Abstract 338

A7471009: Updates for PFS and OS for Relevant EGFR Mutants Subsets

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Disclosures

- LPA: Pfizer, Roche, AZD, Boehringer, Clovis, BMS, MSD
- MJB: Pfizer, Roche, Boehringer-Ingelheim, AstraZeneca, Eli Lilly
- KOB: Pfizer, Boehringer-Ingelheim, MSD, AstraZeneca, Roche, BMS, Eli Lilly
- TSM: AstraZeneca, Boehringer-Ingelheim, Roche, Pfizer, Eli Lilly, Novartis, Clovis, Amgen, Janssen, BioMarin, Merck Serono, Bristol-Myers Squibb, Aveo, Eisai, Taiho Pharmaceuticals
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- ZG, CBM, IT, and HZ: All are employees of Pfizer

Rationale & Objectives

- Dacomitinib is an irreversible pan-HER TKI
- Encouraging activity has been seen in EGFR mutant lung cancer models
- Dacomitinib has yielded promising results in treatment-naïve patients with EGFR mu+ NSCLC (Study 1017)[1]

N=45	RR: 75.6%
Median PFS: 18.2 months	Median OS: 40.2 months

Dacomitinib showed a favorable trend in efficacy when compared with erlotinib in patients with EGFR-mutant tumors previously treated with 1–2 chemotherapy regimens[2]

[1]Janne et al. *Lancet Oncol* 2014
[2]Kris et al. ASCO 2012

Rationale & Objectives

- The Phase 3 ARCHER 1009 study compared dacomitinib to erlotinib as 2/3L therapy for patients with advanced NSCLC
  - Tissue collection was mandatory to allow analysis of *EGFR*, *KRAS*, and other molecular features[3]
- A pre-planned subgroup analysis for patients with activating mutations [EGFR mu+ (del exon 19 and exon 21 substitution mutations)] was performed
- **Objective:** To describe the outcome of the EGFR mu+ patients treated with dacomitinib or erlotinib in the ARCHER 1009 trial

[3]Ramalingam et al. *Lancet Oncol* 2014

ARCHER 1009 Study Design

Trial design	Endpoints	Study sites
Randomized, double-blind, double-dummy	Primary: PFS (independent review) Secondary: OS, OR, PFS per investigator review, PRO (also powered for OS)	Global (US, EU, Latin America, Australia, and Asia – 25 countries)

Populations
- Co-primary = all and *KRAS* wild-type

Advanced NSCLC, measurable disease
- 1–2 prior chemo
- Tissue required from all subjects

RANDOMIZE

Dacomitinib 45 mg QD

1:1

Erlotinib 150 mg QD

N=800
(actual 878)

Stratifcation at baseline based on:
- Histology (adenocarcinoma vs. nonadenocarcinoma)
- Race (Asian vs. non-Asian and Indian sub-continent)
- ECOG PS 0–1 vs. 2
- Smoking status (never smoker, defined as ≤100 cigarettes, cigars, or pipes in lifetime vs. ever-smoker)

Ramalingam SS, et al. *Lancet Oncol* 2014;15:1369–78

EGFR Mutant Subgroups

	Dacomitinib n (%)	Erlotinib n (%)	Total n (%)
EGFR mutant	**47**	**44**	**91**
Treated	46 (97.9)	44 (100)	90 (98.9)
Ongoing on treatment	*10 (21.3)*	*7 (15.9)*	*17 (18.7)*
Ongoing on study[1]	24 (51.1)	21 (47.7)	45 (49.5)
Activating mutant (exon 19 or 21)	**37**	**39**	**76**
Treated	36 (97.3)	39 (100)	75 (98.7)
Ongoing on treatment	*9 (24.3)*	*6 (15.4)*	*15 (19.7)*
Ongoing on study[1]	20 (54.1)	18 (46.2)	38 (50.0)

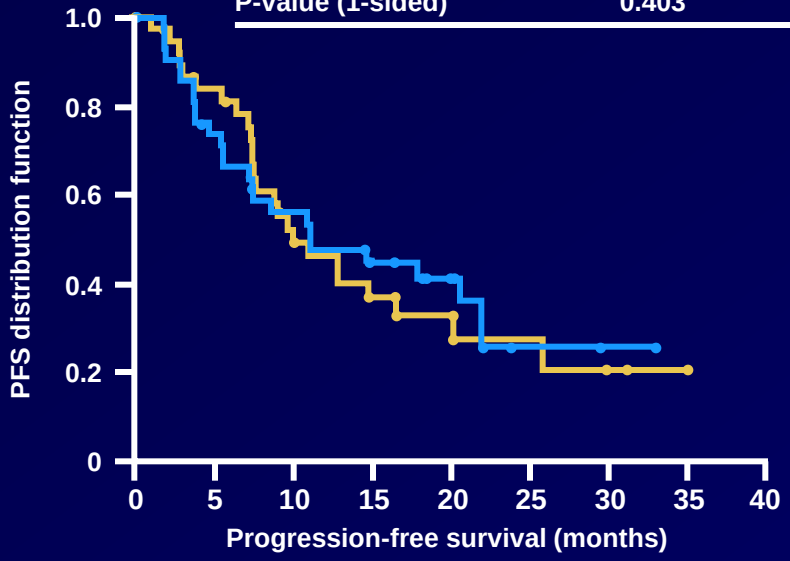
Data cut-off July 31, 2014

[1]On study means either still on treatment or being followed for OS and/or AE

PFS for All EGFR Mutations (n=91)

Per independent review

	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	26 (55.3)	25 (56.8)
Median, mo (95% CI)	11.1 (5.6–21.9)	10.0 (7.4–16.6)
HR* (95% CI)	0.935 (0.539–1.624)	
P-value (1-sided)	0.403	

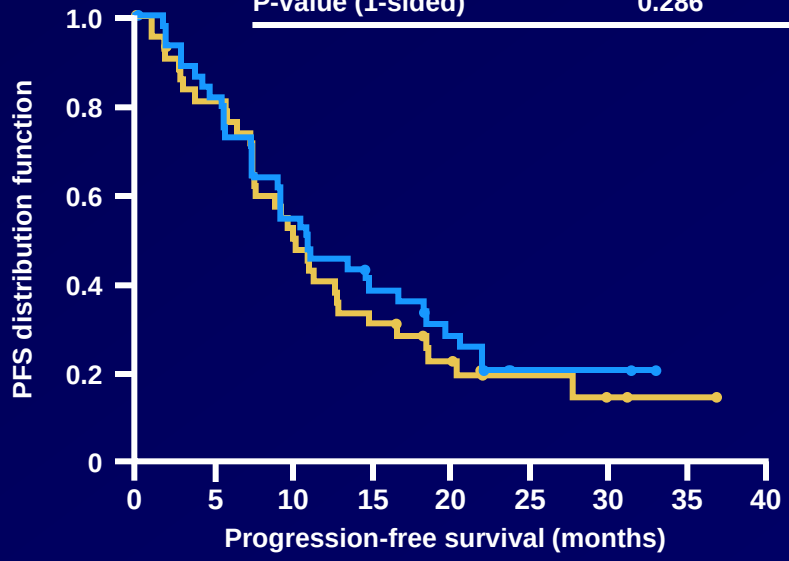


No. of patients at risk

Dacomitinib	47	30	20	14	10	2	1	0	0
Erlotinib	44	30	17	11	7	4	2	1	0

Per investigator's assessment

	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	34 (72.3)	34 (77.3)
Median, mo (95% CI)	10.9 (7.5–18.2)	10.0 (7.4–12.8)
HR* (95% CI)	0.874 (0.542–1.408)	
P-value (1-sided)	0.286	



No. of patients at risk

Dacomitinib	47	36	24	16	11	2	2	0	0
Erlotinib	44	34	21	13	8	4	2	1	0

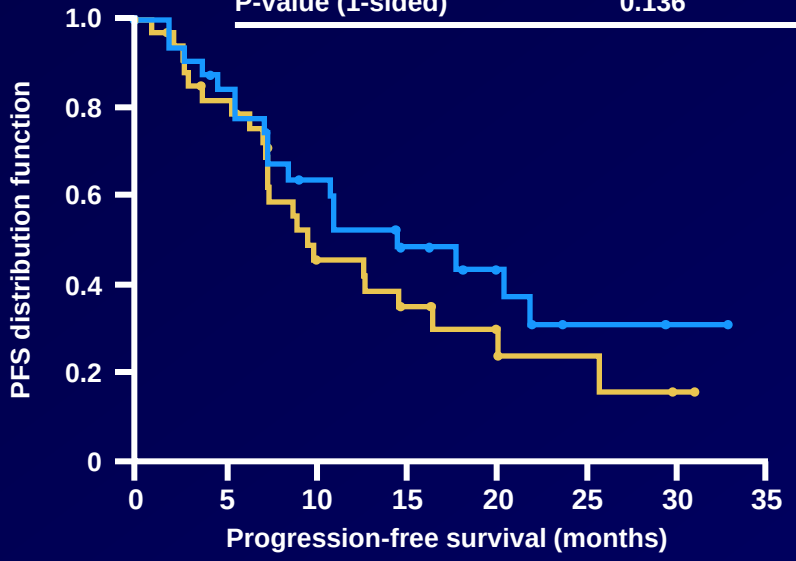
*Unstratified

PFS per independent review was still NOT mature with 56% event rate

PFS for Activating EGFR Mutations in Exon 19 or 21 (n=76)

Per independent review

	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	18 (48.6)	25 (59.0)
Median, mo (95% CI)	14.6 (7.6–NR)	9.6 (7.3–16.6)
HR* (95% CI)	0.707 (0.380–1.315)	
P-value (1-sided)	0.136	

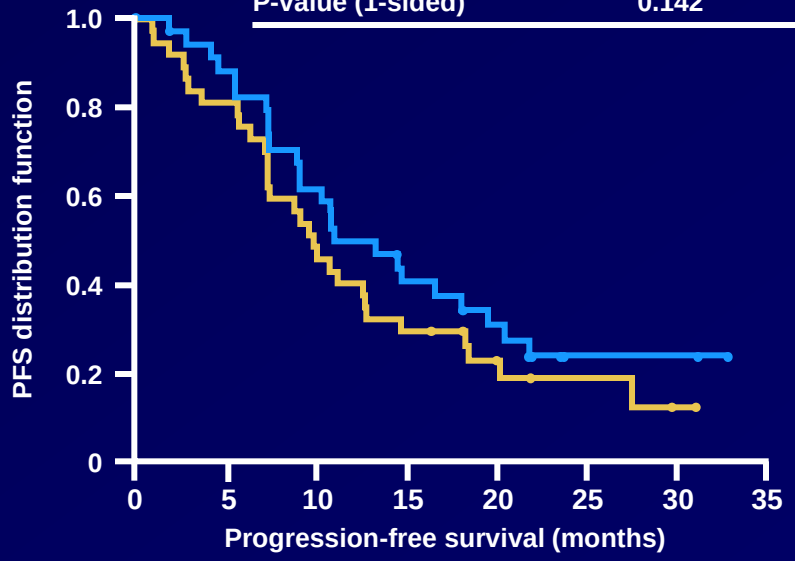


No. of patients at risk

Dacomitinib	37	26	17	11	8	2	1	0
Erlotinib	39	26	14	9	6	3	1	0

Per investigator's assessment

	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	25 (67.6)	30 (76.9)
Median, mo (95% CI)	13.4 (9.0–19.6)	10.0 (7.4–12.8)
HR* (95% CI)	0.749 (0.440–1.275)	
P-value (1-sided)	0.142	



No. of patients at risk

Dacomitinib	37	30	21	13	9	2	2	0
Erlotinib	39	30	18	11	7	3	1	0

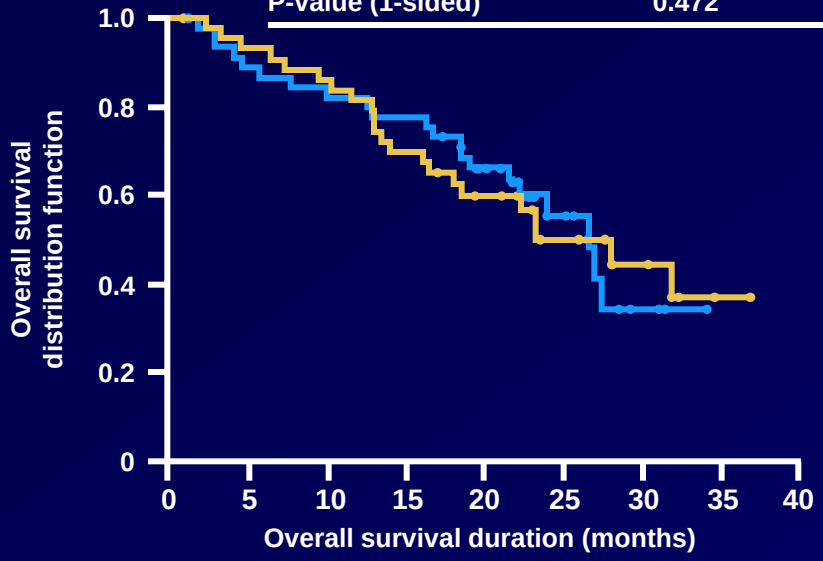
*Unstratified

PFS per independent review was still NOT mature with 56% event rate

OS for EGFR Mutations and Exon 19 and 21

EGFR mu

	Dacomitinib (N=47)	Erlotinib (N=44)
Events (%)	21 (44.7)	22 (50.0)
Median, mo (95% CI)	26.6 (21.6–NR)	28.0 (16.4–NR)
HR* (95% CI)	0.976 (0.534–1.786)	
P-value (1-sided)	0.472	

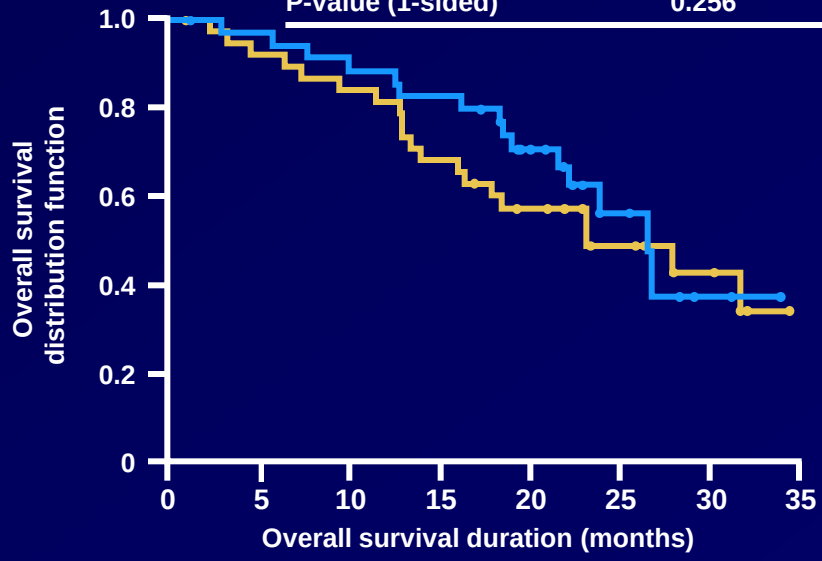


No. of patients at risk

Dacomitinib	47	40	37	35	25	11	3	0	0
Erlotinib	44	40	37	30	22	12	7	1	0

Activating mutation in exon 19 or 21

	Dacomitinib (N=37)	Erlotinib (N=39)
Events (%)	15 (40.5)	20 (51.3)
Median, mo (95% CI)	26.6 (21.6–NR)	23.2 (16.0–NR)
HR* (95% CI)	0.796 (0.405–1.565)	
P-value (1-sided)	0.256	



No. of patients at risk

Dacomitinib	37	34	31	29	20	8	2	0
Erlotinib	39	35	32	28	18	10	8	0

*Unstratified

OS was not mature with <50% deaths

Safety of Dacomitinib

- The KRAS-WT population and the EGFR mutation population had a similar toxicity profile to the overall patient population
  - The most common treatment-related AEs were:
    - Diarrhea, paronychia, stomatitis, rash, dry skin, decreased appetite, and dermatitis acneiform
  - The following were more frequent with dacomitinib:
    - Diarrhea, paronychia, stomatitis, and decreased appetite
  - The following were more frequent with erlotinib:
    - Rash and dermatitis acneiform

Most Frequent Treatment-related Adverse Events by MedDRA Preferred Term (or CLUSTERED Term) in Patients with Activating Mutation in Exon 19 or 21

AE preferred term	Dacomitinib (%)	Erlotinib (%)
Diarrhea	88.9	66.7
PARONYCHIA (CLUSTER)	58.3	38.5
Paronychia	55.6	33.3
STOMATITIS (CLUSTER)	52.8	46.2
Rash	50.0	66.7
Dry skin	33.3	30.8
Stomatitis	33.3	30.8
Decreased appetite	27.8	17.9
DERMATITIS ACNEIFORM (CLUSTER)	25.0	30.8
Dermatitis acneiform	22.2	28.2

DERMATITIS ACNEIFORM is any event having a PT of dermatitis acneiform, acne, acne pustular, acne conglobata, acne cystic or acne fulminans
PARONYCHIA is any event having a PT of paronychia or nail disorder
STOMATITIS is any event having a PT of stomatitis, mouth ulceration, glossodynia, glossitis, cheilitis, oral pain, oropharyngeal pain, oropharyngeal discomfort or mucosal inflammation

Summary

- **The EGFR activating mutation in exon 19/21 subgroup (*n=37 dacomitinib vs. n=39 erlotinib*) appeared to have a favorable trend for dacomitinib in PFS**
  - **Mature PFS per investigator's assessment**
    - ***mPFS: 13.4 vs. 10 months***
    - ***HR=0.75 (95% CI: 0.44–1.28), 1-sided P=0.142***
  - **Not mature PFS per independent review**
    - ***mPFS: 14.6 vs. 9.6 months***
    - ***HR=0.71 (95% CI: 0.38–1.32), 1-sided P=0.136***
- **OS not mature for activating EGFR mutant in exon 19/21**
  - ***mOS: 26.6 vs. 23.2 months***
  - ***HR=0.80 (95% CI: 0.41–1.57), 1-sided P=0.256***
- **Further exploratory analysis of dacomitinib activity in EGFR activating mutation NSCLC (2nd/3rd line) is being reviewed for future presentation**

Protocol DP312804 (A7471050) Study Design

Trial Design

Phase 3 Randomized, open-label, 1st line treatment of locally advanced or metastatic NSCLC with EGFR activating mutation(s)

Endpoints

Primary: PFS as per blinded IRC review
Ha: HR≤ 0.667(50%↑)
One-sided α=0.025
power =90%

Secondary: OS, OS_{30m}, PFS per INV, BOR, DR, PRO & PK

Study Sites

Global (Asia, EU)