Differential clinicopathological features, treatments and outcomes in patients with Exon 19 deletion and Exon 21 L858R EGFR mutation-positive adenocarcinoma non-small-cell lung cancer

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ABSTRACT

The most common oncogenic driver in non-small-cell lung cancer (NSCLC) is the epidermal growth factor receptor (EGFR) gene mutations that occur more frequently among Asians (30%–50%) as opposed to Caucasians (10%–15%). Lung cancer is one of the most prevalent cancers in India, with a reported adenocarcinoma positivity ranging between 26.1% and 86.9% in NSCLC patients. The prevalence of EGFR mutations in adenocarcinoma patients (36.9%) in India is higher than that of Caucasian patients and lower than that of East Asian patients. The exon 19 deletion (Ex19del) is more common than exon 21 L858R mutations in Indian patients with NSCLC. Studies have shown that the clinical behaviour of patients with advanced NSCLC differs between EGFR Ex19del and exon 21 L858R mutation status. In this study, we investigated the differences in clinicopathological features and survival outcomes after first line and second-line treatment with EGFR tyrosine kinase inhibitors (EGFR TKIs) in NSCLC patients with Ex19del and exon 21 L858R EGFR mutation status. This study also focuses on the role and potential benefits of dacomitinib, a second-generation irreversible EGFR TKI, in patients with Ex19del and exon 21 L858R EGFR mutation-positive advanced NSCLC in Indian settings.

INTRODUCTION

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related deaths in the world. Lung cancer claimed 1.8 million lives in 2020 across the globe.1 Lung cancer is responsible for approximately 1 in 10 (11.4%) diagnosed cancers and 1 in 5 (18.0%) deaths globally.1 As per the 2020 Global Burden of Cancer Study data, lung cancer is the leading cause of cancer mortality in men. Moreover, in women, lung cancer is associated with high mortality rates, second only to that of breast cancer.1 Non-small-cell lung cancer (NSCLC) is the most common subtype of lung cancer and accounts for approximately 85% of all lung cancer cases.2 A majority of patients are diagnosed at advanced stages of the disease.2–5

KEY MESSAGES

⇒ Epidermal growth factor receptor (EGFR) mutation status (Ex19del and exon 21 L858R) can be used as a predictive factor for the efficacy of EGFR tyrosine kinase inhibitor (TKI) as the 1L treatment among patients with metastatic non-small-cell lung cancer (NSCLC).53 ⇒ NSCLC patients with Ex19del have significantly better outcomes in terms of response and survival rates compared with patients with a mutation in exon 21 L858R.38 40 42 ⇒ As per the network meta-analysis, dacomitinib showed a numerical improvement of OS compared with all other EGFR TKIs among patients with exon 21 L858R substitution mutation while osimertinib showed a numerical improvement of OS compared with all other EGFR TKIs among patients with exon 19 deletion mutation.48
newly diagnosed advanced NSCLC of adenocarcinoma histology. The study reported a lower EGFR mutation frequency in patients from India (22.2%), in comparison to 6 other Asian regions (47.2%–64.2%). Choughule et al., in their retrospective analysis of 907 patients diagnosed with NSCLC in Tata Memorial Hospital in Mumbai, Maharashtra, India, between August 2011 and December 2012, revealed an overall EGFR mutation rate of 23.2%, with a significantly higher EGFR mutation rate in females versus males (29.8% vs 20%; p=0.002). The study also reported the overall EGFR mutation rate in the adenocarcinoma patient population as 26%. Another retrospective analysis by Doval et al., involving 500 adenocarcinoma NSCLC patients treated at 6 different centres across India, reported a slightly higher EGFR mutation rate of 33%. Several studies have reported regional differences in EGFR mutation rates, with a higher incidence of 65% in the southern Indian population as compared with 33% in the northern Indian population. Recently, a study by Gupta et al. reported the overall prevalence of EGFR-positive adenocarcinoma NSCLC in India as 36.9% (95% CI 33.0 to 40.8). A higher preponderance of EGFR mutation positivity was observed in females than in males (42.2% vs 26.5%) and in non-smokers (40.9% vs 21.4%). Approximately 85%–90% of EGFR mutations in NSCLC comprise exon 19 deletion (Ex19del) and exon 21 L858R point mutations, whereas 10%–15% of mutations include uncommon mutations such as exon 20 insertion mutation (4%–12%), L861Q (3%), G719X (2%) and S768I (1%). Figure 1 illustrates the point mutations, deletions and insertions within exons 18–21 of the EGFR gene.

Platinum-based doublet chemotherapy has been shown to improve survival over best supportive care (BSC) in patients with a good performance status (PS), without impairing the quality of life. However, the therapeutic effect is limited as it is associated with poor clinical outcomes and high toxicity. The 5-year relative survival rate for metastatic NSCLC is nearly 6% in patients receiving cytotoxic chemotherapy regimens. Recently, studies have revealed that epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have significant efficacy and are associated with fewer side effects and improved quality of life, particularly in patients harbouring EGFR Exon 19 deletion and exon 21 L858R point mutations, as compared with chemotherapy regimens. This review article will focus on the clinical characteristics and treatment outcome comparisons of first-line (1L) and second-line (2L) treatment with EGFR TKIs in advanced NSCLC patients with Ex19del and exon 21 L858R mutation status. This review also focuses on the role and potential benefits of dacomitinib, a second-generation irreversible EGFR TKI, in patients with Ex19del and exon 21 L858R EGFR mutation-positive advanced NSCLC in Indian settings.

### CLINICAL CHARACTERISTICS OF NSCLC PATIENTS WITH EX19DEL OR EXON 21 L858R EGFR MUTATION STATUS

**Demographics**

Studies have shown that EGFR gene mutation frequency (Ex19del and exon 21 L858R) varies in different countries and regions around the globe. Recently, Exon 19 deletions are more commonly detected in Northern Asia as compared with Europe, North America and South America. On the other hand, exon 21 L858R mutations are more commonly detected in Southern Asia as compared with other regions. In India, Ex19del (39.3%–81%) is more common than exon 21 L858R point mutations (14.9%–50.7%) in NSCLC patients. Choughule et al. evaluated the incidence of Ex19del and exon 21 L858R point mutations in Indian NSCLC patients based on gender and smoking status. The study concluded that a higher incidence of Ex19del was observed among females with no history of smoking and that exon 21 L858R mutations were more common in male smokers. Similar results were observed in another Indian study by Doval et al., where exon 21 L858R point mutations were found to be predominant in males, and Ex19del was significantly correlated with the female gender and non-smokers (p<0.05). Patients were categorised into three groups based on age (20–40 years, 41–60 years and >60 years) in this study, and a high EGFR mutation rate of 62.8% was observed in the 41–60 years age group (p=0.054).

![Figure 1](https://example.com/figure1.png)

**Figure 1** Point mutations, deletions and insertions within exons 18–21 of the EGFR gene in NSCLC patients. Adapted from: Harrison et al. EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer.

However, in a subgroup analysis, no statistically significant difference was observed between Ex19del and exon 21 L858R mutation in NSCLC patients in terms of age categorisation. However, a study by Zhang et al found that Ex19del was more common than exon 21 L858R mutation in Chinese patients younger than 50 years (p<0.001). Furthermore, in a subgroup analysis of age, the Ex19del mutation rate was higher than the exon 21 L858R mutation rate in patients aged 21–30, 31–40, 41–50 and 51–60 years, whereas the Ex19del rate was lower than the exon 21 L858R mutation rate in patients aged 61–70, 71–80 and 81–90 years.

Lymph node metastasis, degree of differentiation and serum tumour markers

Zhang et al studied the lymph node metastasis rate and incidences of Ex19del and exon 21 L858R EGFR mutations in 1271 NSCLC patients. The study reported that the incidences of Ex19del and L858R varied in different N stages (stratified by N0, N1, N2 and N3; p<0.001). The study concluded that NSCLC patients with 19 Del are more likely than those with L858R to be young and have lymphatic metastases. In a subgroup analysis, no statistical significance was observed in differentiation, tumour maximum diameter and carcinoembryonic antigen (CEA) levels between Ex19del and exon 21 L858R mutation in NSCLC patients. On the contrary, Jin et al found that mutation rates at EGFR Ex19del were significantly higher in the high-CEA (≥5 ng/mL) group than those in the low-CEA (<5 ng/mL) group (p=0.004) in Chinese non-smokers with adenocarcinoma. Regarding the exon 21 L858R mutation rate, the correlation did not show statistical significance, highlighting the Ex19del mutation rate as a more important factor related to serum CEA levels. Brain and bone metastases are life-threatening complications in patients with advanced-stage NSCLC. Studies have revealed that the incidence of brain and bone metastases may be associated with EGFR mutation status in NSCLC patients. A study published by Li et al studied the correlation between EGFR mutation status and the incidence of brain metastasis in patients with advanced NSCLC. The study concluded that NSCLC patients harbouring Ex19del had a potential higher risk of brain metastasis than patients with exon 21 L858R mutation status. Similar results were observed in another Indian study published by Doval et al, where exon 21L858R point mutations were predominant in males and Ex19del was significantly correlated with pleural effusion and distant metastasis, such as brain and bone metastases (p<0.05). A majority of patients (74%) in the study presented with an advanced stage of the disease, and the common sites of metastasis in the study population were bone (42.6%), brain (22.8%), liver (13.8%) and adrenal gland (9.6%). Table 1 highlights the differences in clinical characteristics and prognostic factors between Ex19del and exon 21 L858R EGFR mutation-positive NSCLC patients.

### Table 1

**Summary of differences in clinical characteristics and prognostic factors between Ex19del and exon 21 L858R EGFR mutation-positive NSCLC patients**

<table>
<thead>
<tr>
<th>Gender and smoking</th>
<th>(1) Ex19del EGFR mutation significantly correlated with the female gender and no history of smoking.</th>
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<tbody>
<tr>
<td></td>
<td>(2) Exon 21 L858R mutations are more common in male smokers.</td>
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<td>EGFR Ex19del mutations significantly correlated with a high serum carcinoembryonic antigen level of ≥5 ng/mL.</td>
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<tr>
<td>NSCLC patients with Ex19del EGFR mutation status are associated with a high risk of pleural effusion and lymph node, brain, and bone metastases than those with exon 21 L858R.</td>
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<tr>
<td>Age and N stage may be considered while predicting the EGFR mutation type in NSCLC.</td>
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<td>EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; NSCLC, non-small-cell lung cancer.</td>
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Outcome differences with first-generation EGFR TKIs between patients with Ex19del and exon 21 L858R mutation status in 1L treatment settings

Gefitinib and erlotinib are first-generation reversible EGFR TKIs that compete with ATP for binding to the active site of EGFR kinases. Gefitinib and erlotinib are both efficacious and well tolerated relative to chemotherapy agents, in patients with EGFR mutation-positive advanced NSCLC (with Ex19del or exon 21 L858R substitution mutations), regardless of PS.

**Comparision of treatment outcomes after treatment with EGFR TKIs in patients with Ex19del or exon 21 L858R mutation status**

Until the 2000s, the standard-of-care treatment for patients with advanced NSCLC was platinum-based doublet chemotherapy for patients with a good PS, and BSC for patients with a poor PS. Studies have shown that the use of cisplatin–gemcitabine, cisplatin–paclitaxel, carboplatin–paclitaxel and cisplatin–docetaxel resulted in similar response rates and survival in patients with advanced NSCLC. In fact, survival outcomes were rather unsatisfactory with an overall response rate of 19% and median overall survival (OS) of 7.9 months (95% CI 7.3 to 8.5). Recently, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) Clinical Guidelines recommended 1L treatment with EGFR TKIs, which are both efficacious and well tolerated relative to chemotherapy agents, in patients with EGFR mutation-positive advanced NSCLC (with Ex19del or exon 21 L858R substitution mutations), regardless of PS.
tyrosine kinase domain on the EGFR receptor and inhibit autophosphorylation and downstream signalling. Erlo-
tinib and gefitinib were approved by the Food and Drug Administration (FDA) for 1L treatment in patients with NSCLC, whose tumours harbour the EGFR Ex19del or exon 21 L858R substitution mutation as detected by an FDA-approved test in 2013 and 2015, respectively. On 18 October 2016, the indication for erlotinib was modified to limit its use in patients with tumours with specific EGFR mutations (Ex19del or exon 21 L858R substitution mutation) in maintenance or second-line or greater-line treatment. The 1L indication for erlotinib was limited to patients with EGFR Ex19del or exon 21 substitution mutations. In the phase 3 OPTIMAL trial, significant progression-free survival (PFS) benefit with 1L erlo-
tinib versus gemcitabine plus carboplatin chemotherapy (median PFS: 13.1 vs 4.6 months; p<0.0001) was reported in Chinese patients. The study found an association between reduced PFS and the presence of the L858R mutation status as compared with that with Ex19del (p=0.02). The phase 3 ENSURE trial was the largest trial (N=217) that demonstrated significant PFS benefit with 1L erlotinib in a wider EGFR mutation-positive NSCLC Asian patient population from China, Malaysia and the Philippines as compared with gemcitabine plus cisplatin chemotherapy (median PFS: 11.0 months vs 5.5 months; p<0.0001). The PFS benefit seen in the erlo-
tinib versus gemcitabine/cisplatin arm was greater in the Ex19del subgroup (HR 0.20; 95% CI 0.11 to 0.37) than in the exon 21 L858R subgroup (HR 0.57; 95% CI 0.31 to 1.05). The data from the phase 3 IPASS study confirmed findings with 1L gefitinib in a wider EGFR mutation-positive NSCLC Asian patient population as compared with carboplatin plus paclitaxel chemotherapy (median PFS: 9.5 vs 6.3 months; p<0.001). In a subgroup analysis, PFS due to Ex19del was significantly greater with gefitinib versus carboplatin plus paclitaxel chemotherapy group (median PFS: 11.0 vs 6.9 months; p=0.0018); however, PFS due to L858R exon 21 mutation subtype was similar between treatment arms. Neither erlotinib nor gefitinib treatment prolonged OS according to the EGFR mutation types (L858R exon 21 or Ex19del).
mutation and Asian patients, whereas osimertinib was associated with an improvement in OS among NSCLC patients with Ex19del-positive tumours and non-Asian ethnicity.  

Table 2 summarises the clinical trial results of EGFR TKIs in patients with EGFR mutation-positive NSCLC in 1L treatment settings.  

Based on the published clinical trials and the reported PFS for the TKIs, we propose an algorithm for the first-line systemic treatment of NSCLC with EGFR mutations Ex19del and 21 L858R (figure 2).  

Role of dacomitinib in EGFR mutation-positive (Ex19del and exon 21 L858R) NSCLC patients with brain metastasis  
Dacomitinib showed good brain penetration in preclinical models, with measurable concentrations in the cerebrospinal fluid. Recently, a retrospective study published by Peng et al evaluated the effects of 1L dacomitinib on 14 EGFR mutant-positive NSCLC patients with brain metastasis. Eight patients harbouring Ex19del, five harbouring exon 21 L858R and one harbouring EGFR G719A and I706 T comutations. Among these patients, five patients were administered dacomitinib at a starting dose of 45 mg once daily (OD), whereas nine patients received 30 mg OD until disease progression or unbearable toxicity. A measurable response of the intracranial metastases was observed in 85.7% of patients (12 of 14), together with 92.3% of patients with brain parenchymal metastasis. All patients had grade 1–2 adverse events (rash, paronychia, stomatitis or diarrhoea), but none discontinued treatment or required a dosage adjustment.  

Outcome differences with 2L EGFR TKIs between patients with Ex19del and exon 21 L858R mutation status  
A study published by Zheng et al evaluated the efficacy of 2L EGFR TKIs (gefitinib, erlotinib or icotinib) after 1L platinum-based doublet chemotherapy in metastatic NSCLC patients with Ex19del or exon 21 L858R substitution mutations. The study found that the Ex19del group of NSCLC patients had a significantly longer median PFS (6.7 vs 4.5 months, p=0.002) and median OS (13.7 vs 11.7 months, p=0.02) as compared with patients with the exon 21 L858R mutation status. The estimated 6-month and 1-year OS rates were 93.8% and 54.5%, respectively, in the Ex19del group of NSCLC patients with brain metastases, and 96.0% and 63.1% in the Ex19del group of NSCLC patients with bone metastases.  

GUIDELINE RECOMMENDATIONS FOR DACOMITINIB IN NSCLC PATIENTS WITH EX19DEL OR EXON 21 L858R EGFR MUTATION STATUS  
The 2019 Pan-Asian adaptation of the ESMO guideline recommends the systematic analysis of EGFR mutation status in patients with metastatic NSCLC. The guideline mentions that the test methodology should have adequate coverage of mutations in exons 18–21, including those associated with resistance to some therapies. When resources or materials are limited, the most common activating mutations (Ex19del and exon 21 L858R point mutations) should be determined. The guideline also recommends that NSCLC patients with sensitising EGFR mutation status should receive 1L EGFR TKI therapy with erlotinib, gefitinib or afatinib. However, none of the three EGFR TKIs are consensually considered a preferred option. Currently, 1L osimertinib is considered one of the options for patients with a tumour with sensitising EGFR mutations. Decisions regarding maintenance therapy must take into account histology, residual toxicity after 1L chemotherapy, response to platinum doublets, PS and patient preference. The 2022 NCCN clinical practice guidelines for NSCLC also recommend testing for EGFR mutations in patients with metastatic non-squamous NSCLC or not otherwise specified NSCLC based on clinical data showing the efficacy of several agents for patients with EGFR mutations. Osimertinib is the preferred 1L EGFR TKI option for patients with EGFR mutation-positive metastatic NSCLC. Dacomitinib is a category 1 option (other recommended) and may be considered if an Ex19del or exon 21 L858R mutation is discovered before giving 1L systemic therapy. In addition, dacomitinib is an option if Ex19del or exon 21 L858R mutation is discovered during 1L systemic therapy (carboplatin/(pemetrexed or paclitaxel)). For NSCLC patients with Ex19del or exon 21 L858R mutations who progress during or after 1L erlotinib, afatinib, gefitinib, dacomitinib or osimertinib therapy, the recommended subsequent therapy depends on whether the progression is asymptomatic or symptomatic and include (1) considering local therapy; (2) continuing erlotinib, afatinib, gefitinib, dacomitinib or osimertinib therapy; (3) switching to osimertinib (T790M-positive and if not previously administered and) or (4) consider systemic chemo/immunotherapy for patients who are T790M-negative.  

CONCLUSION  
We aimed at providing a descriptive comparative overview of clinicopathological features and survival outcomes after treatment with EGFR TKIs in NSCLC patients with Ex19del and exon 21 L858R EGFR mutation status. NSCLC patients with Ex19del mutation status are associated with a high risk of pleural effusion and lymph node, brain and bone metastases than patients with exon 21 L858R substitution mutation. Epidermal growth factor receptor mutation status (Ex19del and exon 21 L858R) can be used as a predictive factor for the efficacy of EGFR TKI as the 1L treatment among patients with metastatic NSCLC. Studies have shown that NSCLC patients with Ex19del have significantly better outcomes in terms of response and survival rates compared with patients with a mutation in exon 21 L858R. Osimertinib in 1L improved OS among NSCLC patients harbouring Ex19del mutation. Among NSCLC patients with exon 21 L858R substitution
<table>
<thead>
<tr>
<th>EGFR TKIs</th>
<th>Clinical trial</th>
<th>Comparator arm</th>
<th>Median PFS (months) (HR (95% CI))</th>
<th>Median OS (months) (HR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ex19del</td>
<td>Exon 21 L858R</td>
<td>Ex19del</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Common mutations</td>
<td></td>
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</tr>
<tr>
<td>Erlotinib</td>
<td>ENSURE (n=217)</td>
<td>Gemcitabine±cisplatin</td>
<td>11.0 (0.34 (0.22 to 0.51))‡</td>
<td>8.3 (0.57 (0.31 to 1.05))‡</td>
</tr>
<tr>
<td>(first generation)</td>
<td></td>
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<tr>
<td></td>
<td>EURTAC (n=174)</td>
<td>Platinum double chemotherapy</td>
<td>9.7 (0.37 (0.25 to 0.54))†</td>
<td>8.4 (0.55 (0.29 to 1.02))‡</td>
</tr>
<tr>
<td></td>
<td>OPTIMAL (n=165)</td>
<td>Platinum double chemotherapy</td>
<td>13.1 (0.16 (0.10 to 0.26))‡</td>
<td>12.5 (0.26 (0.14 to 0.49))‡</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>IPASS (n=1217)</td>
<td>Carboplatin±paclitaxel</td>
<td>11.0 (0.38 (0.26 to 0.56))‡</td>
<td>9.2 (0.55 (0.35 to 0.87))‡</td>
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<td>(first generation)</td>
<td></td>
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<tr>
<td></td>
<td>NEJ002 (n=228)</td>
<td>Carboplatin±paclitaxel</td>
<td>10.8 (0.30 (0.22 to 0.41))‡</td>
<td>11.5‡</td>
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<td></td>
<td>WJTOG3405 (n=172)</td>
<td>Cisplatin±docetaxel</td>
<td>9.2 (0.49 (0.34 to 0.71))‡</td>
<td>10.8‡</td>
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<td>Afatinib</td>
<td>LUX-Lung 3 (n=345)</td>
<td>Pemetrexed±cisplatin</td>
<td>13.6 (0.47 (0.34 to 0.65))‡</td>
<td>13.7 (0.28 (0.18 to 0.44))</td>
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<td>(second generation)</td>
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<td>10.8 (0.73 (0.46 to 1.17))</td>
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<td></td>
<td>LUX-Lung 6 (n=364)</td>
<td>Gemcitabine±cisplatin</td>
<td>11.0 (0.25 (0.18 to 0.35))</td>
<td>13.7 (0.20 (0.13 to 0.33))</td>
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<td></td>
<td>LUX-Lung 7 (n=319)</td>
<td>Gefitinib</td>
<td>11.0 (0.73 (0.57 to 0.95))</td>
<td>12.7 (0.76 (0.55 to 1.06))</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>ARCHER 1050 (n=452)</td>
<td>Gefitinib</td>
<td>14.7 (0.59 (0.47 to 0.74))§</td>
<td>16.5 (0.55 (0.41 to 0.75))</td>
</tr>
<tr>
<td>(second generation)</td>
<td></td>
<td></td>
<td></td>
<td>12.3 (0.63 (0.44 to 0.88))*</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>FLAURA (n=556)</td>
<td>Gefitinib or erlotinib</td>
<td>17.7 (0.45 (0.36 to 0.57))‡</td>
<td>21.4 (0.43 (0.32 to 0.56))*</td>
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<tr>
<td>(third generation)</td>
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<td></td>
<td></td>
<td>14.4 (0.51 (0.36 to 0.71))*</td>
</tr>
</tbody>
</table>

*HR for PFS between the TKI and the chemotherapy comparator in each study.
†HR for OS between the TKI and the comparator in each study.
‡Investigator review.
§BICR.
EGFR, epidermal growth factor receptor; NR, not reported; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; TKIs, tyrosine kinase inhibitors.
mutation and Asian ethnicity, dacomitinib improved OS in 1L treatment settings. In 2L treatment settings, there are limited studies that assess outcome differences with EGFR TKIs between patients with Ex19del and exon 21 L858R mutation status.

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