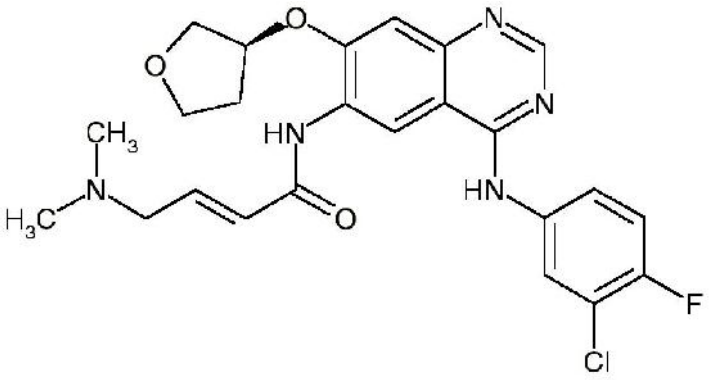
BIBW-2992、PF00299804 和特罗凯的疗效比较

（1）Tovok（Afatinib，BIBW-2992）是勃林格殷格翰公司开发的表皮生长因子受体（EGFR）和人表皮生长因子受体 2（HER2）酪氨酸激酶的强效、不可逆的双重抑制剂。

CAS Number:439081-18-2

Mol. Formula: C24H25ClFN5O3

Mol. Weight: 485.94



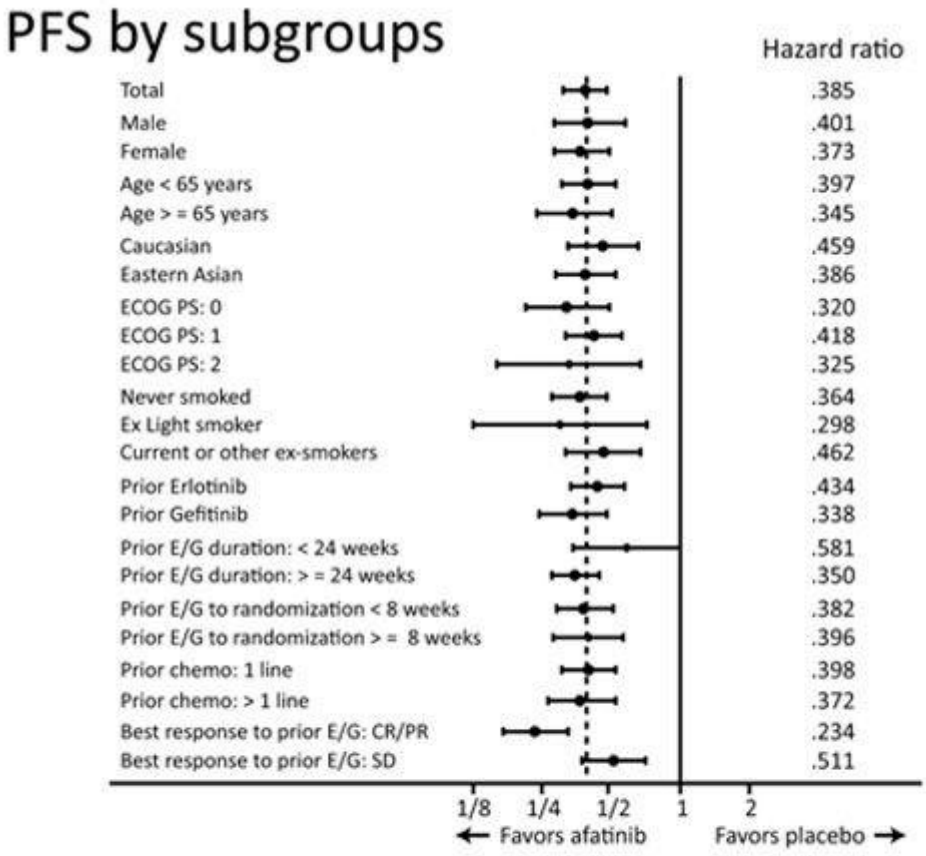


Figure 2. Afatinib and progression-free survival. *CR = complete response; ECOG = Eastern Oncology Group; E/G = erlotinib/gefitinib; PR = partial response; SD = stable disease*

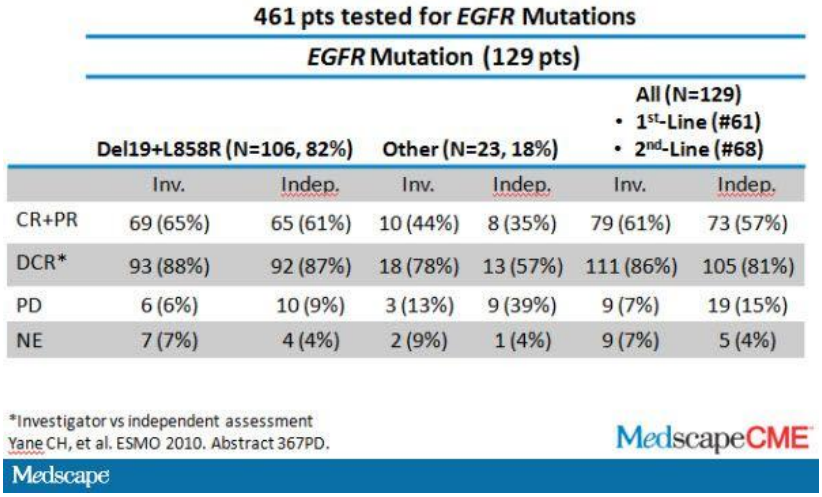


Figure 3. Afatinib in patients with *EGFR* mutations. *CR = complete response; DCR = disease control rate; NE = non-evaluable; PD = progressive disease; PR = partial response; Inv = investigator; Indep. = Independent.*

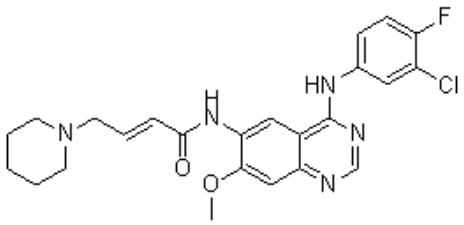
	BIBW2992	lapatinib	canertinib	gefitinib
EGFR-phosphorylation in A431 cells	13	105	22	35
HER2-phosphorylation in NIH-3T3-HER2 cells	71	171	85	2300
HER2-phosphorylation in BT-474 cells	35	99	184	3710
HER2-phosphorylation in NCI-N87cells	48	101	288	541

The EC_{50} values were determined as described in "Materials and Methods", confirmed in independent experiments and reported as nM values.

	BIBW2992 (nM)	**Erlotinib (nM)**
L858R	**4**	**16**
L858R-T790M	**119**	**>10000**
E746_A750del5	**0.9**	**5**
E746_A750del5+T790M	**64**	**>10000**
S752_I759del8	**0.2**	**33**
S752_I759del8+T790M	**103**	**>10000**
L747_A750del4insP	**1**	**5**
L747_A750del4insP+T790M	**60**	**>10000**
L747_P753del7insS	**2**	**0.3**
L747_P753del7insS+T790M	**49**	**>10000**
E746_S752del7insV	**0.2**	**25**
E746_S752del7insV+T790M	**102**	**>10000**
EGFR variant III deletion	**0.9**	**144**

（2）PF-00299804 (dacomitinib)

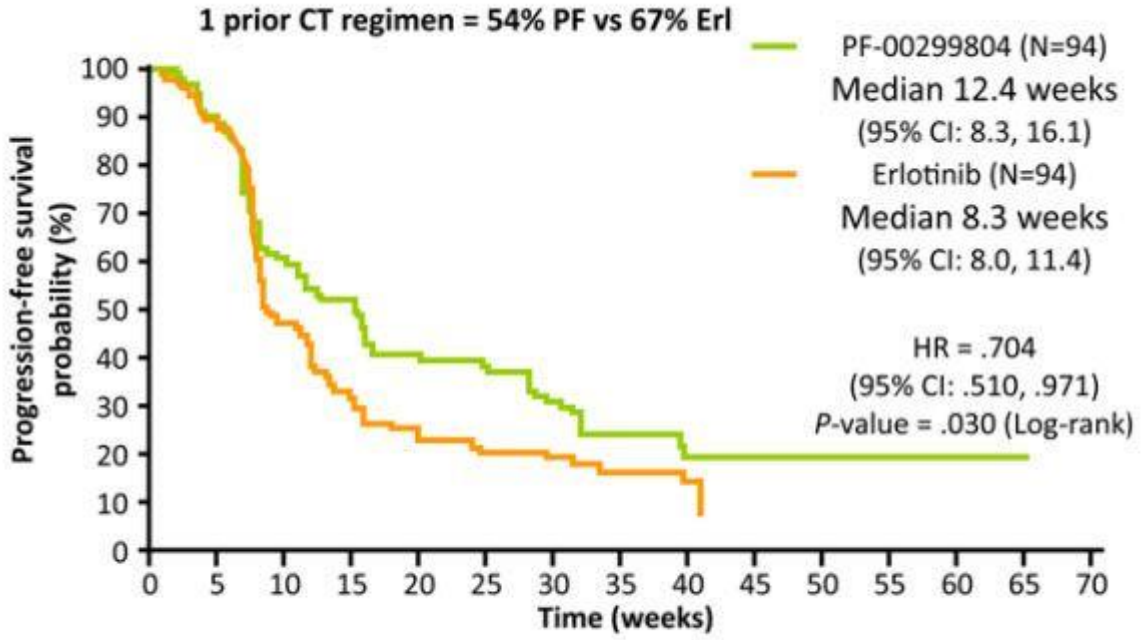
PF-00299804 是辉瑞作为一线药物治疗晚期非小细胞肺癌（NSCLC）患者使用而研制的 pan-HER 抑制剂，作用于 HER 家族当中的 HER1、HER2 和 HER4。



	In vitro Kinase Assays				
	EGFR	ERRB2	ERRB4	Cellular EGFR (NIH3T3/EGFR)	Cellular ERRB2 (NIH3T3/ERRB2)
	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)	IC_{50} (nM)
PF-00299804	**6.0**	**45.7**	**73.7**	**5.8**	**41**
gefitinib	**3.1**	**343**	**476**	**14.4**	**>500**
erlotinib	**0.56**	**512**	**790**	**19.3**	**299**

PF-00299804 in *vitro* Activity against EGFR, HER2 and KRASmut NSCLC Cell Lines

Cell Line	EGFR mutation	ERBB2 mutation	K-*ras* mutation	Gefitinib IC_{50}	PF00299804 IC_{50}
A549	WT	WT	G12S	> 10 μM	> 10 μM
H441	WT	WT	G12V	> 10 μM	4 μM
Calu-3	WT	WT HER2 +++	WT	1.4 μM	0.063 μM
H1819	WT	WT HER2 +++	WT	0.42 μM	0.029 μM
H1781	WT	Ins G776V, C	WT	> 10 μM	0.275 μM
HCC 827	Del E746_A750	WT	WT	0.008 μM	0.002 μM
HCC 4006	Del L747_E749	WT	WT	0.050 μM	0.004 μM
PC-9	Del E746_A750	WT	WT	0.023 μM	0.002 μM
H3255	L858R	WT	WT	0.075 μM	0.007 μM
H3255 GR	L858R/T790M	WT	WT	> 10 μM	0.119 μM
H1975	L858R/T790M	WT	WT	> 10 μM	0.44 μM



Ramalingam SS, et al. ESMO 2010. Abstract 365PD.

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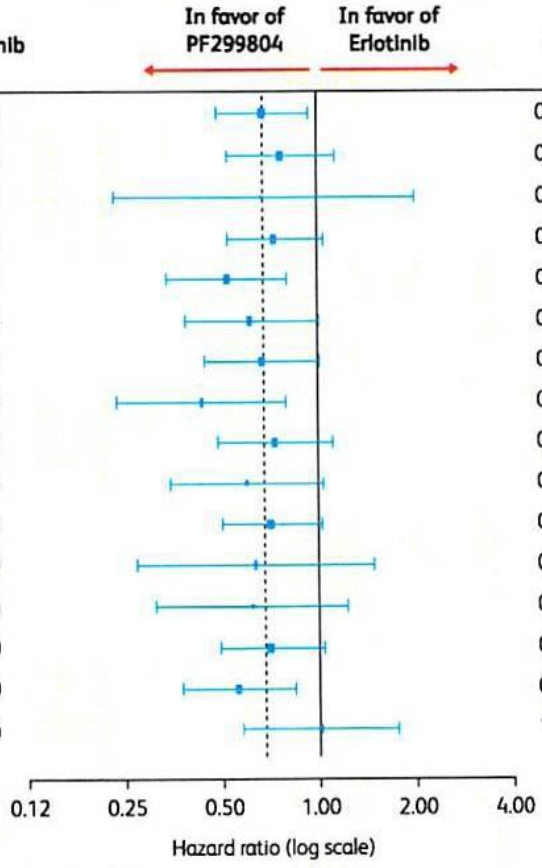
Figure 2. Progression-free survival in patients receiving PF299804 versus patients receiving erlotinib.

Population	PF299804 n	Erlotinib n	Hazard ratio (95% CI)
All patients	94	94	0.68 (0.49–0.95)
EGFR wt	57	65	0.78 (0.53–1.14)
EGFR mutant	19	11	0.69 (0.24–2.00)
EGFR wt or unknown	75	83	0.74 (0.52–1.05)
KRAS wt	56	61	0.52 (0.34–0.80)
KRAS wt and *EGFR* wt	37	49	0.62 (0.39–1.00)
Histology: adenocarcinoma	62	61	0.67 (0.44–1.02)
Histology: nonadenocarcinoma	32	33	0.70 (0.41–1.19)
Gender: male	55	56	0.74 (0.49–1.12)
Gender: female	39	38	0.60 (0.35–1.04)
Smoking status: ever-smoker	75	74	0.72 (0.50–1.03)
Smoking status: non-smoker	19	20	0.64 (0.27–1.50)
Ethnicity: East Asian	23	24	0.62 (0.31–1.23)
Ethnicity: non-East Asian	71	70	0.71 (0.49–1.04)
Age: <65	66	60	0.56 (0.37–0.85)
Age: ≥65	28	34	1.01 (0.58–1.77)



CI = confidence interval; EGFR = epidermal growth factor receptor; wt = wild type.
— = overall population hazard ratio.

	ORR w/ TKI %	DCR w/ TKI %	Median PFS (mos)	PFS HR (95% CI)
OPTIMAL (erlotinib) n=154; 82 E	82.9	96.3	13.1	.16 (.10-.26)
SLCG (erlotinib) n=217; 217 E	70.6	89.8	14.0	N/A
CALGB30406 (erlotinib) n=33; 33 E	NR	NR	15.7	N/A
IPASS (gefitinib) n=261; 132 G	71.2	91.7	9.5	.48 (.36-.64)
First-SIGNAL (gefitinib) n=42; 26 G	84.6	88.5	8.4	.61 (.31-1.22)
WJTOG3405** (gefitinib) n=172; 86 G	62.1	93.1	8.4	.33 (.20-.54)
NEJSG002 (gefitinib) n=228; 114 G	73.7	89.5	10.8	.30 (.22-.41)

*48% pts overall received erlotinib 2L
**data for stage IIIB/IV pts (for overall population: median PFS=9.2 mos; HR .49 [.34-.71])

1. Zhou et al. ESMO 2010. Abstract LBA13; 2. Rosell et al. *N Engl J Med.* 2009;361:958-967; 3. Janne et al. *J Clin Oncol.* 2010;28(15s):7503; 4. Mok et al. *N Engl J Med.* 2009;361:947-957; 5. Lee et al. WCLC 2009. Abstract PRS; 6. Mitsudomi et al. *Lancet Oncol.* 2010;11:121-128; 7. Maemondo et al. *N Engl J Med.* 2010;362:2380-238.

（4）BIBW-2992、PF00299804 和特罗凯的副作用比较

参考文献：http://www.current-oncology.com/index.php/oncology/article/view/877/685

EGFR-TKI	Reference (study name)	Description	Patients (n)	Grades of rash (%) All	Grades of rash (%) ≥3	Grades of diarrhea (%) All	Grades of diarrhea (%) ≥3
Erlotinib	All studies	Dose: 150 mg		33–79	3–10	10–69	0–17
	Herbst *et al.*, 2005 [28] (TRIBUTE)	Phase III; erlotinib 150 mg vs. placebo; first-line combination therapy with paclitaxel and carboplatin; chemotherapy-naïve	Total: 1079 Erlotinib: 539 Placebo: 540	61.7	7.2	67.9	12.4
	Shepherd *et al.*, 2005 [11] (BR.21)	Phase III; erlotinib 150 mg vs. placebo; second- or third-line monotherapy after failure with standard first- or second-line chemotherapy	Total: 731 Erlotinib: 488 Placebo: 243	76	9	55	6
	Cho *et al.*, 2007 [29]	Phase II; second-line erlotinib 150 mg after failure with gefitinib	Total: 21	33.3	4.8	9.5	0
	Gatzemeier *et al.*, 2007 [30] (TALENT)	Phase III; erlotinib 150 mg vs. placebo; first-line combination therapy with gemcitabine and cisplatin; chemotherapy-naïve	Total: 1172 Erlotinib: 586 Placebo: 586	NR	10	40	6
	Jackman *et al.*, 2007 [31]	Phase II; first-line erlotinib 150 mg; chemotherapy-naïve	Total: 80	78.8	6	68.8	5
	Felip *et al.*, 2008 [12]	Phase II; second-line erlotinib 150 mg after failure with platinum-based chemotherapy	Total: 83	61	7	23	2
	Lilenbaum *et al.*, 2008 [32]	Phase II; first-line erlotinib 150 mg vs. chemotherapy (carboplatin and paclitaxel); chemotherapy-naïve	Total: 103 Erlotinib: 52 Chemotherapy: 51	65	8	44	6
	Mok *et al.*, 2009 [33] (FAST-ACT)	Phase II; first-line sequential erlotinib 150 mg and platinum-based doublet chemotherapy [gemcitabine and cisplatin (GC) or carboplatin] vs. chemotherapy alone	Total: 154 GC+erlotinib: 76 GC+placebo: 78	65	3	22	0
	Bennouna *et al.*, 2010 [34]	Phase II; everolimus plus erlotinib 150 mg (EE) vs. erlotinib 150 mg monotherapy (EM); previously-treated patients	Total: 133 EE: 66 EM: 67	NR	NR	NR	EE: 8 EM: 5
	Groen *et al.*, 2010 [35]	Phase II; sunitinib plus erlotinib 150 mg (SE) vs. placebo plus erlotinib 150 mg (PE); 2 or fewer previous chemotherapy regimens, including 1 or more platinum-based regimens	Total: 132	NR	NR	NR	SE: 17.2 PE: 1.6
	Kelly *et al.*, 2010 [36]	Phase IIB; pralatrexate vs. erlotinib 150 mg; previously treated with platinum-based chemotherapy	Total: 201	NR	Erlotinib: ≤10	NR	NR

EGFR-TKI	Reference (study name)	Description	Patients (n)	Grades of rash (%) All	Grades of rash (%) ≥3	Grades of diarrhea (%) All	Grades of diarrhea (%) ≥3
	Scagliotti *et al.*, 2010[37]	Phase III; sunitinib plus erlotinib 150 mg (SE) vs. placebo plus erlotinib 150 mg (PE); 2 or fewer previous chemotherapy regimens	Total: 960	NR	SE: 8.2 PE: 2.5	NR	SE: 10.4 PE: 1.7
	Zhao *et al.*, 2010[38] (ML 22206)	Phase II; erlotinib 150 mg plus capecitabine; first-line in elderly patients with advanced disease	Total: 62	NR	NR	NR	NR
Gefitinib	All studies	Doses: 250 mg and 500 mg		34–75	0–13	27–75	0–25
	Fukuoka *et al.*, 2003[8] (IDEAL 1)	Phase II; second-line gefitinib 250 mg or 500 mg after failure with 1 or 2 chemotherapy regimens, at least 1 platinum-based	Total: 210 250-mg Arm: 104 500-mg Arm: 106	250 mg: 46.6; 500 mg: 68.9	250 mg: 1; 500 mg: 6.6	250 mg: 39.8; 500 mg: 57.5	250 mg: 0; 500 mg: 6.6
	Kris *et al.*, 2003[39] (IDEAL 2)	Phase II; gefitinib 250 mg vs. gefitinib 500 mg after failure with 2 or more chemotherapy regimens containing cisplatin or carboplatin and docetaxel	Total: 221 Gefitinib 250 mg: 106 Gefitinib 500 mg: 115	250 mg: 62; 500 mg: 75	250 mg: 0; 500 mg: 4	250 mg: 57; 500 mg: 75	250 mg: 1; 500 mg: 5
	Giaccone *et al.*, 2004[40] (INTACT 1)	Phase III; gefitinib 250 mg or 500 mg vs. placebo; first-line combination therapy with gemcitabine and cisplatin; chemotherapy-naïve	Total: 1093 Gefitinib 250 mg: 365 Gefitinib 500 mg: 365 Placebo: 363	250 mg: 44.5; 500 mg: 56.7	250 mg: 3.6; 500 mg: 12.6	250 mg: 28.7; 500 mg: 50.8	250 mg: 3.6; 500 mg: 12.0
	Herbst *et al.*, 2004[41] (INTACT 2)	Phase III; gefitinib 250 mg or 500 mg vs. placebo; first-line combination therapy with paclitaxel and carboplatin; chemotherapy-naïve	Total: 1037 Gefitinib 250 mg: 345 Gefitinib 500 mg: 347 Placebo: 345	250 mg: 54.4; 500 mg: 67.3	250 mg: 3.2; 500 mg: 11.7	250 mg: 58.2; 500 mg: 69.3	250 mg: 9.9; 500 mg: 25.4
	Thatcher *et al.*, 2005[13] (ISEL)	Phase III; second- or third-line gefitinib 250 mg vs. placebo after failure of 1 or 2 previous chemotherapy regimens	Total: 1692 Gefitinib: 1129 Placebo: 563	37	2	27	3
	Kim *et al.*, 2008[14] (INTEREST)	Phase III; second-line gefitinib 250 mg vs. docetaxel after failure with up to 2 chemotherapy regimens, at least 1 platinum-based	Total: 1466 Gefitinib: 733 Docetaxel: 733	49.4	2.1	35.0	2.5
	Goss *et al.*, 2009[42] (INSTEP)	Phase II; first-line gefitinib 250 mg vs. placebo; chemotherapy-naïve	Total: 201 Gefitinib: 100 Placebo: 101	34	0	51	3

EGFR-TKI	Reference (study name)	Description	Patients (n)	Grades of rash (%) All	Grades of rash (%) ≥3	Grades of diarrhea (%) All	Grades of diarrhea (%) ≥3
	Mok *et al.*, 2009[43] (IPASS)	Phase III; first-line gefitinib 250 mg vs. carboplatin plus paclitaxel (CP); chemotherapy-naïve	Total: 1217 Gefitinib: 609 CP: 608	66.2	3.1	46.6	3.8
	Sumont *et al.*, 2010[44] (EORTC 08021–ILCP)	Phase III; maintenance gefitinib 250 mg vs. placebo; patients non-progressing on 4 cycles of platinum-based chemotherapy	Total: 175 Gefitinib: 86 Placebo: 87	40	NR	29	NR
Afatinib (BIBW 2992)	All studies	Doses: 20 mg, 40 mg, 50 mg		33–100	0–25	0–100	0–33
	Miller *et al.*, 2010[15] (LUX-Lung 1)	Phase IIb/III; afatinib 50 mg vs. placebo after failure with chemotherapy (including platinum) and erlotinib or gefitinib	Total: 585 Afatinib: 390 Placebo: 195	78	14	87	17
	Yamamoto *et al.*, 2010[17] (LUX-Lung 4)	Phase I; afatinib 20 mg, 40 mg, or 50 mg after failure with any combination of chemotherapy, erlotinib, and gefitinib	Total: 12	20 mg: 33.3 40 mg: 100 50 mg: 66.7	20 mg: 0 40 mg: 0 50 mg: 0	20 mg: 0 40 mg: 66.7 50 mg: 100	20 mg: 0 40 mg: 0 50 mg: 33.3
	Yang *et al.*, 2010[16] (LUX-Lung 2)	Phase II; afatinib 40 mg or 50 mg in patients with activating *EGFR* mutations after failure with 1 chemotherapy regimen and no previous EGFR-TKI	Total: 129	40 mg: 90.0 50 mg: 91.9	40 mg: 6.7 50 mg: 25.3	40 mg: 96.7 50 mg: 93.9	40 mg: 6.7 50 mg: 21.2
	Ongoing study[18] (LUX-Lung 5)	Phase II; afatinib 40 mg plus paclitaxel vs. investigator's choice of single-agent chemotherapy after progression with afatinib monotherapy	Total: 900	NR	NR	NR	NR
	Ongoing study[19] (LUX-Lung 6)	Phase III; afatinib vs. cisplatin plus gemcitabine; first-line in patients with *EGFR*-activating mutation	Total: 330	NR	NR	NR	NR
PF-00299804	All studies	Doses: 15 mg, 30 mg, and 45 mg		68–100	0–15	77–97	0–15
	Janne *et al.*, 2009[20] (A7471002)	Phase II; PF-00299804 45 mg in adenocarcinoma and non-adenocarcinoma patients after failure with at least 1 chemotherapy regimen and erlotinib	Total: 34 Adenocarcinoma: 30 Non-adenocarcinoma: 4	84.9	15.1	81.1	13.2
	Mok *et al.*, 2010[20]	Phase II; first-line PF-00299804 30 mg or 45 mg in advanced NSCLC with *EGFR* mutation	Total: 74	30 mg: 59 45 mg: 58	30 mg: 0 45 mg: 15	30 mg: 77 45 mg: 97	30 mg: 0 45 mg: 15

EGFR-TKI	Reference (study name)	Description	Patients (n)	Grades of rash (%) All	Grades of rash (%) ≥3	Grades of diarrhea (%) All	Grades of diarrhea (%) ≥3
	Ramalingam *et al.*, 2010[19]	Phase II; PF-00299804 45 mg vs. erlotinib 150 mg in advanced NSCLC patients who were erlotinib-naïve and had failed at least 1 chemotherapy regimen	Total: 188 Erlotinib: 94 PF-00299804: 94	Tolerable in both agents		Tolerable in both agents	
	Takahashi *et al.*, 2010[21]	Phase I; PF-00299804 15 mg, 30 mg, or 45 mg in advanced solid-tumour patients who had failed all standards of care	Total: 13	100[a]	45 mg: 15.4	92[a]	NR
	Ongoing study[24] (BR.26)	Phase III; PF-00299804 45 mg vs. placebo in advanced NSCLC patients after failure with at least 1 chemotherapy regimen and erlotinib or gefitinib (or both)	Total: 720	NR	NR	NR	NR
	Ongoing study[25] (A7471028)	Phase II; PF-00299804 45 mg vs. erlotinib 150 mg in advanced NSCLC patients after failure with at least 1 chemotherapy regimen	Total: 160	NR	NR	NR	NR

[a] Adverse events by dose subgroup not given.
NR = not reported; EORTC = European Organisation for Research and Treatment of Cancer.

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EGFR-TKI	*Description*	*Grades (%)*	
		All	*≥3*
Erlotinib 150 mg	All studies	33–79	3–10
	Phase III studies	62–76	3–10
Gefitinib 250 mg and 500 mg	All studies	34–75	0–13
	250 mg	34–66	0–4
	500 mg	57–75	4–13
	Phase III studies	37–67	2–13
	250 mg	37–66	2–4
	500 mg	57–67	12–13
Afatinib 40 mg and 50 mg	All studies	67–100	0–25
	40 mg	90–100	0–7
	50 mg	67–92	0–25
	Phase III studies	78	14
	50 mg		
PF-00299804 30 mg and 45 mg	All studies (phase II)[a]	68–100	0–15
	30 mg	69	0
	45 mg	68–85	15

[a] No phase III study results using PF-00299804 are available to date.

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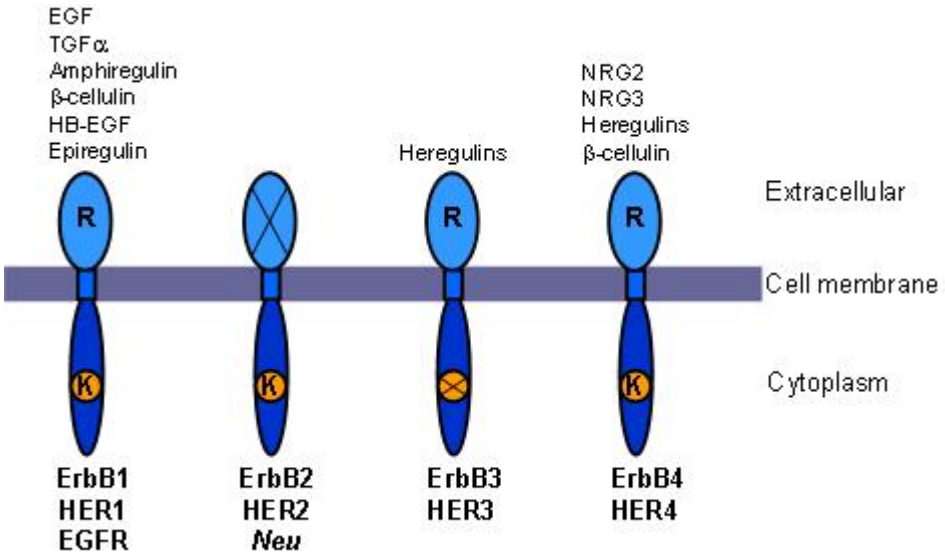
EGFR-TKI	*Description*	*Grade (%)*	
		All	*≥3*
Erlotinib	All studies	10–69	0–17
150 mg	Phase III studies	40–68	2–12
Gefitinib	All studies	27–75	0–25
250 mg and 500 mg	250 mg	27–58	0–10
	500 mg	51–75	5–25
	Phase III studies	27–69	3–25
	250 mg	27–58	3–10
	500 mg	51–69	12–25
Afatinib	All studies	67–100	0–33
40 mg and 50 mg	40 mg	67–97	0–7
	50 mg	87–100	17–33
	Phase III studies		
	50 mg	87	17
PF-00299804	All studies (phase II)[a]	77–97	0–15
15 mg, 30 mg, and 45 mg	30 mg	77	0
	45 mg	81–97	13–15

[a] No phase III study results using PF-00299804 are available to date.

（5）Erb（HER）家族


EGF
TGFα
Amphiregulin
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Heregulins
NRG2
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R
R
R
K
K
K
Extracellular
Cell membrane
Cytoplasm
ErbB1
HER1
EGFR
ErbB2
HER2
Neu
ErbB3
HER3
ErbB4
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