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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.

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.[49]

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] Adenocarcinoma is considered the most common histology in NSCLC and comprises approximately 40% of all lung cancer cases globally.[2] In India, lung cancer is one of the most common cancers, with a reported adenocarcinoma positivity ranging between 26.1% and 86.9% in patients with NSCLC.[6] The most common oncogenic driver in NSCLC is the epidermal growth factor receptor (*EGFR*) gene mutations that occur more frequently in Asian patients (30%–50%) as opposed to Caucasians (10%–15%).[7] The PIONEER study was the first, prospective, multinational, molecular epidemiological study that reported *EGFR* mutations in Asian patients (China, Hong Kong, India, Philippines, Taiwan, Thailand and Vietnam) with

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%).[8] Chougule *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).[9] The study also reported the overall *EGFR* mutation rate in the adenocarcinoma patient population as 26%.[9] 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%.[10] 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.[9 11–14] 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).[6] A higher preponderance of *EGFR* mutation positivity was observed in females than in males (42.2% vs 26.5%) and in non-smokers than in smokers (40.9% vs 21.4%).[6] 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%).[15 16] 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.[5 17] The 5-year relative survival rate for metastatic NSCLC is nearly 6% in patients receiving cytotoxic chemotherapy regimens.[18] 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.[5] 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.[19 20] Exon 19 deletions are more commonly detected in Northern Asia as compared with Europe, North America and South America.[19] On the other hand, exon 21 L858R mutations are more commonly detected in Southern Asia as compared with other regions.[19] In India, Ex19del (39.3%–81%) is more common than exon 21 L858R point mutations (14.9%–50.7%) in NSCLC patients.[6] Choughule *et al* evaluated the incidence of Ex19del and exon 21 L858R point mutations in Indian NSCLC patients based on gender and smoking status.[21] 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.[21] 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).[11] 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).[11]

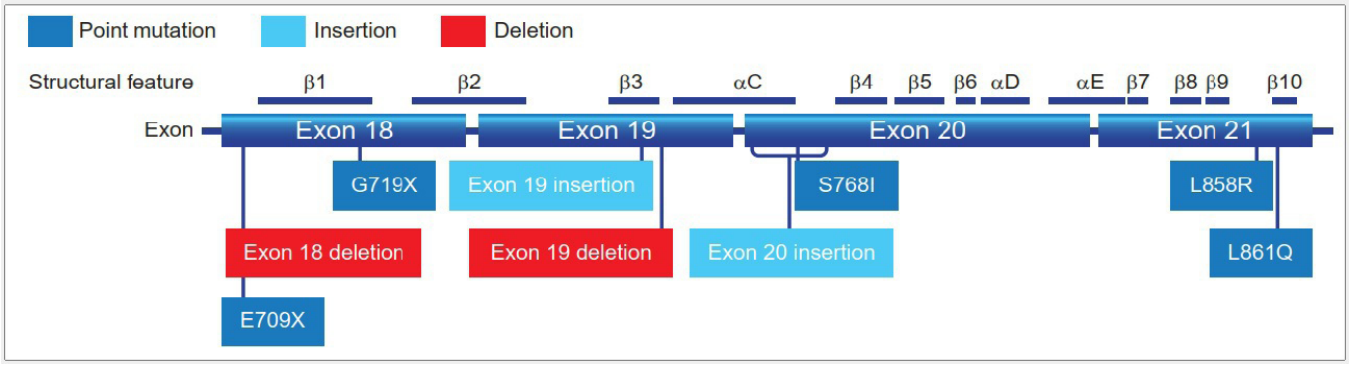

Figure 1 Point mutations, deletions and insertions within exons 18–21 of the *EGFR* gene in NSCLC patients. Adapted from: Harrison *et al*.[15] EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer.

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.[11] 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).[22] 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.[22]

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.[22] 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.[22] 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.[23] 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.[23] Brain and bone metastases are life-threatening complications in patients with advanced-stage NSCLC.[24] Studies have revealed that the incidence of brain and bone metastases may be associated with *EGFR* mutation status in NSCLC patients.[11 24–28] 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.[29] The study concluded that NSCLC patients harbouring Ex19del had a potential higher risk of brain metastasis than patients with exon 21 L858R mutation status.[29] Similar results were observed in another Indian study published by Doval *et al*, where exon 21 L858R 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).[11] 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%).[11] Table 1 highlights the differences in clinical characteristics and prognostic factors between Ex19del and exon 21 L858R *EGFR* mutation-positive NSCLC patients.

COMPARISON 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.[30] 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.[31] 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).[31] 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.[18 32 33]

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

Table 1 Summary of differences in clinical characteristics and prognostic factors between Ex19del and exon 21 L858R *EGFR mutation*-positive NSCLC patients

Summary: differences in clinical characteristics and prognostic factors (Ex19del vs exon 21 L858R *EGFR* mutation status)	
Gender and smoking status	(1) Ex19del *EGFR* mutation significantly correlated with the female gender and no history of smoking.
	(2) Exon 21 L858R mutations are more common in male smokers.
EGFR Ex19del mutations significantly correlated with a high serum carcinoembryonic antigen level of ≥5 ng/mL.	
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.	
Age and N stage may be considered while predicting the *EGFR* mutation type in NSCLC.	

EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; NSCLC, non-small-cell lung cancer.

tyrosine kinase domain on the *EGFR* receptor and inhibit autophosphorylation and downstream signalling.[34] Erlotinib 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.[35 36] 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.[37] In the phase 3 OPTIMAL trial, significant progression-free survival (PFS) benefit with 1L erlotinib versus gemcitabine plus carboplatin chemotherapy (median PFS: 13.1 vs 4.6 months; p<0.0001) was reported in Chinese patients.[38] 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).[38] 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).[39] The PFS benefit seen in the erlotinib 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).[39] The data from the phase 3 IPASS study confirmed PFS benefit with 1L gefitinib in *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).[40] 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.[40] Neither erlotinib nor gefitinib treatment prolonged OS according to the *EGFR* mutation types (L858R exon 21 or Ex19del).[41]

Outcome differences with second-generation EGFR TKIs between patients with Ex19del and exon 21 L858R mutation status in 1L treatment settings

Second-generation *EGFR* TKI afatinib irreversibly inhibits *EGFR*, *HER2* and *HER4* by blocking transphosphorylation of tyrosine residues in the C-terminus, resulting in a longer suppression of ErbB signalling and efficient total blockade of the *EGFR* signalling pathway.[42] However, with time, a majority of patients acquire resistance to these agents. Studies have demonstrated that, similar to first-generation *EGFR* TKIs (gefitinib and erlotinib), the *EGFR* T790M secondary point mutation is a prevalent mechanism of resistance to afatinib, detected in 50%–70% of patients.[42] In patients with NSCLC harbouring Ex19del-positive tumours, 1L afatinib significantly improved OS as compared with that with chemotherapy, as reported in LUX-Lung 3 (comparator arm: cisplatin plus pemetrexed; median OS: 33.3 vs 21.1 months; p=0.0015) and LUX-Lung 6 (comparator arm: gemcitabine plus cisplatin; median OS: 31.4 vs 18.4 months; p=0.023) phase 3 studies.[42] Conversely, no significant differences were found in OS between afatinib and chemotherapy for patients with *EGFR* L858R exon 21 mutations.[42] In the phase 2b LUX-Lung 7 trial, no significant difference was observed in OS between afatinib and gefitinib in patients with NSCLC harbouring an Ex19del or L858R exon 21 mutation status.[43] Dacomitinib is another highly selective second-generation *EGFR* TKI that irreversibly inhibits *EGFR*, *HER2* and *ErbB4*, but it is significantly more potent in inhibiting *EGFR* than other members of the *HER* family.[42] It was approved in 2018 in the USA for the 1L treatment of *EGFR* mutation-positive metastatic NSCLC patients harbouring Ex19del or L858R exon 21 substitution mutations, based on the results from the phase 3 ARCHER 1050 study.[42 44 45] Subsequently, dacomitinib received marketing authorisation from the European Medicine Agency in April 2019.[45] In addition, dacomitinib has been approved in Japan for the treatment of *EGFR* mutation-positive recurrent or inoperable NSCLC patients.[45] PFS benefit with dacomitinib versus gefitinib was observed in NSCLC patients with Ex19del (median PFS 16.5 vs 9.2 months; HR 0.55; 95% CI 0.41 to 0.75) and exon 21 L858R (median PFS 12.3 vs 9.8 months; HR 0.63; 95% CI 0.44 to 0.88) mutations.[42 46 47] No significant differences were found in OS between dacomitinib and gefitinib for NSCLC patients with Ex19del-positive tumours.[47] In the updated OS analysis of ARCHER 1050, significant improvement of OS with dacomitinib versus gefitinib was observed in patients with exon 21 L858R substitution mutation. For the subgroup with exon 21 L858R substitution mutation the HR for OS with dacomitinib versus gefitinib was 0.665 (95% CI 0.470 to 0.941; two-sided p=0.0203), and the median OS was 32.5 months (95% CI 25.5 to 39.5) vs 23.2 months (95% CI 19.6 to 28.9).[47]

Outcome differences with third-generation versus older-generation EGFR TKIs among patients with Ex19del and exon 21 L858R mutation status in 1L treatment settings

Osimertinib is a third-generation irreversible *EGFR* TKI for both *EGFR*-sensitising and T790M-resistance mutations, with selectivity over the wild-type form of the receptor.[42] The PFS benefit with osimertinib in the FLAURA trial was consistent across the NSCLC patient subgroups, including patients with Ex19del and L858R mutations.[48] In a network meta-analysis study by Farris *et al*, dacomitinib had a numerical improvement of OS compared with afatinib, erlotinib and osimertinib, with significant improvement versus gefitinib.[49] Furthermore, dacomitinib was associated with an improvement in OS among NSCLC patients with exon 21 L858R substitution

mutation and Asian patients, whereas osimertinib was associated with an improvement in OS among NSCLC patients with Ex19del-positive tumours and non-Asian ethnicity.[49] Table 2 summarises the clinical trial results of *EGFR* TKIs in patients with *EGFR* mutation-positive NSCLC in 1L treatment settings.[42]

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).[40 43 46 48 50]

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.[46] 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.[51] Eight patients harboured Ex19del, five harboured exon 21 L858R and one harboured *EGFR* G719A and I706 T comutations.[51] 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.[51] 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.[51] All patients had grade 1–2 adverse events (rash, paronychia, stomatitis or diarrhoea), but none discontinued treatment or required a dosage adjustment.[51]

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.[24] 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.[24] 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 metastasis.[24]

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.[52] 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.[52] When resources or materials are limited, the most common activating mutations (Ex19del and exon 21 L858R point mutations) should be determined.[52] The guideline also recommends that NSCLC patients with sensitising *EGFR* mutation status should receive 1L *EGFR* TKI therapy with erlotinib, gefitinib or afatinib.[52] 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.[52] Decisions regarding maintenance therapy must take into account histology, residual toxicity after 1L chemotherapy, response to platinum doublets, PS and patient preference.[52] 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.[17] Osimertinib is the preferred 1L *EGFR* TKI option for patients with *EGFR* mutation-positive metastatic NSCLC.[17] 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.[17] In addition, dacomitinib is an option if Ex19del or exon 21 L858R mutation is discovered during 1L systemic therapy (carboplatin/(pemetrexed or paclitaxel)).[17] 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.[17]

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 2 A summary of the clinical trial results of *EGFR* TKIs in patients with *EGFR* mutation-positive NSCLC in first-line treatment settings. Adapted from: Shah *et al*.[42]

Clinical trial results of *EGFR* TKIs in patients with *EGFR* mutation-positive NSCLC (First-line treatment settings)							
***EGFR* TKIs**	**Clinical trial**	**Comparator arm**	**Median PFS (months) (HR (95% CI))***			**Median OS (months) (HR (95% CI))†**	
			Common mutations	**Ex19del**	**Exon 21 L858R**	**Ex19del**	**Exon 21 L858R**
Erlotinib (first generation)	ENSURE (n=217)	Gemcitabine±cisplatin	11.0 (0.34 (0.22 to 0.51))‡	11.1 (0.20 (0.11 to 0.37))‡	8.3 (0.57 (0.31 to 1.05))‡	NR (0.79 (0.48 to 1.30))	NR (1.05 (0.60 to 1.84))
	EURTAC (n=174)	Platinum double chemotherapy	9.7 (0.37 (0.25 to 0.54))‡	11.0 (0.30 (0.18 to 0.50))‡	8.4 (0.55 (0.29 to 1.02))‡	NR (0.94 (0.57 to 1.54))	NR (0.99 (0.56 to 1.76))
	OPTIMAL (n=165)	Platinum double chemotherapy	13.1 (0.16 (0.10 to 0.26))‡	15.3 (0.13 (0.07 to 0.25))‡	12.5 (0.26 (0.14 to 0.49))‡	27.0 (1.52 (0.92 to 2.52))	21.5 (0.92 (0.55 to 1.54))
Gefitinib (first generation)	IPASS (n=1217)	Carboplatin±paclitaxel	NR	11.0 (0.38 (0.26 to 0.56))‡	9.2 (0.55 (0.35 to 0.87))‡	27.2 (0.79 (0.54 to 1.15))	18.7 (1.44 (0.90 to 2.30))
	NEJ002 (n=228)	Carboplatin±paclitaxel	10.8 (0.30 (0.22 to 0.41))‡	11.5‡	10.8‡	28.9 (0.83 (0.52 to 1.34))	28.0 (0.82 (0.49 to 1.38))
	WJTOG3405 (n=172)	Cisplatin±docetaxel	9.2 (0.49 (0.34 to 0.71))‡	NR (0.45 (0.27 to 0.77))‡	NR (0.51 (0.29 to 0.90))‡	35.2 (NR)	32.2 (NR)
Afatinib (second generation)	LUX-Lung 3 (n=345)	Pemetrexed±cisplatin	13.6 (0.47 (0.34 to 0.65))	13.7 (0.28 (0.18 to 0.44))	10.8 (0.73 (0.46 to 1.17))	33.3 (0.54 (0.36 to 0.79))	27.6 (1.30 (0.80 to 2.11))
	LUX-Lung 6 (n=364)	Gemcitabine±cisplatin	11.0 (0.25 (0.18 to 0.35))	13.7 (0.20 (0.13 to 0.33))	9.6 (0.32 (0.19 to 0.52))	31.4 (0.64 (0.44 to 0.94))	19.6 (1.22 (0.81 to 1.83))
	LUX-Lung 7 (n=319)	Gefitinib	11.0 (0.73 (0.57 to 0.95))	12.7 (0.76 (0.55 to 1.06))	10.9 (0.71 (0.48 to 1.06))	30.7 (0.83 (0.58 to 1.17))	25.0 (0.91 (0.62 to 1.36))
Dacomitinib (second generation)	ARCHER 1050 (n=452)	Gefitinib	14.7 (0.59 (0.47 to 0.74))§	16.5 (0.55 (0.41 to 0.75))	12.3 (0.63 (0.44 to 0.88))*	34.1 (0.88 (0.61 to 1.26))	32.5 (0.71 (0.48 to 1.05))
Osimertinib (third generation)	FLAURA (n=556)	Gefitinib or erlotinib	17.7 (0.45 (0.36 to 0.57))‡	21.4 (0.43 (0.32 to 0.56))*	14.4 (0.51 (0.36 to 0.71))*	NR (0.68 (0.51 to 0.90))	NR (1.00 (0.74 to 1.40))

*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.

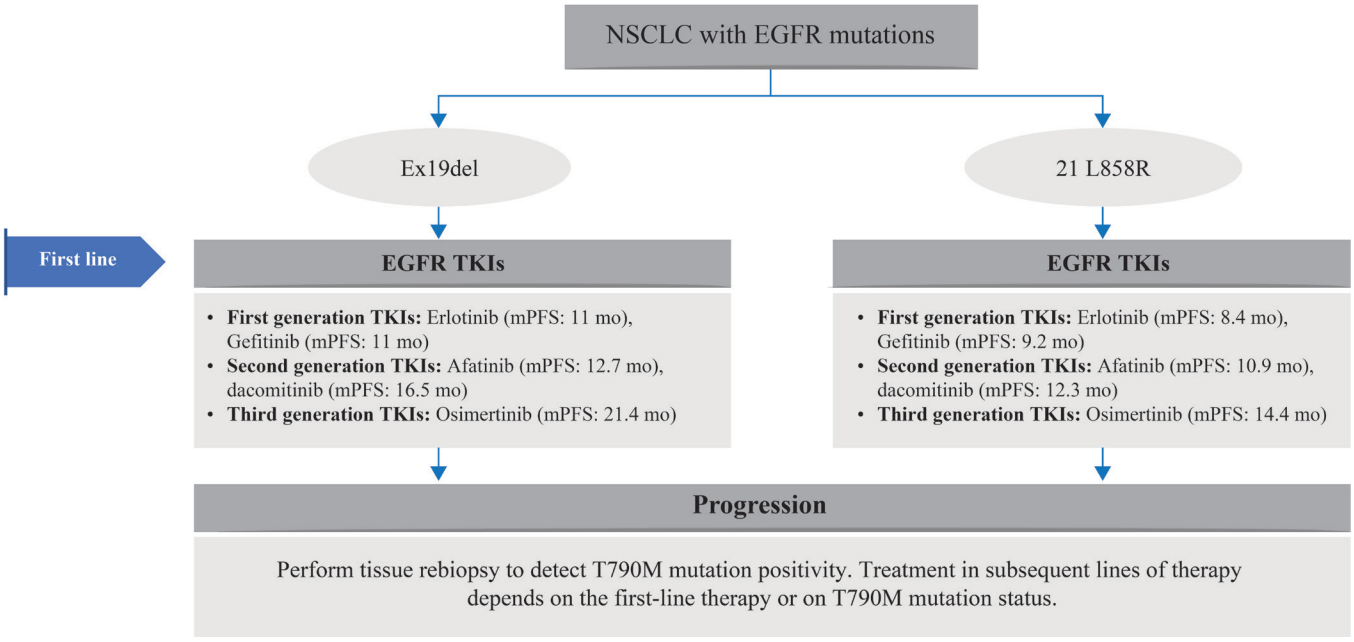

Figure 2 Proposed algorithm for the first line systemic treatment of NSCLC with EGFR mutations Ex19del and 21 L858R.[40 43 46 48 50] mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; TKI, tyrosine kinase inhibitor.

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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