

## Non-small Cell Lung Cancer in South Wales: Are Exon 19 Deletions and L858R Different?

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**Abstract.** *Background/Aim:* In advanced non-small cell lung cancer (NSCLC), the epidermal growth factor receptor (EGFR) mutations L858R and exon 19 deletion (del19) predict response to EGFR tyrosine kinase inhibitors (TKIs). Trials have suggested a differential response to the second-generation EGFR TKI afatinib in favour of del19. We investigated whether this differential response is observed in clinical practice. *Materials and Methods:* Retrospective demographic, treatment and outcome data were collected on patients with: stage III/IV NSCLC and either del19 or L858R, receiving an EGFR TKI as first-line treatment. *Results:* There was no significant difference in overall survival (OS) between del19 (648 days, 95% confidence interval (CI)=461-835) and L858R (813 days, 95%CI=387-1,238), ( $p=0.616$ ), or in duration of therapy between del19 (365 days, 95% CI=192-538) and L858R (428 days, 95% CI=263-593), ( $p=0.928$ ). *Conclusion:* Patients with exon del19 did not have a significantly longer OS with first-generation TKIs.

In recent years there have been advances in the identification and understanding of molecular subsets of lung cancer, defined by specific oncogenic aberrations. An important subgroup of non-small cell lung cancer (NSCLC) is characterised by harbouring an activating epidermal growth factor receptor (EGFR) mutation. The EGFR is a member of the ErbB family of cell surface receptors that are required for essential functions in healthy tissues. Activation of the EGFR results in a cascade of downstream signaling pathways that control proliferation, apoptosis, angiogenesis and metastasis (1). Mutations in the EGFR gene may cause this process to become deregulated in NSCLC, with the most

common of these mutations being exon 19 deletions (exon del19) and the Leu858Arg exon 21 point mutation (L858R) (2). Exon del19 and L858R are considered 'driver' mutations as they confer growth advantage on lung cancer cells and are found in a subset of lung cancers whose tumour cell survival is exquisitely dependent on EGFR pathway signaling (3, 4). Patients with these EGFR mutation-positive lung cancers may experience significant and durable tumour responses with the reversible oral EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib (5-9). Randomised phase III trials of a first-generation oral TKI (gefitinib or erlotinib) versus chemotherapy in EGFR mutation-positive advanced NSCLC have shown a significant increase in progression-free survival (PFS) but no improvement in overall survival (OS) in patients treated with the oral TKI (5-9).

Afatinib, a second-generation irreversible TKI, has shown clinical activity in patients with EGFR mutation-positive lung cancer. First-line afatinib was compared with standard platinum-based doublet chemotherapy in two large, randomised phase III trials (LUX-lung 3 and LUX-lung 6) in previously untreated patients with EGFR mutation-positive advanced lung adenocarcinoma (10, 11). Findings from both studies showed improved PFS for patients receiving afatinib, in line with the findings from the first-generation oral TKI trials (5-9). However, LUX-lung 3 and LUX-lung 6 also showed differences in OS with afatinib on the basis of EGFR mutation subtype. In patients with exon del19, LUX-Lung 3 median OS was 33.3 months in the afatinib group versus 21.1 months in the chemotherapy group ( $p=0.0015$ ); in LUX-Lung 6, OS was 31.4 months versus 18.4 months, respectively ( $p=0.023$ ). By contrast, there were no significant differences in OS by treatment group for patients with the L858R mutation in either trial. None of the studies looking at first-generation oral EGFR TKIs were designed to detect a difference in the OS in del19 or L858R mutation subgroups. Only the IPASS, NEJ002 and EURTAC trials examined OS with reversible EGFR TKIs specifically in EGFR del19 or L858R mutation subgroups and no differences in OS were reported (8, 12, 13). Following the results of LUX-lung 3 and 6, we evaluated the outcomes of patients with del19 or

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L858R mutations in South Wales treated with oral TKIs prior to the routine introduction of afatinib into clinical practice. The aim was to investigate whether clinical outcomes suggested a differential response of the patients with the two mutations to treatment.

## Materials and Methods

**Patients.** One hundred and nine patients with *EGFR* mutations in South Wales were identified from the database held in the Genetics Laboratory in University Hospital Wales, Cardiff. Data were collected for all patients who have been tested since the introduction of the service in 2010.

**Methods.** Patients were included in the analysis if they had all of the following: incurable stage III or IV NSCLC, either exon del19 or L858R and had received gefitinib, erlotinib or afatinib as first-line treatment.

Data were collected on age, sex, smoking status, disease stage, histological subtype, mutation subtype, treatment received and duration of treatment, reason for stopping treatment, subsequent therapy and OS.

Duration of treatment with TKI was used as a surrogate of response to treatment. Kaplan-Meier estimation of median duration of treatment and OS, as well as comparison according to mutation type using log-rank analysis were performed using SPSS Statistics (version 21; IBM, Armonk, NY, USA).

## Results

**General demographics of patients.** In total, 61 patients were included in the analysis. Forty of 61 (65.6%) patients were females and 21/61 (34.4%) males. The median age of all patients was 66 years (range=27-86). Fourteen of 39 (35.9%) patients were non-smokers, 17/39 (43.6%) ex-smokers and 8/39 (20.5%) current smokers. No information was available on smoking history in 22/61 (36.0%) patients. Also, 53/61 (86.9%) patients had adenocarcinoma, 7/61 (11.4%) NSCLC not otherwise specified and 1/61 (1.6%) squamous carcinoma.

**Comparison of the mutations.** MutaDel19 mutation was found in 36/61(59.0%) patients and the L858R mutation was found in 25/61 (41.0%) patients. Demographic and disease data for the del19 and L858R subgroups are shown in Table I. Del19 was more common in females; otherwise, demographic, disease and treatment details were similar between the two subgroups.

**Median OS.** The median OS of the complete 61-patient cohort was 655 days (95% confidence interval (CI)=456-854 days) (Figure 1A) and median duration of therapy was 400 days (95% CI=270-529 days) (Figure 1B). The OS of the exon del19 subgroup was 648 days (95% CI=461-835 days) and OS of the L858R subgroup was 813 days (95% CI=387-1238 days). There was no significant difference in OS between the two subgroups ( $p=0.616$ ) (Figure 1C).

Table I. *Demographics and clinical data of the patients in this study.*

	Del19	L858R
Total number	36	25
Female	27 (75.0%)	13 (52.0%)
Male	9 (25.0%)	12 (48.0%)
Median age	65 (range=27-85)	68 (range=49-86)
Smokers	5 (13.9%)	3 (12.0%)
Ex-smokers	8 (22.2%)	9 (36.0%)
Non-smokers	8 (22.2%)	6 (24.0%)
Unknown	15 (41.7%)	7 (28.0%)
Stage 3	5 (13.9%)	3 (12.0%)
Stage 4	31 (86.1%)	22 (88.0%)
Histology		
Adenocarcinoma	31 (86.1%)	22 (88.0%)
NSCLC	4 (11.1%)	3 (12.0%)
Squamous	1 (2.8%)	
TKI received		
Gefitinib	29 (80.6%)	20 (80.0%)
Erlotinib	5 (13.9%)	4 (16.0%)
Afatinib	2 (5.6%)	1 (4.0%)
Subsequent therapy		
Other TKI	0 (0%)	1 (4.0%)
Chemotherapy	10 (27.8)	4 (16.0%)
Unknown	26 (72.2%)	20 (80%)

NSCLC, Non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

**Duration of first-line therapy.** There was no significant difference in the duration of first-line therapy, that was 365 days (95% CI=192-538 days) in the exon del19 subgroup and 428 days (95% CI=263-593 days) in the L858R subgroup ( $p=0.928$ ) (Figure 1D).

## Discussion

LUX lung 3 and LUX lung 6 are the first prospective randomized phase III trials to show a significant difference in the survival of patients with the two commonest sensitising *EGFR* mutations (exon del19 and L858R) with an oral *EGFR* TKI (10, 11). When treatment with afatinib was compared to chemotherapy, the greater than 12-month improvement in OS seen in the LUX lung 3 and 6 trials in exon del19 patients was not seen in L858R patients, despite a significant PFS advantage. It is not clear whether the difference in outcomes between the two commonest mutations is specific to afatinib or might also be seen with the first-generation oral TKIs. We carried out this study to investigate whether clinical outcomes suggested a differential response of the two mutations in the real world setting where the vast majority of patients received first-line first-generation TKIs. Before discussing the data in our patient cohort, it is useful to summarize the findings from the pivotal randomised trials in the therapy area.

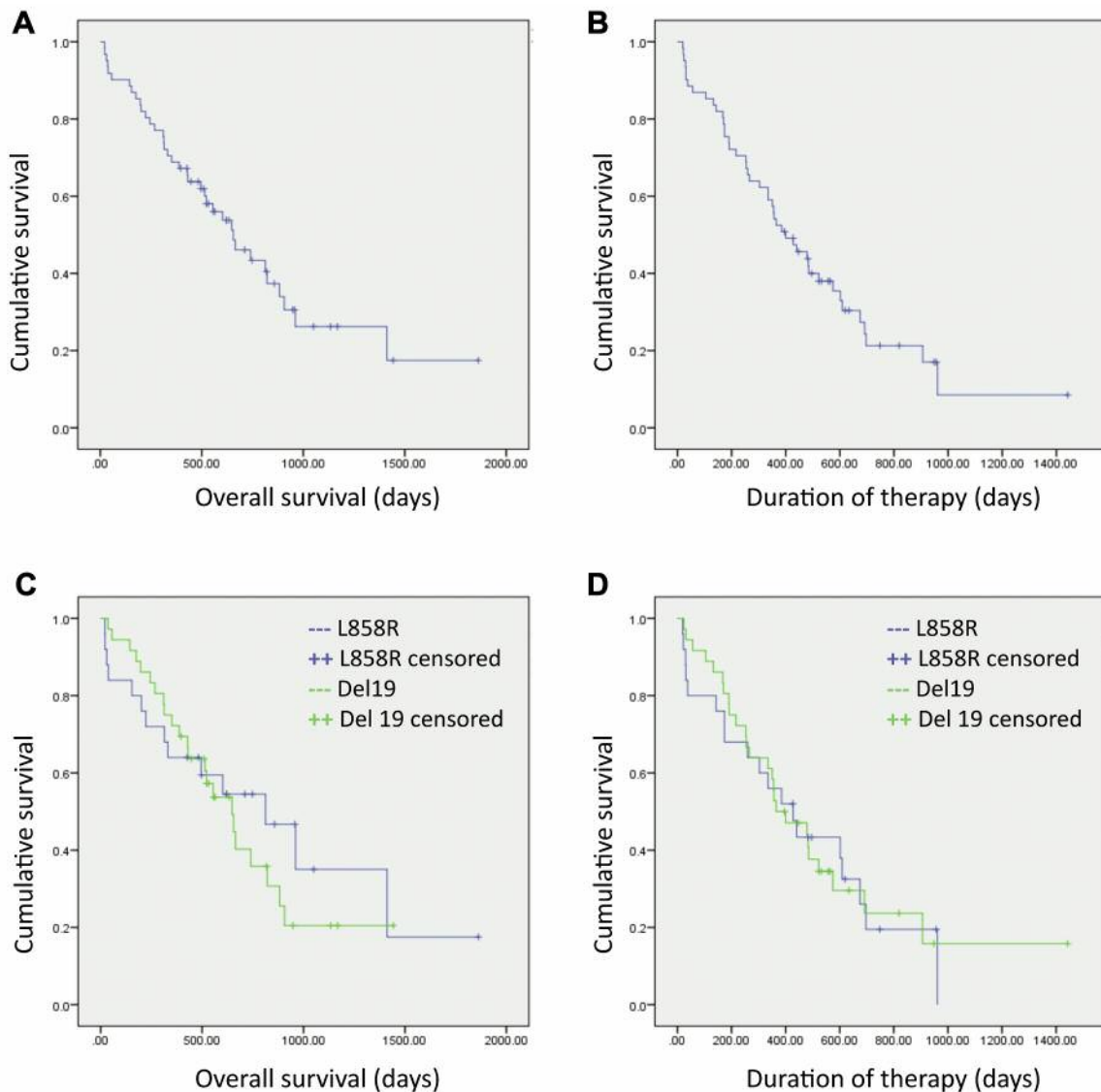


Figure 1. Kaplan-Meier estimation of overall survival and duration of therapy for the whole population and by mutation subtype. A) Overall survival, whole population. B) Duration of therapy, whole population. C) Overall survival, by mutation. D) Duration of therapy, by mutation.

In the IPASS trial, patients were randomized to gefitinib or carboplatin-paclitaxel chemotherapy (5). In a post-hoc analysis, PFS was significantly longer for gefitinib *versus* carboplatin-paclitaxel in both the exon del19 (hazard ratio (HR)=0.38; 95% CI=0.26-0.56) and the L858R mutation (HR=0.55; 95% CI=0.35-0.87) subgroups. Analysis indicated no significant difference in PFS with gefitinib in the *exon* 19 deletions *versus* the L858R mutation subgroup (HR=0.78; 95% CI=0.51-1.19). However, the direction of HR suggests gefitinib may be more effective in exon del19 (14).

NEJ002 had a similar design to IPASS and randomized *EGFR* mutation-positive patients to gefitinib or carboplatin-

paclitaxel chemotherapy (7). NEJ002 suggested no significant difference between the two commonest mutation subtypes. The median PFS and response rate did not differ significantly between patients with the exon del19 (11.5 months and 82.8%) and those with the L858R mutation (10.8 months and 67.3%) (7). An updated analysis reported that the type of *EGFR* mutation had no significant impact on OS ( $p=0.181$ ) (12).

In the WJTOG3405 trial, advanced NSCLC patients with either the exon del19 or L858R mutation were randomly assigned to gefitinib or cisplatin-docetaxel chemotherapy. A pre-planned comparison of exon del19 to L858R showed, in

patients randomized to gefitinib, median PFS in exon del19 patients of 9.0 months (95% CI=6.7-13) compared to 9.6 months (95% CI=8.0-18.8) in patients with the L858R mutation. HR was 1.130 (95% CI=0.631-2.025,  $p=0.681$ ). OS data by mutation subtype was not presented and the PFS data did not suggest any difference in response to gefitinib by mutation subtype (6). For gefitinib then, in two of the large randomized phase 3 trials (NEJ002, WJTOG3405), there is no signal that exon del19 behaves in a different fashion to L858R (6, 12). In the IPASS trial, post hoc analyses by mutation type showed that PFS was significantly longer with gefitinib than with chemotherapy in both the exon del19 and L858R subgroups, with a slightly greater advantage seen in the exon del19 subgroup. This difference, however, did not reach statistical significance (14).

In the EURTAC trial, patients with advanced NSCLC and either the exon del19 or L858R mutation were stratified by mutation type and randomised to erlotinib or cisplatin/carboplatin-docetaxel/gemcitabine. The hazard ratio for patients harbouring the exon del19 was 0.30 (95% CI=0.18-0.50;  $p<0.0001$ ) in favour of erlotinib with a median PFS of 11.0 months (95% CI=8.8-16.4) in the erlotinib group compared with 4.6 months (95% CI=4.1-5.6) for those in the standard chemotherapy group. Although still favouring erlotinib, the hazard ratio in the L858R group was less impressive at 0.55 (95% CI=0.29-1.02;  $p=0.0539$ ) with a median PFS of 8.4 months (95% CI=5.2-10.8) in the erlotinib group compared with 6.0 months (95% CI=4.9-6.8) in the standard chemotherapy group. Multivariate analysis did not show mutation subtype was significant with respect to PFS in either the erlotinib or chemotherapy arms and there was no difference in OS between the two mutation subtypes. Despite the lack of statistical significance, the near 3-month numerical difference in PFS and the difference in hazard ratios suggested there may be differences in treatment response to erlotinib between the exon del19 and L858R subgroups, favouring exon del19 (8).

In the OPTIMAL trial, patients with advanced NSCLC and either an exon del19 or L858R mutation were stratified according to mutation subtype and randomized to either oral erlotinib or gemcitabine-carboplatin chemotherapy (9). The hazard ratios for PFS strongly favoured erlotinib in both mutations; 0.13 (95% CI=0.07-0.25) in exon del19 and 0.26 (95% CI=0.14-0.49) in L858R. As in the EURTAC trial, although no statistical differences were seen in PFS between the two subgroups, numerically, the patients with exon del19 appeared to fare better than the L858R with regards to PFS (9).

Zhang *et al.* carried out a meta-analysis in an attempt to establish whether the efficacy of EGFR-TKIs differs between exon del19 and the L858R mutation (15). Based on data from six randomised phase III clinical trials (5, 6, 8-11), it was reported that patients with the exon del19 had a significantly longer PFS than those with the L858R mutation (HR=0.59, 95% CI=0.38-0.92;  $p=0.019$ ).

Overall, the randomised phase III trials in *EGFR* mutation-positive patients suggest a trend towards longer PFS with first-generation TKIs in exon del19 compared to the L858R mutation but without, however, clear indication of a survival advantage. This observation is supported by the Zhou *et al.* meta-analysis (9). Overall, the clinical trial data indicate it is unlikely for any significant survival difference to exist between the two commonest sensitising mutations when treated with a first-generation oral TKI.

Our real-world results show no significant difference in duration of treatment or OS between exon del19 and L858R. It is worth noting that 58/61 (95.1%) patients in our cohort were treated with a first-generation TKI and, therefore, the impact of the three patients treated with afatinib is highly unlikely to have had a significant impact on patient outcomes. Numerically, however, in our cohort of patients, the L858R patients appear to have a longer duration of therapy and longer OS. One possible explanation is differences in second-line treatment between the two groups; however, given the retrospective nature of the study and incomplete data on second-line treatment, we have been unable to establish whether this was a contributory factor. The only discernible difference in demographics between the two mutation groups is the greater proportion of females in the del19 group (75% vs. 52%). Intuitively, this imbalance would be expected to favour the del19 subgroup as it is well established that females with NSCLC have a better outcome than males. It is unlikely that the differences in sex distribution explain our observed results. Given the lack of plausible explanation for the observed numerical (not statistical) differences in our study and the conflicting data from randomised trials, it is likely that the results seen were due to the relatively small number of patients included in our study.

In conclusion, this study supports the observation that patients with del19 do not have a significantly longer OS with first-generation TKIs compared to patients with the L858R mutation. It is reasonable to assume that, following afatinib treatment, the longer OS in del19 patients than L858R ones is specific to afatinib, which cannot be seen after treatment with first-generation TKIs.

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