Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L

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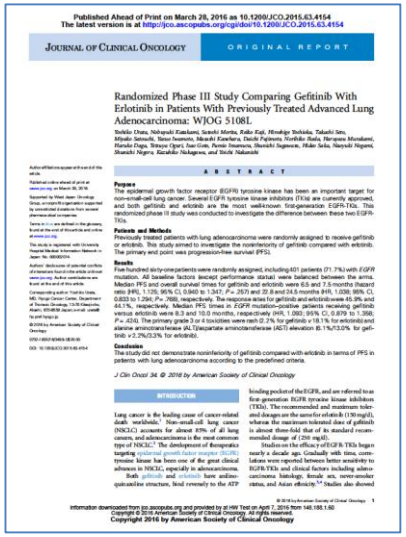
Key Finding

- A comparison between gefitinib and erlotinib in a mixed, chemo-pretreated population of 561 patients (72% EGFRM+, 30% >3rd line, 23% recurrent NSCLC) for non-inferiority did not meet the pre-specified non-inferiority boundary for PFS.



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ABSTRACT

Purpose
The epidermal growth factor receptor (EGFR) tyrosine kinase has been an important target for non–small-cell lung cancer. Several EGFR tyrosine kinase inhibitors (TKIs) are currently approved, and both gefitinib and erlotinib are the most well-known first-generation EGFR-TKIs. This randomized phase III study was conducted to investigate the difference between these two EGFR-TKIs.

Patients and Methods
Previously treated patients with lung adenocarcinoma were randomly assigned to receive gefitinib or erlotinib. This study aimed to investigate the noninferiority of gefitinib compared with erlotinib. The primary end point was progression-free survival (PFS).

Results
Five hundred sixty-one patients were randomly assigned, including 401 patients (71.7%) with *EGFR* mutation. All baseline factors (except performance status) were balanced between the arms. Median PFS and overall survival times for gefitinib and erlotinib were 6.5 and 7.5 months (hazard ratio [HR], 1.125; 95% CI, 0.940 to 1.347; *P* = .207) and 22.8 and 24.5 months (HR, 1.038; 95% CI, 0.833 to 1.294; *P* = .768), respectively. The response rates for gefitinib and erlotinib were 45.9% and 44.1%, respectively. Median PFS times in *EGFR* mutation–positive patients receiving gefitinib versus erlotinib were 8.3 and 10.0 months, respectively (HR, 1.090; 95% CI, 0.879 to 1.358; *P* = .434). The primary grade 3 or 4 toxicities were each 2.2% for gefitinib v 18.1% for erlotinib and alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation (6.1%/13.0% for gefitinib v 2.2%/3.3% for erlotinib).

Conclusion
The study did not demonstrate noninferiority of gefitinib compared with erlotinib in terms of PFS in patients with lung adenocarcinoma according to the predefined criteria.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for almost 85% of all lung cancers, and adenocarcinoma is the most common type of NSCLC.[2] The development of therapeutics targeting epidermal growth factor receptor (EGFR) tyrosine kinase has been one of the great clinical advances in NSCLC, especially in adenocarcinoma. Both gefitinib and erlotinib have anilinoquinazoline structure, bind reversely to the ATP binding pocket of the EGFR, and are referred to as first-generation EGFR tyrosine kinase inhibitors (TKIs). The recommended and maximum tolerated dosages are the same for erlotinib (150 mg/d), whereas the maximum tolerated dose of gefitinib is almost three-fold that of its standard recommended dosage of (250 mg/d).

Studies on the efficacy of EGFR-TKIs began nearly a decade ago. Gradually with time, correlations were reported between better sensitivity to EGFR-TKIs and clinical factors including adenocarcinoma histology, female sex, never-smoker status, and Asian ethnicity.[3,4] Studies also showed

PFS and OS in FAS

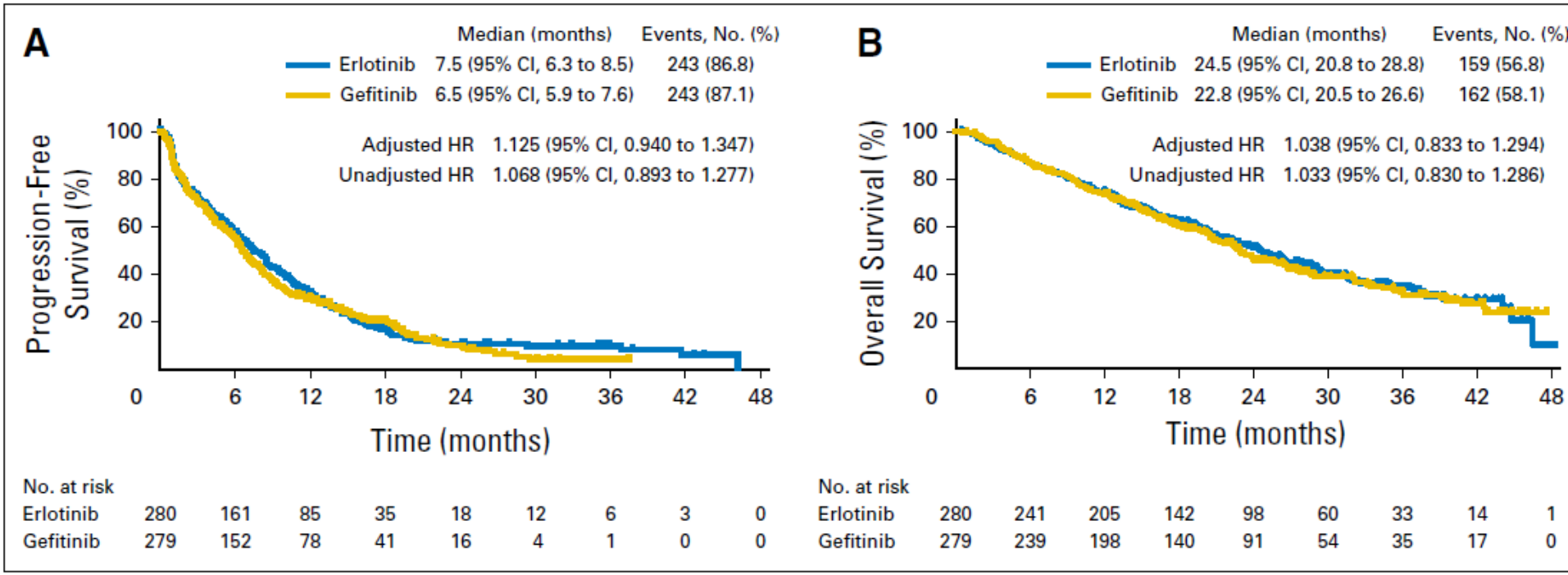

Fig 2. Kaplan-Meier graphs of (A) progression-free survival and (B) overall survival for full analysis set. HR, hazard ratio.

FAS: full analysis set

Subpopulation EGFRM+

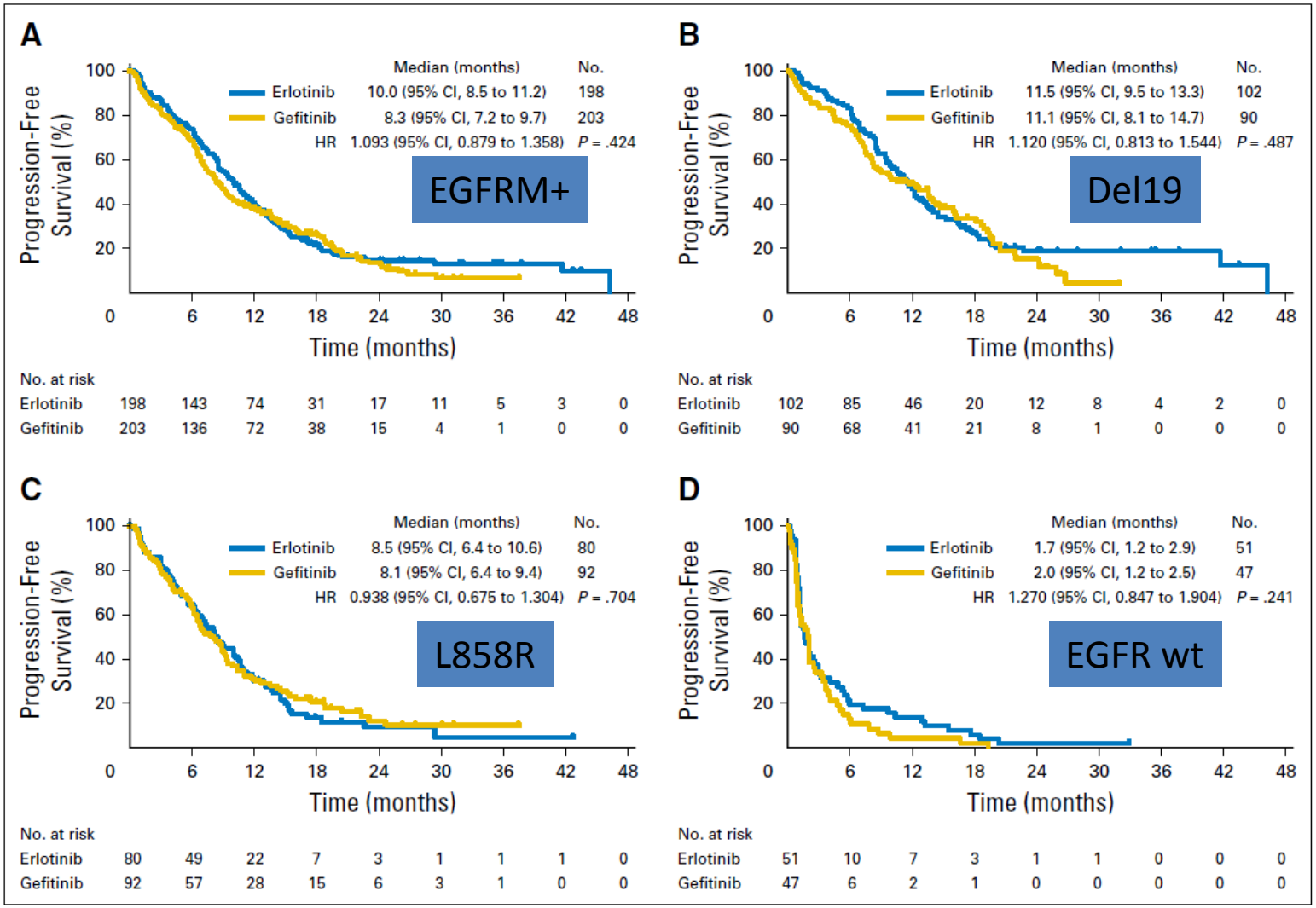

Fig 4. Kaplan-Meier graphs of progression-free survival for the following patient groups: (A) *EGFR* mutation–positive, (B) Ex19del mutation, (C) L858R mutation, and (D) *EGFR* wild type. HR, hazard ratio.

Key Findings: Summary

		Erlotinib	Gefitinib	HR (95% CI)	P-value
ORR	**FAS**	44.1 %	45.9 %		0.686
	EGFRM+	55.0 %	58.9 %		0.476
PFS	**FAS**	7.5 mo	6.5 mo	1.125 (0.940, 1.347)	0.257
	EGFRM+	10.0 mo	8.3 mo	1.093 (0.879, 1.358)	0.424
OS	**FAS**	22.8 mo	24.5 mo	1.038 (0.833; 1.294)	0.768
	EGFRM+	31.4 mo	26.5 mo	1.189 (0.900, 1.570)	0.221

FAS: full analysis set

Putting Into Perspective

- This a Japanese-only Non-inferiority trial in a pre-treated mixed population including EGFR-wt as well as EGFRM+ patients.
- The trial was (only after adjustment) not able to show non-inferiority of gefitinib for PFS according to the pre-specified boundary of 1.3 for upper CI.
- However, efficacy parameter of erlotinib and gefitinib are not different (look at the curves!) with HRs around 1.1 and ORR numerically slightly better for gefitinib.

Is This Trial Relevant for LUX-Lung 7?

- **No**, as this trial does not show superiority of erlotinib over gefitinib and it was performed in a different setting. EGRFM+ is a subgroup analysis (and also not showing superiority).
- Efficacy parameter of erlotinib and gefitinib are not different (look at the curves!) with HRs around 1.1 showing that we didn‘t selected the ‚weaker‘ comparator.
- A recent H2H trial from China addressing superiority of erlotinib over gefitinib in EGFRM+ failed (CTONG 0901, presented at WCLC 2015 Denver).

Statistical Comments

- Non-inferiority is not shown, but conclusion that Gefitinib is inferior is not valid. In particular, KM curves for PFS cross and p-values for difference in PFS are rather large
- KM curves for PFS cross, PFS rates at 12 months are identical and KM curve of Gefitinib even above the KM curve for Erlotinib e.g. at 18 months. So no sign that one of the treatments is better than the other.
- As KM curves cross, the proportional hazards assumption is questionable and the HR, as it is calculated under the assumption of PH, is not a good measure to describe treatment difference and also the adjusted HR via the Cox model could have caused problems.
- Although the adjusted HR does not show non-inferiority, the unadjusted HR shows non-inferiority. Usually, one would not expect in a randomized trial a large effect on the point estimate by adjusting for variables already balanced at baseline due to the randomization.
- The HR in the EGFR mutation-positive subgroup is closer to 1 with p-value of 0.424 for test of differences in PFS, but sample size is too small to show non-inferiority. KM curves also cross and e.g. PFS rate at 18 months is higher for Gefitinib. As before, HR is not a good measure to describe the difference in that setting.