EGFR Exon20 Insertion PDX Models

WuXi AppTec Research Service Division, Oncology & Immunology Unit

2020.09

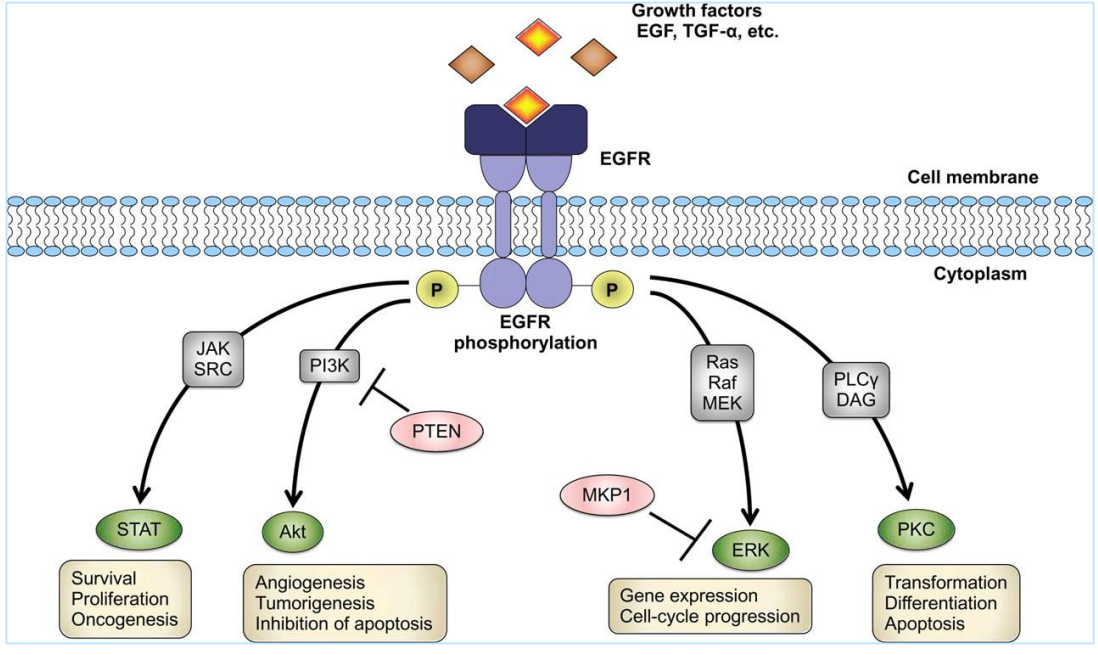
OncoWuXi Newsletter

Outline

- EGFR background as a drug target
- List of EGFR exon20 insertion PDX models
- EGFR exon20 insertion PDX models and SOC data

EGFR signaling pathway

- EGFR is a receptor tyrosine kinase belonging to the ErbB family including three other members (ErbB2/HER-2, erbB3/HER-3, and erbB4/HER-4). Normally EGFR is activated via ligand binding, while its mutations or over-expression could induce ligand-independent activation.
- Upon activation, EGFR can further promote multiple downstream signaling pathways, such as PI3K-AKT pathway, JAK-STAT pathway, RAS-MEK/ERK pathway and PLCr-PKC pathway, resulting in enhanced cell proliferation and survival as well as suppressed cell death.



Exp Biol Med (Maywood) 2011 236(4):375-389

EGFR role in cancers

- Dysregulation of EGFR is often observed in association with carcinogenesis, which can be caused by receptor over expression, mutations or deletions.
  - **Overexpression and/or amplification** of the EGFR gene and its family members are prevalent in many cancer types. Table on the right showed high EGFR expression percentage in different cancer types.
  - EGFR is found to be **mutated** in different cancers, including EGFR exon 20 insertion mutation, exon 19 deletion mutation (such as delE746-A750), L858R sensitive mutation, and T790M drug-resistant mutation in exon 21 (see next slide for details) .

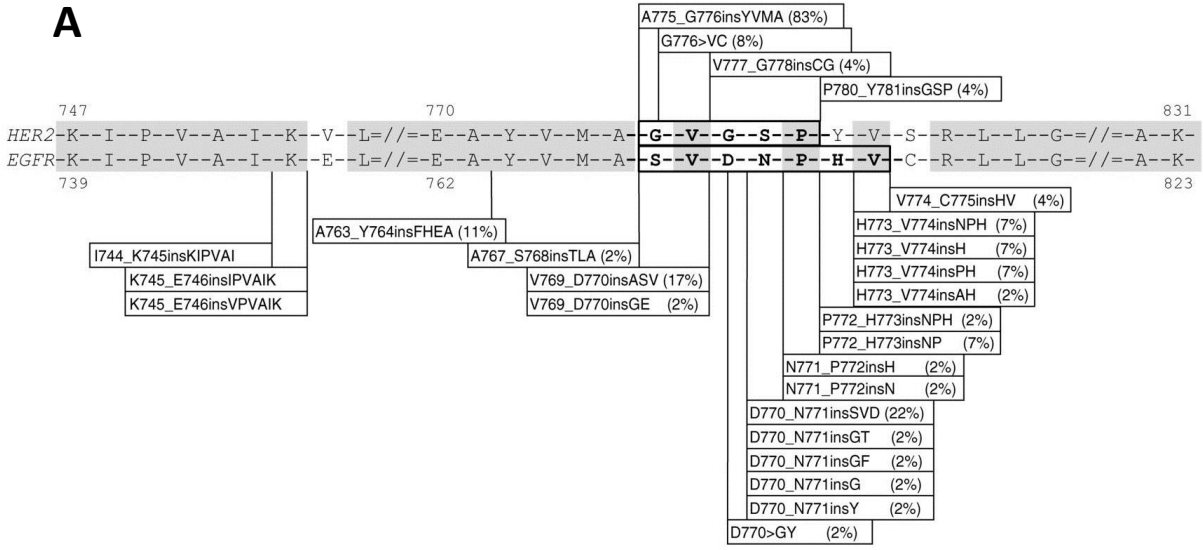
Expression of ErbB receptors in human carcinomas

Type of cancer	EGFR (%)	ErbB-2 (%)	ErbB-3 (%)	ErbB-4 (%)
Lung	40–80	18–60	25–85	NA*
Breast	14–91	9–39	22–90	82
Stomach	33–74	8–40	35–100	NA
Colon	25–77	11–20	65–89	NA
Esophagus	43–89	7–64	64	NA
Liver	47–68	0–29	84	61
Pancreas	30–50	19–45	57–63	81
Prostate	40–80	40–80	22–96	NA
Kidney	50–90	0–40	0	NA
Bladder	35–86	9–50	30–56	30
Ovary	35–70	8–32	85	93
Head and neck	36–100	17–53	81	28–69

*NA, not assessed.

Endocrine-Related Cancer (2003) 10 1–21

Response to EGFR TKIs of NSCLCs harboring EGFR exon 20 insertion



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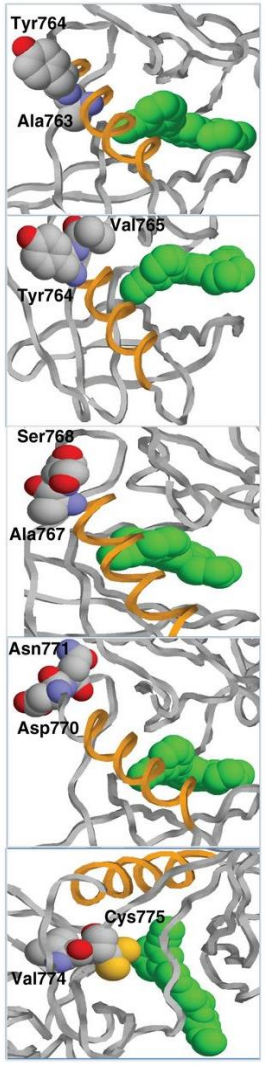


Predicted effect of insertion	Response data
A763_Y764insFQEA: likely to cause significant rearrangement of the C helix 753-766 (orange). The insertion does not affect the drug-binding pocket directly but the disturbance of the helix may reduce drug-binding affinity.	None reported.
Y764_V765insHH: affects C-terminus of the C helix 753-766 helix (orange). The insertion does not affect the drug-binding pocket directly but the disturbance of the helix may reduce drug-binding affinity.	None reported. One patient reported with prolonged stable disease for 10 mo on gefitinib (ref. 33).
A767_S768insTLA: affects the loop region after the C helix 753-766 (orange) and does not affect the drug-binding pocket directly. Effect on drug binding may be less significant.	None reported.
D770ins_N771insSVD: affects a loop region after the C helix 753-766 (orange) and does not affect directly the drug-binding pocket. The effect on drug binding may be less significant.	Resistance reported but some responders. One patient with partial response to gefitinib for 24 mo (ref. 8).
V774_C775insHV: directly affects a loop region that forms a drug-binding pocket. This is likely to result in a significant reduction of the drug-binding affinity.	None reported. Two patients in our study showed no response (1 treated with single agent erlotinib, 1 patient treated with neratinib).

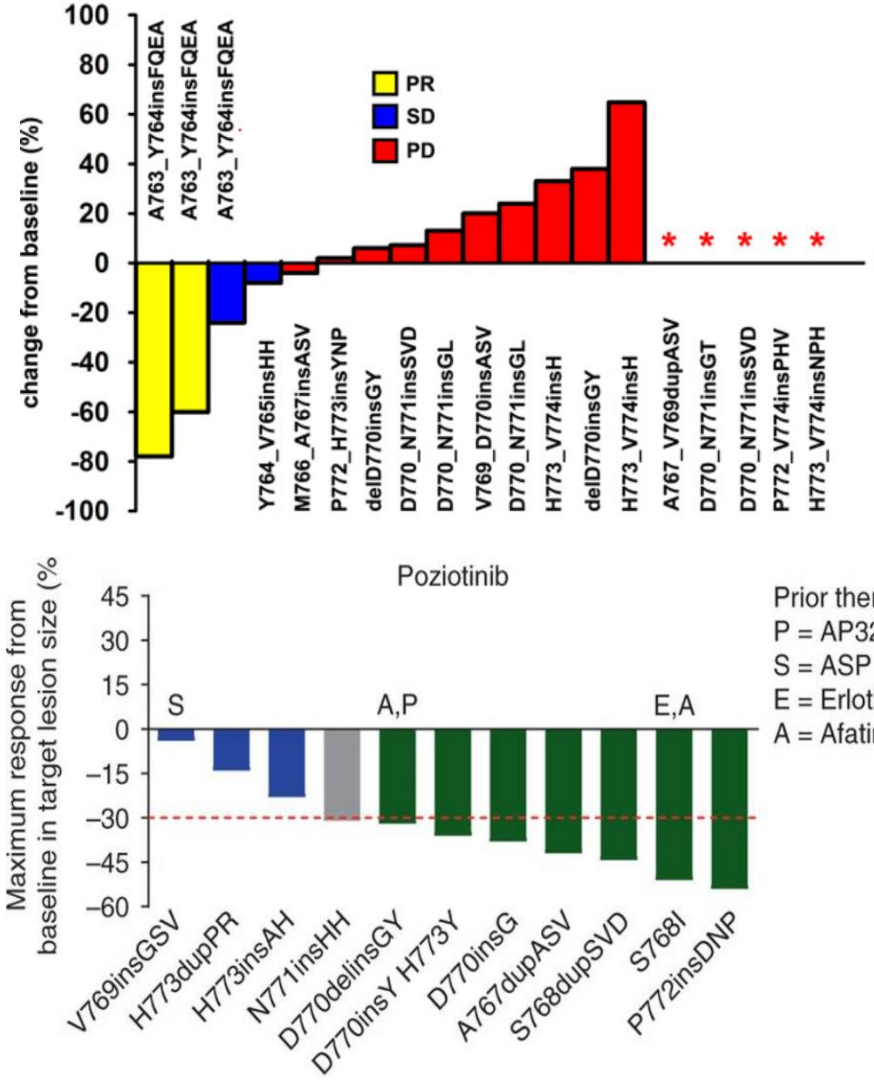
A: Positions of the *EGFR* exon 20 insertions identified and comparison with the spectrum of *EGFR* exon 19 and *HER2* insertion mutations detected

B: Modeling of EGFR exon 20 insertions using the 3-dimensional structure of the EGFR kinase domain predicts different interactions with the erlotinib-binding region

Molecular Cancer Therapeutics, 2013, 12(2):220-229.

Response to EGFR TKIs of NSCLCs harboring EGFR exon 20 insertion

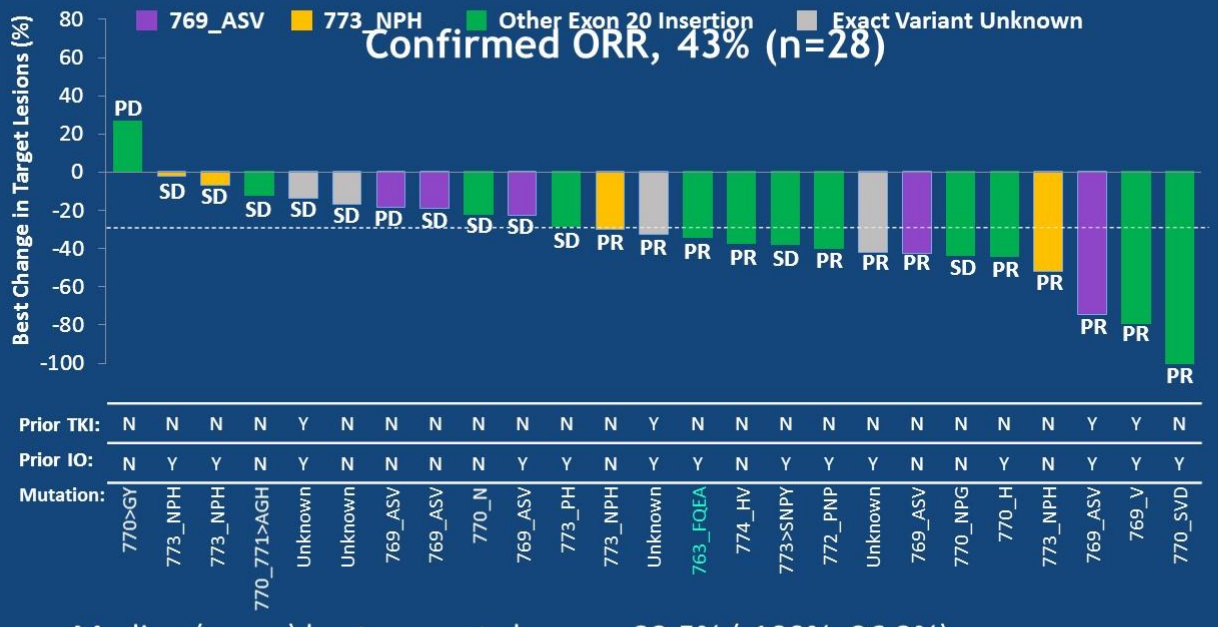
- Waterfall plot of best responses of target tumor lesions after exposure to gefitinib or erlotinib. A763_Y764insFQEA bearing tumors decreased in size after exposure to erlotinib, while other mutations had either minimal changes or increase in target lesions.
- Waterfall plot of the first 11 patient responses to poziotinb on clinical trial NCT03066206. Objective partial responses are shown in green, stable disease is shown in blue, and unconfirmed response is shown in gray.



Sci Transl Med. 2013 Dec 18; 5(216) 216ra177
Nat Med. 2018 May; 24(5): 638–646.

Response to EGFR TKIs of NSCLCs harboring EGFR exon 20 insertion

TAK-788 Antitumor Activity in Patients With *EGFR* Exon 20 Insertions



Exon 20 Insertion Variant	No. of Patients	No. of Confirmed Responders, n	Confirmed ORR
769_ASV	5	2	40%
773_NPH	4	2	50%
Exact variant unknown	4	2	50%
Other	15	6	40%

- Median (range) best percent change: -32.5% (-100%, 26.3%)
- Three patients were excluded from the waterfall plot: 1 patient had nonmeasurable baseline target lesions, and 2 patients had no follow-up scans

IO, immuno-oncology therapy; PD, progressive disease.

· *Janne PA, et al.* 2019 ASCO Abstract9007

EGFR inhibitors launched or in clinical trial

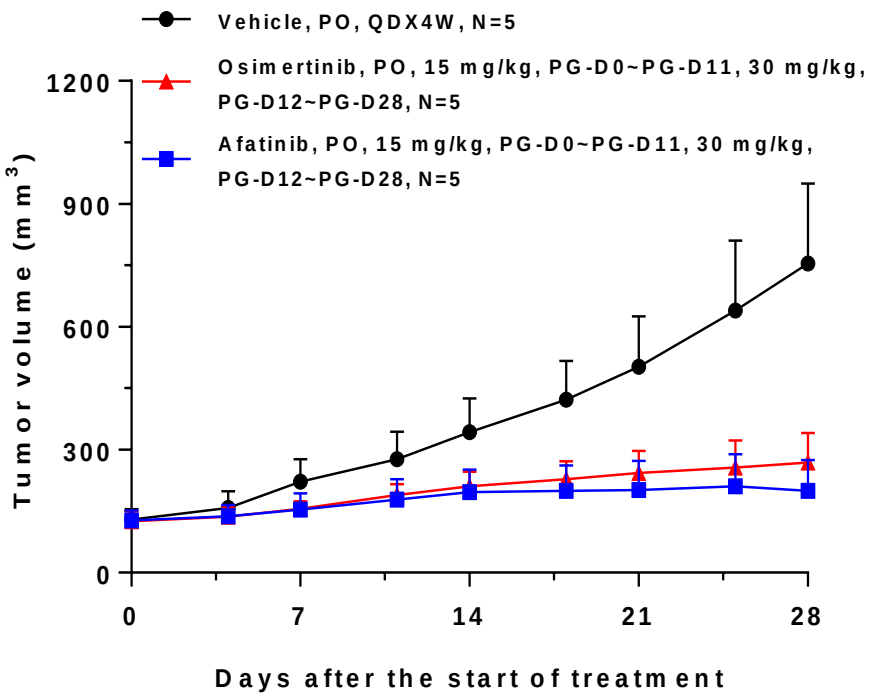
Drug	Inventor	Target	Indications	Status
Gefitinib	AstraZeneca	EGFR inhibitor	EGFR-positive NSCLC	Launched in 2003
Erlotinib	Genentech	EGFR inhibitor	EGFR-positive NSCLC	Launched in 2005
Cetuximab (Ebtiux)	BMS/Eli Lilly	Anti-EGFR mono-antibody	Head and Neck cancer, colorectal cancer	Launched in 2006
Panitumumab	Amgen	Anti-EGFR mono-antibody	Colorectal cancer	Launched in 2006
Afatinib	Boehringer Ingelheim	EGFR/HER2 inhibitor	EGFR-positive NSCLC	Launched in 2013
Dacomitinib	Pfizer	EGFR/HER2 inhibitor	EGFR-positive NSCLC	Launched in 2018
Tagrisso (AZD9291)	AstraZeneca	EGFR T790M inhibitor	NSCLC	Launched in 2015
Poziotinib	Spectrum Pharmaceuticals	Pan-EGFR inhibitor	EGFR exon20 insertion NSCLC	Phase II
AP32788 (TAK-788)	Millennium Pharmaceuticals	EGFR/HER2 Inhibitor	EGFR exon 20 insertion NSCLC	Phase I/II

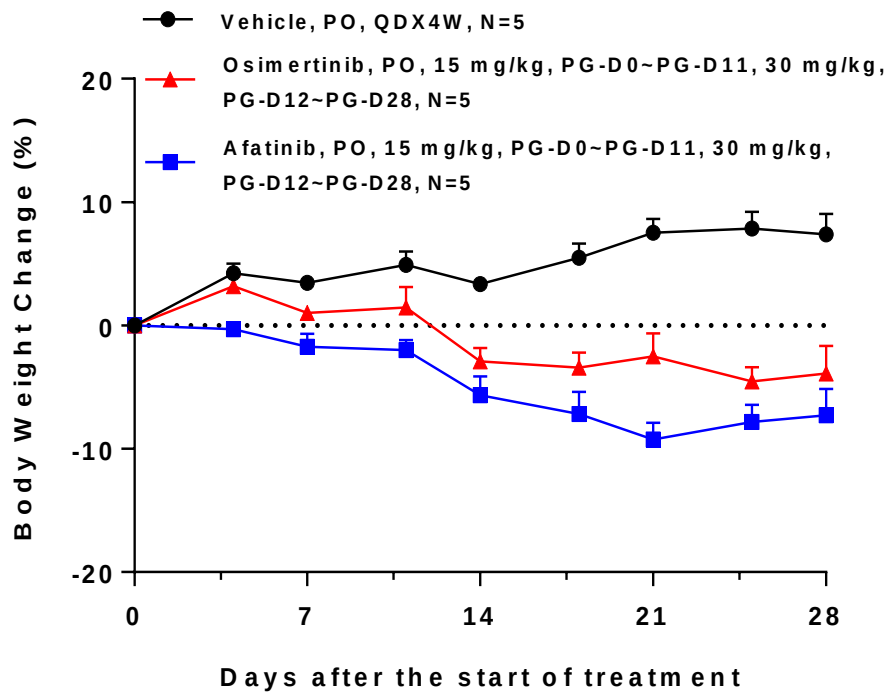
EGFR exon20 insertion PDX models

Model ID	Cancer type	Drugs tested	Dosage	TGI (%)	Model genomics
LU-01-0426	Lung cancer	Afatinib	15-30 mg/kg, p.o., QD	88.6	Exon20: p.V769_D770insASV
		Osimertinib	15-30 mg/kg, p.o., QD	77.1	
LU-01-0493		Afatinib	15 mg/kg, p.o., QD	31.3	Exon20: p.P772_H773insH
		Osimertinib	15 mg/kg, p.o., QD	76.8	
		Poziotinib	0.5 mg/kg, p.o., QD	28.0	

EGFR TKIs on LU-01-0426 PDX model

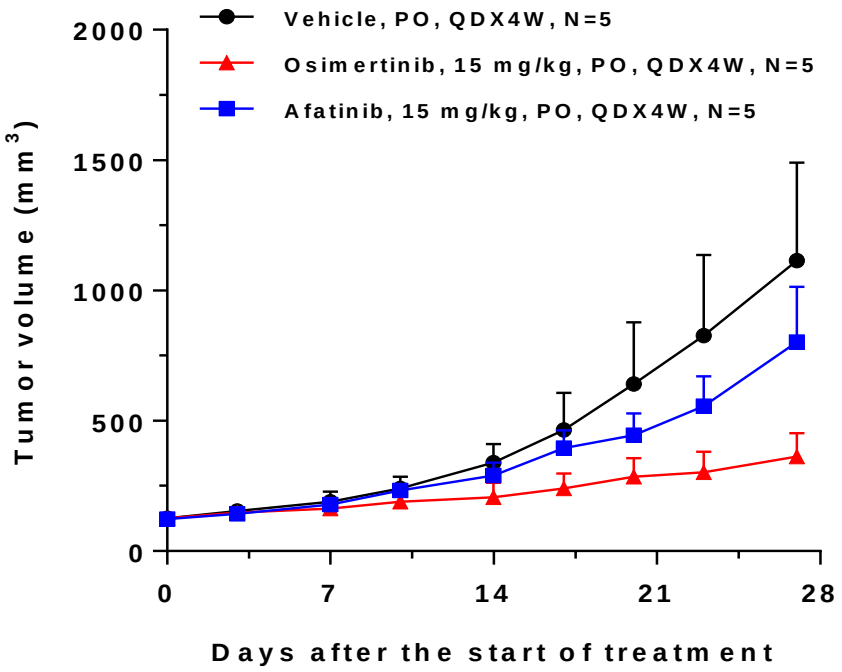
Model ID	Cancer Type	Pathology diagnosis	Gender	Age	Tumor Grade	Tumor Stage
LU-01-0426	Lung cancer	Adenosquamous carcinoma	Female	58	NA	T2N0M0

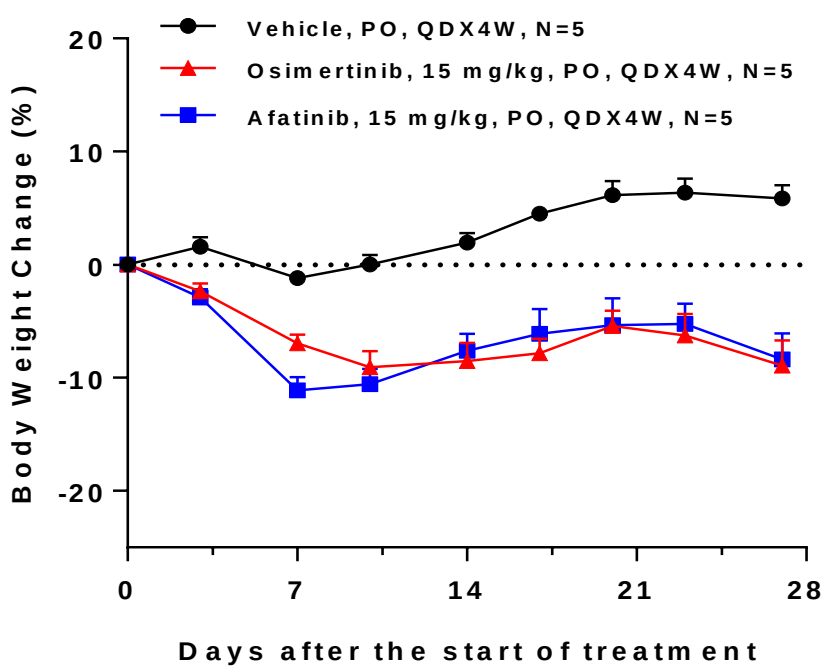




EGFR TKIs on LU-01-0493 PDX model

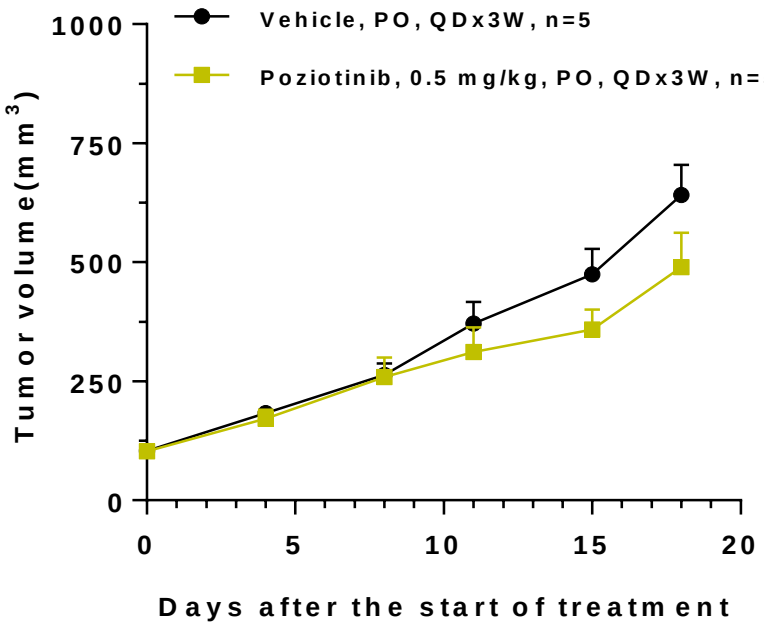
Model ID	Cancer Type	Pathology diagnosis	Gender	Age	Tumor Grade	Tumor Stage
LU-01-0493	Lung cancer	Adenocarcinoma	Male	56	G3	T2bN2M0

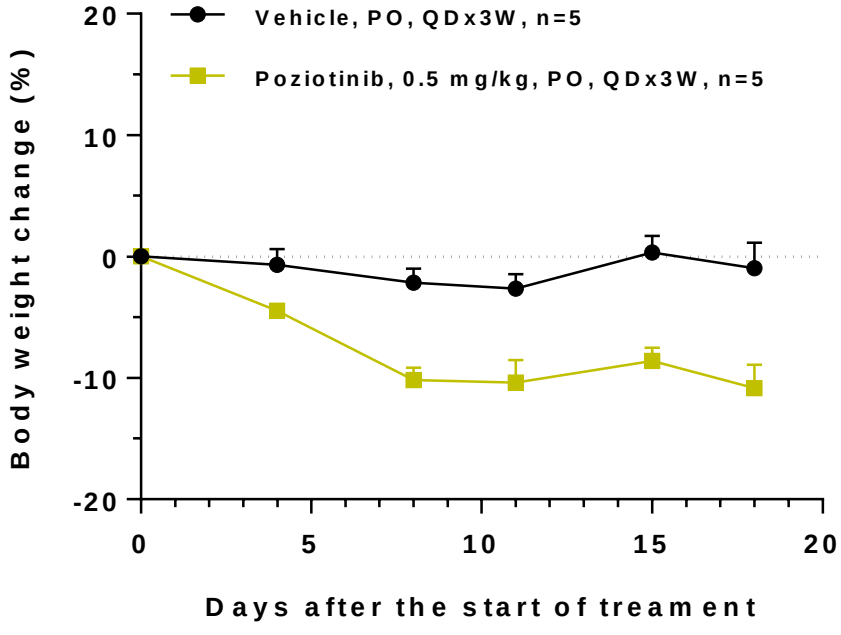




EGFR TKIs on LU-01-0493 PDX model

Model ID	Cancer Type	Pathology diagnosis	Gender	Age	Tumor Grade	Tumor Stage
LU-01-0493	Lung cancer	Adenocarcinoma	Male	56	G3	T2bN2M0





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