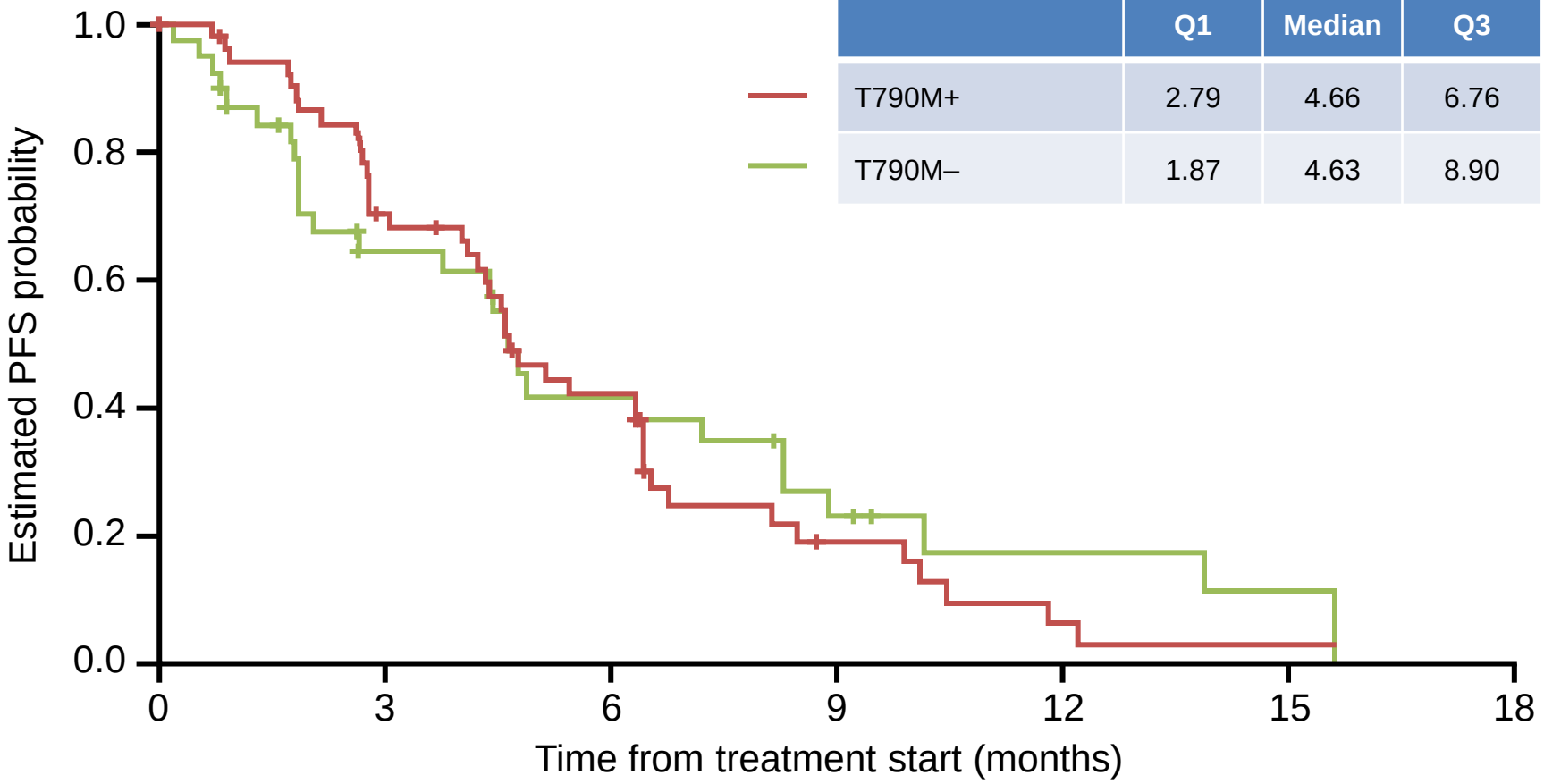
PFS by T790M (±) and (Del 19/L858R) status

	T790M+	T790M–	Del 19+	L858R+
Total evaluable, n	53	39	61	31
Patients progressed or died, n (%)	42 (79)	29 (74)	48 (79)	23 (74)
PFS time (months) (95% CI)				
25th percentile* (Q1)	2.79 (1.87–4.23)	1.87 (0.82–4.40)	1.87 (1.70–2.79)	4.33 (2.66–4.66)
Median*	4.66 (4.10–6.43)	4.63 (2.06–8.31)	4.59 (2.79–5.45)	6.43 (4.40–8.31)
75th percentile* (Q3)	6.76 (6.34–10.48)	8.90 (4.89–15.63)	7.22 (5.45–11.82)	8.47 (6.50–10.18)

*Median, 25th and 75th percentiles are calculated from the Kaplan-Meier curve.
CI = confidence interval.

Kaplan-Meier of PFS by T790M mutation status

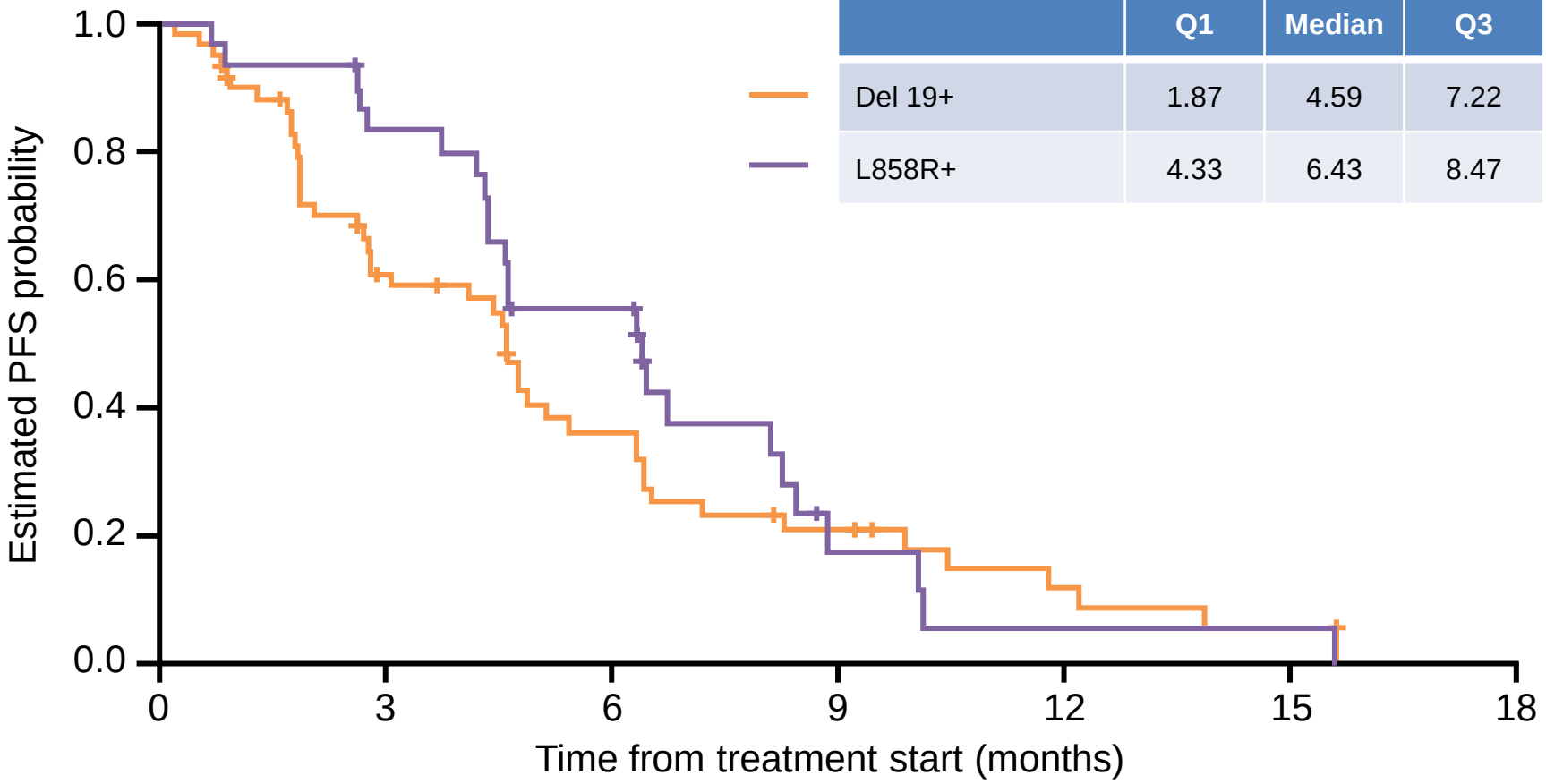
	Q1	Median	Q3
T790M+	2.79	4.66	6.76
T790M–	1.87	4.63	8.90



Number at risk							
T790M+	53	34	19	6	2	1	0
T790M–	39	21	12	6	3	2	0

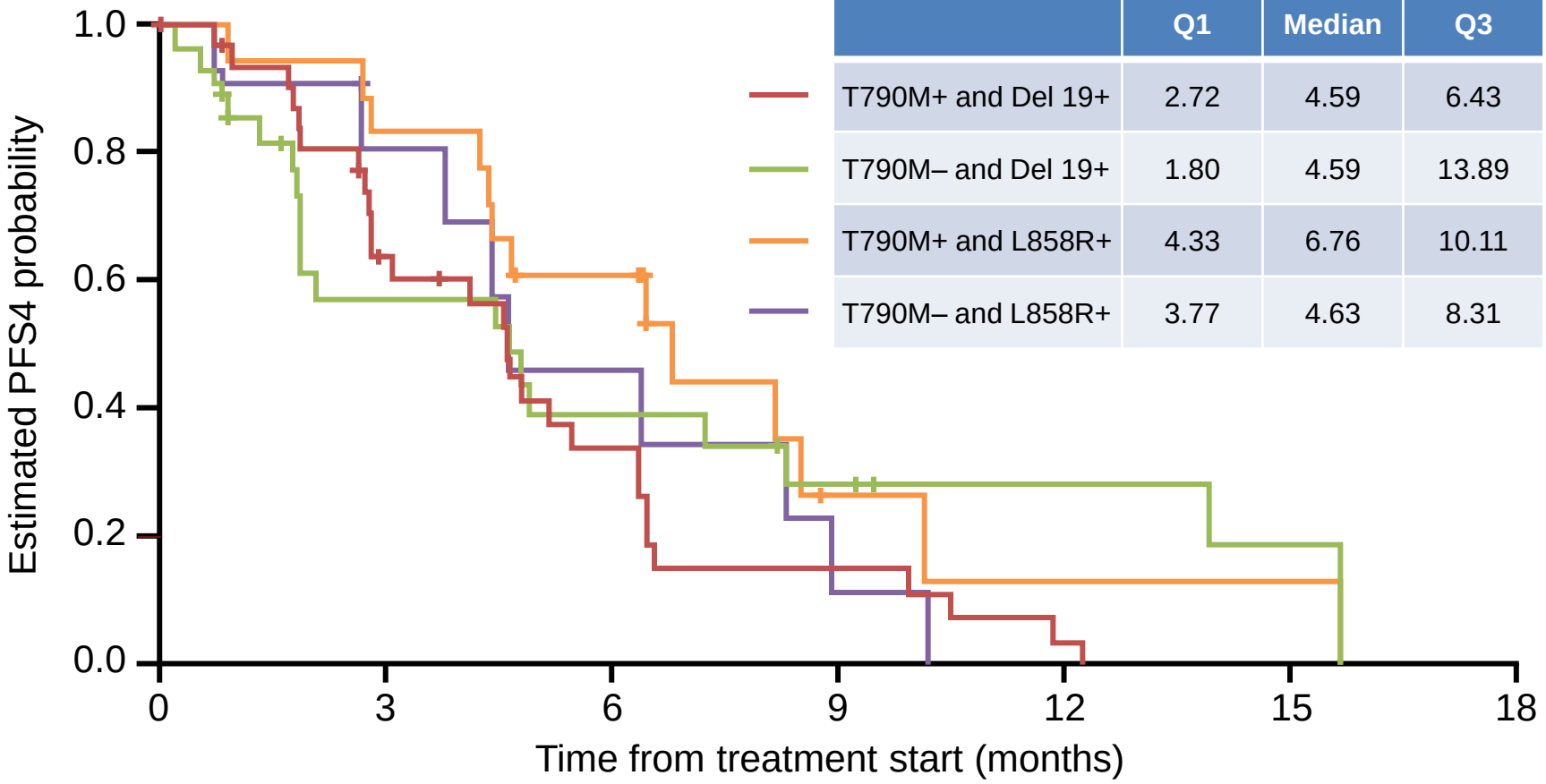
Kaplan-Meier of PFS by Del 19/L858R mutation status

	Q1	Median	Q3
Del 19+	1.87	4.59	7.22
L858R+	4.33	6.43	8.47



Number at risk							
Del 19+	61	32	17	9	4	2	0
L858R+	31	24	15	3	1	1	0

Kaplan-Meier of PFS by T790M and Del 19/L858R mutation status



	Q1	Median	Q3
T790M+ and Del 19+	2.72	4.59	6.43
T790M– and Del 19+	1.80	4.59	13.89
T790M+ and L858R+	4.33	6.76	10.11
T790M– and L858R+	3.77	4.63	8.31

Number at risk

Del 19+	61	32	17	9	4	2	0
L858R+	31	24	15	3	1	1	0