

Expanding Possibilities in *EGFR*-Mutated Advanced NSCLC: Interviews with Four Key Opinion Leaders

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Interview Summary

Recent studies have identified several driver gene mutations in non-small cell lung cancer (NSCLC).¹ Epidermal growth factor receptor (*EGFR*) mutations are the second most common oncogenic driver event in NSCLC.²⁻⁴ Furthermore, the two most common *EGFR* mutations are exon 19 deletion and L858R substitution mutation.⁵⁻⁷ Advances in the understanding of these mutations have led to new approaches to the diagnosis and the development of *EGFR*-targeted therapies, enabling personalised treatment and improved outcomes for patients with advanced NSCLC.⁷ In this article, four leading experts discuss the expanding possibilities for patients with *EGFR*-mutated advanced NSCLC. These valuable insights were

obtained from a series of interviews conducted with EMJ. The topics discussed include the epidemiology and emerging treatment paradigm of *EGFR*-mutated advanced NSCLC. Consideration is also given to factors that potentially influence the choice of appropriate treatment for patients, particularly in the first-line setting, in light of recent clinical evidence, including FLAURA overall survival (OS) data⁸ and RELAY progression-free survival (PFS) data.⁹

WHAT ARE THE UNMET NEEDS IN TREATING NSCLC?

Doctor Maximilian Hochmair

Background and Epidemiology

Worldwide, there were approximately 2.10 million patients diagnosed with, and 1.77 million deaths caused by, lung cancer in 2018.¹⁰ Approximately 85% of these cases were NSCLC,¹¹ and the majority of patients presented with advanced disease at diagnosis.¹² Traditionally, NSCLC was classified by histology but the classification paradigm has evolved to incorporate molecular subtypes to guide treatment decision making. One molecular subtype, *EGFR* mutations, was discovered in 2004 to be present in a subset of patients with NSCLC,^{13,14} and prevalence has ranged from 50–60% in Asian populations,^{5,6,15} 10–15% in European populations,^{3,4,16} and 22% in North American populations.^{17,18} The aetiology, clinicopathological features, prognosis, and treatment paradigms in patients with *EGFR*-mutated NSCLC are distinct when compared with other NSCLC molecular subtypes.^{7,13–15,17}

Current Treatment

Historically, chemotherapy was recommended as the first-line treatment in patients with advanced NSCLC.^{19–21} However, chemotherapy has significant toxicity, the therapeutic effect is limited, and the clinical outcomes are modest (median OS time of 8–10 months and a 5-year survival rate of approximately 15%).^{22,23} Discovery of mutations within the kinase domain of the *EGFR* gene has enabled a new era of targeted therapy in lung cancer.^{14,15,24} *EGFR*-tyrosine kinase inhibitors (TKI) have shown significant efficacy, are associated with fewer side effects, and have improved quality of life for patients with *EGFR*-mutated NSCLC, particularly those harbouring the exon 19

deletion or L858R.^{8,9,25–33} Currently, there are five different *EGFR*-TKI available for first-line use in *EGFR*-mutated NSCLC. The first-generation *EGFR*-TKI bind competitively and reversibly to the ATP-binding site of the *EGFR* tyrosine kinase domain and include erlotinib and gefitinib. Second-generation *EGFR*-TKI include afatinib and dacomitinib, which can covalently and irreversibly inhibit the enzymatic activation of *EGFR* (T790M), wild-type *EGFR*, and activating *EGFR* mutations. The third-generation *EGFR*-TKI osimertinib selectively and irreversibly blocks *EGFR* (T790M) and activating *EGFR* mutations, but not wild-type *EGFR*.^{34–36} Since 2004, there has been a number of randomised studies clearly showing the benefits of targeted therapy.^{6,8,9,25–33}

Unmet Needs Associated with Current Treatment

Dr Hochmair believes that the availability of three generations of *EGFR*-TKI with different clinical profiles has revolutionised the treatment of *EGFR*-mutated NSCLC. However, despite initial clinical response to *EGFR*-TKI, virtually all advanced *EGFR*-mutated NSCLC inevitably acquire resistance mechanisms and progress at some point during treatment with gefitinib, erlotinib, dacomitinib, afatinib, and osimertinib. The most common acquired resistance to first- and second-generation *EGFR*-TKI is via a unique gatekeeper mutation: the exon 20 point-mutation T790M in the ATP-binding site of *EGFR*.³⁷ The T790M mutation activates wild-type *EGFR* and increases ATP affinity.³⁷ The incidence of T790M ranges from 49–63%.^{38–41} Other mechanisms of secondary resistance include activation of *HER2*, *MET*, *PIK3CA*, *BRAF*, *NF1*, *FGFR*, *AXL*, and the hedgehog signalling pathway.⁴¹ There are currently no further targeted therapy options available following osimertinib failure, and most patients will proceed to chemotherapy.^{22,42} Thus, there is an unmet need in *EGFR*-mutated advanced

NSCLC for new treatment strategies, such as drug combinations, to delay the emergence of acquired resistance and disease progression.⁹

Rationale of Dual Blockade Treatment for *EGFR*-Mutated Advanced NSCLC

Angiogenesis and neovascularisation are critical for the growth, progression, and metastasis of NSCLC. Therefore, angiogenic pathways, including vascular endothelial growth factor (VEGF), fibroblast growth factor, and platelet-derived growth factor, are important biologic targets for tumour growth inhibition. Targeted therapies include neutralising antibodies to VEGFA (bevacizumab) and VEGF receptor 2 (VEGFR2) (ramucirumab), as well as receptor TKI that have preferential selectivity for the VEGFR.⁴³ Preclinical studies have demonstrated that dual blockade of the EGFR and VEGF pathways improved antitumour activity compared with inhibition of the EGFR pathway alone. Several clinical trials have shown promising results with the combination of the anti-VEGFA antibody bevacizumab with an EGFR-TKI; however, conclusions in these trials were limited by small sample sizes, Asian-only populations, and open-label designs.^{9,42} More recently, the RELAY study demonstrated the benefit of dual blockade treatment with the monoclonal antibody ramucirumab in combination with the EGFR-TKI erlotinib. Ramucirumab is a human IgG1 antibody selective for VEGFR2 that inhibits binding of the VEGFA, VEGFC, and VEGFD ligands to VEGFR2. The RELAY study showed a significantly improved PFS with the combination of ramucirumab plus erlotinib versus erlotinib plus placebo as a front-line treatment for patients with *EGFR*-mutated NSCLC. The median PFS for the ramucirumab combination was higher than observed historically.^{6,9,25-33} These outcomes led Dr Hochmair to advocate the use of dual blockade with an antiangiogenic and an EGFR-TKI as first-line therapy in appropriate patients with *EGFR*-mutated NSCLC. He concluded: "The availability of three generations of *EGFR*-TKI with different clinical profiles has revolutionised the treatment of *EGFR*-mutated NSCLC. I believe that liquid-biopsy-based identification

(versus cobas[®] [Roche Holding AG, Basel, Switzerland] *EGFR*-mutation testing) of *EGFR* T790M mutation-mediated resistance can better inform treatment sequencing decisions in *EGFR*-mutated NSCLC. I would advocate the use of ramucirumab plus erlotinib as first-line therapy in appropriate patients with *EGFR*-mutated NSCLC."

WHAT DID THE RELAY CLINICAL TRIAL SHOW?

Professor Martin Reck

RELAY Trial Study Design

RELAY⁹ was a multicentre, double-blind, randomised clinical trial comparing an anti-VEGFR2 antibody plus a first-generation EGFR-TKI to the standard of care alone. The primary question Prof Reck wanted to answer was whether the combination regimen could improve efficacy in *EGFR*-mutated metastatic NSCLC. The study enrolled 449 patients in 100 centres in 13 countries. Adult patients with Stage IV NSCLC, confirmed *EGFR* exon 19 deletion or L858R mutation, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for enrolment. Patients were ineligible if they had a known *EGFR* T790M mutation, prior treatment with an EGFR-TKI or chemotherapy, or had brain metastases.

Patients were randomised in a 1:1 ratio to receive either combination therapy with ramucirumab 10 mg/kg every 2 weeks plus erlotinib 150 mg/day, or monotherapy with erlotinib 150 mg/day plus placebo. Patients were stratified by sex, geographical region, *EGFR* mutation type, and *EGFR* testing method.

The primary endpoint was investigator-assessed PFS in the intention-to-treat population. Independent PFS was also performed using a centralised radiological review of CT or MRI scans. Secondary endpoints included OS, overall response rate, duration of response (DoR), safety and toxicity, pharmacokinetics and immunogenicity, and patient-reported outcomes. Exploratory endpoints were PFS2 (defined as the time from randomisation to progression after a

subsequent therapy) and the identification of biomarkers.

RELAY Trial Efficacy

At a median follow-up of 20.7 months, the investigator-assessed median PFS in the ramucirumab arm was 19.4 months (95% confidence interval [CI]: 15.4–21.6), which was significantly longer than the 12.4 months in the placebo arm (95% CI: 11.0–13.5; hazard ratio [HR]: 0.59; 95% CI: 0.461–0.760; $p<0.0001$) (Figure 1).⁹ The 1-year PFS also improved in the combination (ramucirumab plus erlotinib) group (71.9%; 95% CI: 65.1–77.6) compared with the placebo plus erlotinib group (50.7%; 95% CI: 43.7–57.3). The blinded independent radiological review (440 patients had evaluable scans) and analysis in the per-protocol population (437 evaluable patients)

showed PFS results consistent with the primary investigator-assessed PFS analysis.

In addition, DoR and PFS2 were improved with ramucirumab plus erlotinib compared with erlotinib plus placebo (median DoR: 18.0 months [95% CI: 13.9–19.8] versus 11.1 months [95% CI: 9.7–12.3], respectively, PFS2: HR: 0.690; 95% CI: 0.490–0.972).

This PFS benefit appeared not to be driven by an improvement in the overall response rate, which was not significantly different in the combination and monotherapy arms (76% versus 75%). OS data were immature at data cut-off for this analysis; however, at this stage, there was no significant difference between treatment groups. Prof Reck believes that, in the absence of mature OS data, the favourable PFS2 that incorporates the next line of therapy suggest the possibility of OS benefit.

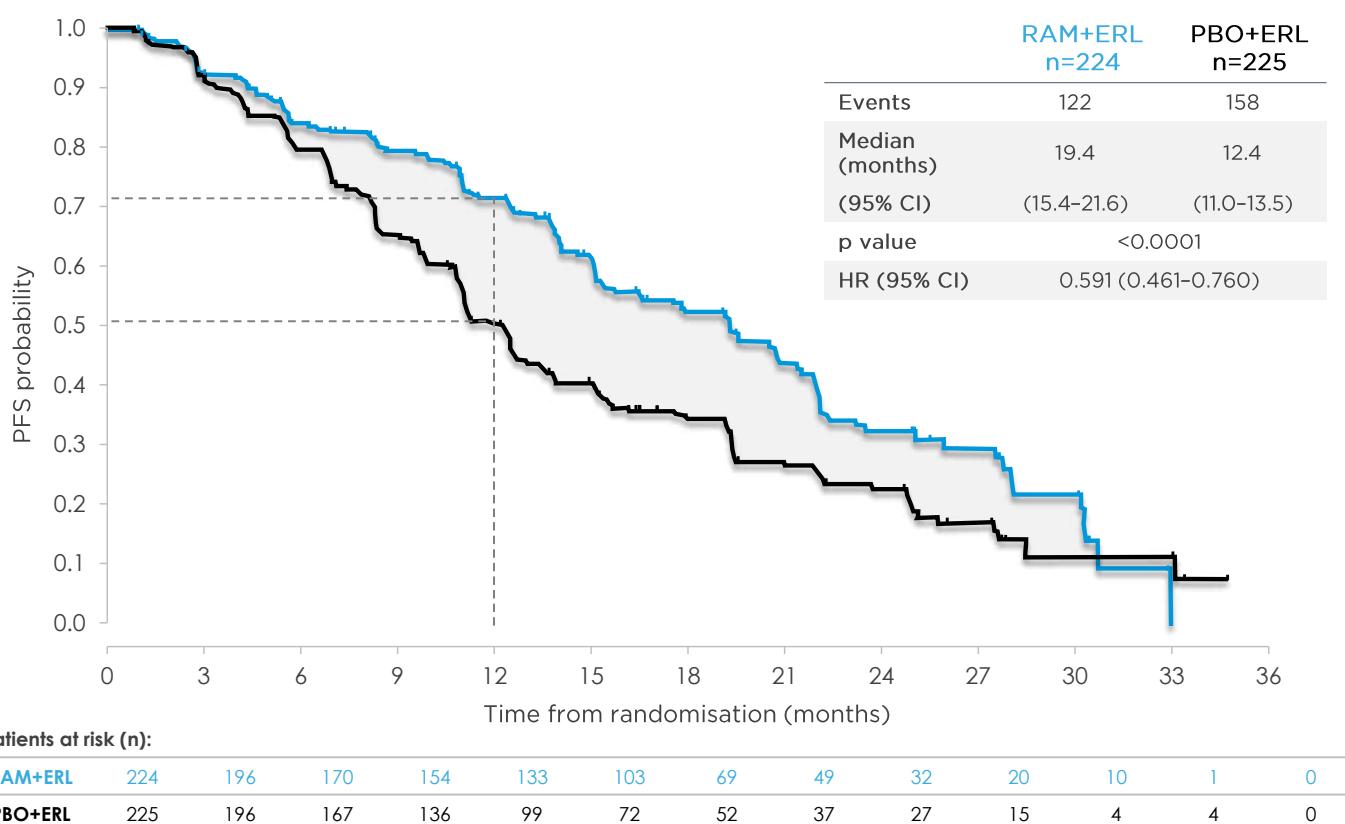


Figure 1: RELAY primary endpoint: investigator-assessed progression-free survival.

Data from Nakagawa K et al. Lancet Oncol. 2019;20(12):1655–1669.⁹

Consistent PFS benefit by independent, blinded central review (HR: 0.671; 95% CI: 0.518–0.869; $p=0.0022$).

CI: confidence interval; ERL: erlotinib; HR: hazard ratio; PBO: placebo; PFS: progression-free survival; RAM: ramucirumab.

At the time the data were presented, 29% (64/224) of patients in the combination arm and 19% (43/225) in the monotherapy arm were still receiving the study treatment.

RELAY Trial Study Safety

No new adverse events (AE) were identified in this study. The rate of treatment-emergent AE (TEAE) of at least Grade 3 was higher among the combination-treated than monotherapy-treated patients, at 72% and 54%, respectively (Table 1).⁹ Most of the TEAE could be addressed with treatment discontinuation or dose reduction. Hypertension was the most common TEAE; 24% experienced Grade 3 hypertension in the combination arm compared with 5% in the monotherapy arm, and there were no incidences of Grade 4 or 5 hypertension in either group. A comparable 13% in the combination group and 11% in the monotherapy group discontinued all study drugs because of TEAE (Table 1). The majority of the observed bleeding events that occurred were related to epistaxis and there was no increased rate of severe pulmonary bleeding events in the

combination arm. Two deaths (0.9%) occurred in the combination treatment group: one was considered a related AE (haemothorax) and one was considered a TEAE not related to study treatment (encephalitis influenza). No deaths occurred in the monotherapy group.

To Prof Reck, the most interesting result was that the PFS benefit in the ramucirumab arm was observed regardless of mutation type. This is the first study showing comparable efficacy rates in both mutation types, as commonly patients with L858R mutation have poorer outcomes.

In this study, most subgroups appeared to have a PFS advantage following the addition of ramucirumab to erlotinib. Furthermore, comparable and consistent efficacy was achieved in both East Asian (75% were Asian) and non-East Asian populations. The treatment-emergent, resistance-mediating *EGFR* T790M rates were also similar between groups ($p=0.849$); ramucirumab plus erlotinib (43%; 95% CI: 30–58%) and erlotinib plus placebo (47%; 95% CI: 36–58%).

	Ramucirumab + erlotinib (n=221)	Placebo + erlotinib (n=225)
Any TEAE	221 (100.0)	225 (100.0)
Grade ≥ 3	159 (71.9)	121 (53.8)
Serious TEAE	65 (29.4)	47 (20.9)
Discontinued all study treatment due to TEAE*	28 (12.7)	24 (10.7)
Discontinued all study treatment due to Grade ≥ 3 TEAE	15 (6.8)	13 (5.8)
Discontinued due to SAE	10 (4.5)	9 (4.0)
TEAE leading to dose adjustment, any drug	187 (84.6)	160 (71.1)
Deaths on study treatment due to AE†	2 (0.9)	0 (0.0)

Table 1: RELAY safety overview.

Data from Nakagawa K et al. Lancet Oncol. 2019;20(12):1655-1669.⁹

*The most frequent reasons for discontinuation because of an AE were increased alanine aminotransferase (n=3, ramucirumab arm; n=4, placebo arm), paronychia (n=3, ramucirumab; n=0, placebo), and abnormal hepatic function (n=0, ramucirumab; n=3, placebo).

†Of the two deaths in the ramucirumab plus erlotinib group, one was considered a related AE (haemothorax) and one was considered a TEAE not related to study treatment (encephalitis influenza).

Data shown as: n (%).

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

Therefore, both groups could qualify for post-progression sequential osimertinib therapy. In summary, Prof Reck considers that the RELAY trial provided prospective confirmation that dual blockade with an antiangiogenic agent and an EGFR inhibitor is a viable and valuable first-line treatment strategy for patients with *EGFR*-mutated metastatic NSCLC. He summarised: “The RELAY regimen of ramucirumab plus erlotinib is, therefore, a viable new treatment option for the initial treatment of patients with *EGFR*-mutated advanced NSCLC.”

ARE ALL *EGFR*-MUTATIONS SIMILAR?

Doctor Ignacio Gil-Bazo

Common *EGFR* Mutations

NSCLC is associated with a poor prognosis:⁴⁴ the 5-year survival for patients with *EGFR*-

mutated NSCLC is 14.6%.⁴⁵ The identification of specific actionable mutations and development of molecular profiling in advanced NSCLC has enabled more personalised therapeutic strategies and resulted in improved outcomes.¹⁸ EGFR, a member of the ErbB receptor TK family, plays an important role in the development and progression of NSCLC.⁴⁶ *EGFR* activates JAK, PI3K, reactive oxygen species, and Ras pathways and overexpression can cause cell proliferation, angiogenesis, tumour invasion, metastasis, and inhibition of cell apoptosis.⁴⁷⁻⁴⁹ The most common *EGFR* mutations are exon 19 deletion (45% of patients) and L858R mutations (40%).⁷ The ‘uncommon’ *EGFR* mutations account for 10–18% of all *EGFR* mutations and primarily consist of a heterogeneous group of genetic alterations (exon 18 G719, exon 21 L861, and exon 20 S768I mutations).⁵⁰⁻⁵²

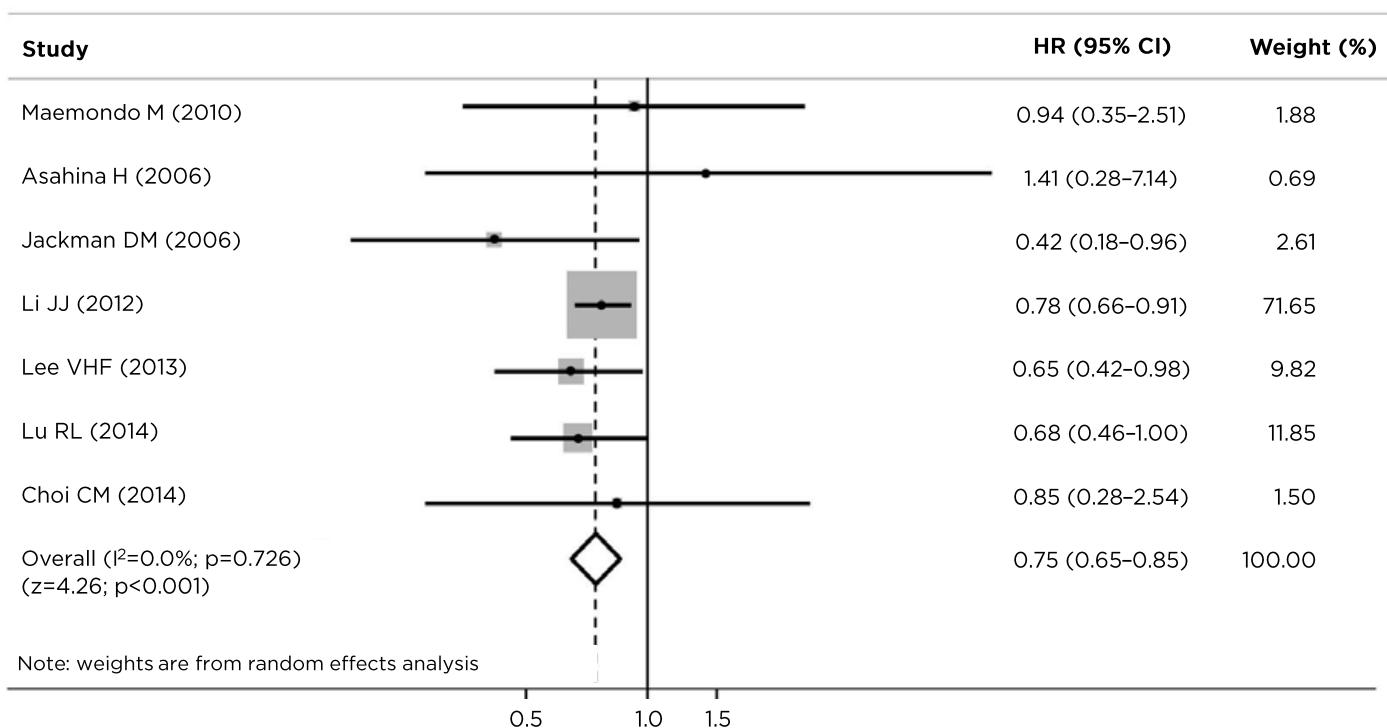


Figure 2: Progression-free survival with tyrosine kinase inhibitor therapy in patients with *EGFR* exon 19 deletions versus L858R mutations.

Based on the data from seven studies, patients with advanced non-small cell lung cancer with exon 19 deletion benefited from longer progression-free survival than those with an L858R mutation (HR [exon 19/21]: 0.75; 95% CI: 0.65–0.85; $p<0.001$).

CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio.

Data from Zhang *et al.*⁶²

More clinicians are requesting *EGFR* mutation tests for their patients with NSCLC during initial diagnosis because of improved detection techniques, availability of clinical guidelines and working group recommendations, and the increased number of testing facilities.⁵³⁻⁵⁸

Exons 19 and 21

Several studies have demonstrated that *EGFR* is uniquely expressed in tumour tissues, particularly NSCLC.^{13,14} Increasing use of TKI in patients with *EGFR*-mutated NSCLC has provided accumulating evidence that exon 19 deletions and L858R mutations are associated with differing clinicopathological characteristics and predictive and prognostic values and outcomes.^{7,59-61} Exon 21 mutations are more common in females, never-smokers, adenocarcinomas, and low-grade tumours.⁷ A pooled meta-analysis of patients with advanced NSCLC found that patients with exon 19 deletion had significantly reduced risk of disease progression than those with L858R mutation, after front-line TKI. Additionally, patients with exon 19 deletion had a longer median PFS than those with L858R mutation (HR [exon 19/21]: 0.75; 95% CI: 0.65–0.85; $p<0.001$) (Figure 2).⁶² Similar findings were demonstrated in the recent FLAURA trial, a double-blind, Phase III trial in 556 patients with previously untreated, *EGFR*-mutated (exon 19 deletion or L858R mutation) advanced NSCLC, which compared osimertinib (a third-generation *EGFR*-TKI) to gefitinib or erlotinib (a first-generation *EGFR*-TKI). The primary endpoint was investigator-assessed PFS. At baseline, 63% of patients had an exon 19 deletion. The investigator-assessed PFS were 21.4 months (95% CI: 16.5–24.3) and 14.4 months (95% CI: 11.1–18.9) for exon 19 deletion and L858R mutation, respectively.³² Dr Gil-Bazo believes that this difference in PFS may be because of differing tumour biology (exon 21 tumours are less angiogenic), more efficient inhibition by *EGFR*-TKI, and less resistance and hypersensitivity to reversible *EGFR*-TKI.^{7,62}

Benefit with Ramucirumab Regardless of Mutation Type

In the RELAY trial, 54% of enrolled patients had an exon 19 deletion and 45% had an L858R mutation. Most notably, ramucirumab plus

erlotinib provided PFS benefit across most of the subgroups, with patients with exon 19 deletions and L858R mutations deriving similar benefits (19.6 months versus 19.4 months; HR: 0.651 and 0.618, respectively).⁹ Dr Gil Bazo evaluated the findings: “The PFS benefit with ramucirumab versus placebo was similar regardless of mutation type: exon 19 deletion (19.6 versus 12.5 months) and L858R mutations (19.4 versus 11.2 months).”

Dr Gil-Bazo explained he felt that the combined blockage of the VEGFR and *EGFR* pathways with ramucirumab plus erlotinib may delay the emergence of resistance to *EGFR*-directed therapy. The clinical implications of this trial demonstrate that combination therapy with an antiangiogenic agent and an *EGFR* inhibitor should be considered in the first-line setting in patients with *EGFR*-mutated advanced NSCLC.⁹ “The clinical implication of the RELAY study is that ramucirumab should be considered in the first-line setting in patients with *EGFR*-mutated advanced NSCLC,” he concluded.

WHAT IS THE BEST SEQUENCE OF TREATMENT FOR *EGFR*-MUTATED ADVANCED NSCLC?

Professor Marina Garassino

Personalised Treatment Plans

Historically, standard care prescribed to patients with cancer was without any tailored selection, with the exception of the primary site and histology of the tumour; patients with NSCLC were exclusively treated with chemotherapy without selection for histology or any other biomarker, such as *EGFR* mutation.^{21,22} The era of precision medicine has revolutionised cancer care by enabling selection of individual treatment based on specific biomarkers to reduce toxicity risk and improve treatment benefits. The therapeutic armamentarium for NSCLC has expanded significantly with the emergence of multiple targeted therapies. NSCLC was once a ‘limited-survival disease’, but now many patients are living longer because of personalised, targeted therapies.⁶³

To match a patient's cancer to the best treatment, clinicians need to understand the molecular profile. The use of EGFR-TKI is, therefore, based on the detection of *EGFR* mutations, detected via solid tissue or liquid biopsies.⁶⁴ Clinical standards and testing are rapidly evolving, but based on available evidence, all patients with advanced NSCLC should be tested for *EGFR* mutations.⁵³

Clinicians now need to consider several EGFR-TKI and combination strategies for the treatment of *EGFR*-mutated NSCLC. Randomised trials have demonstrated that second- and third-generation TKI confer significantly improved PFS versus first-generation TKI.²⁸⁻³² Unfortunately, in the absence of direct head-to-head studies, it remains unclear which is the best treatment strategy for front-line use and for sequencing of agents to maximise survival benefit. Furthermore, despite initial clinical response to EGFR-TKI, acquired resistance and disease progression is inevitable at some point during treatment with EGFR-TKI.

Dual blocking of EGFR and VEGF pathways, with angiogenesis inhibition by neutralising antibodies such as ramucirumab with an EGFR-TKI, may be beneficial for improving treatment outcomes.^{9,43}

Clinicians also have an important role in improving the patient experience with patient-centred communication and shared decision making, taking the time to inform, actively listen, understand needs and preferences, and assess a patient's understanding of treatment options. The following factors should be considered for personalised treatment: age, comorbidities, concurrent medications, patient preference for oral medications, contraindications, presence of exon 19 deletion mutation, or presence of resistance mutation T790M.

These outcomes led Prof Garassino to advocate for an alternative standard of care with ramucirumab plus erlotinib as first-line therapy in appropriate patients with *EGFR*-mutated NSCLC (Figure 3).⁶⁵ This would potentially enable a longer survival benefit by delaying subsequent osimertinib and chemotherapy treatment.⁴⁵

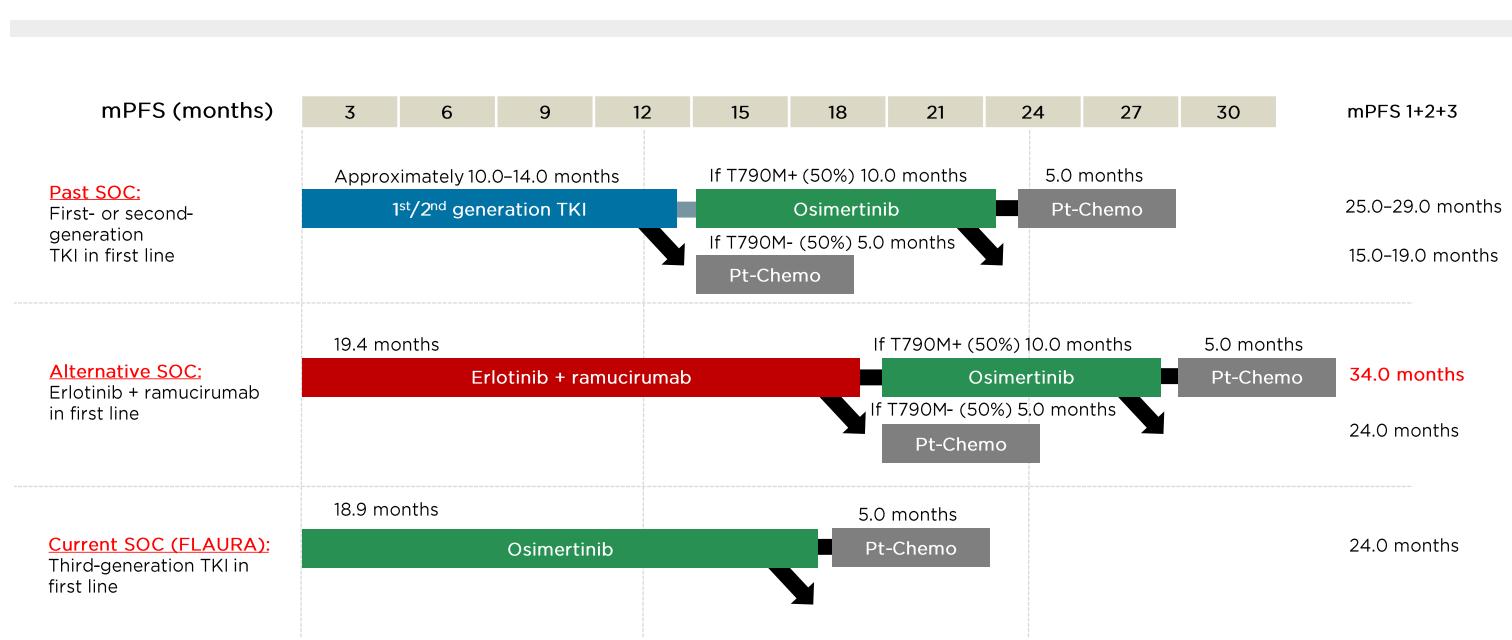


Figure 3: Potential sequencing options for patients with *EGFR*-mutated advanced non-small cell lung cancer.

mPFS: median progression-free survival; Pt-Chemo: platinum chemotherapy; SOC: standard of care; TKI: tyrosine kinase inhibitor.

Adapted from Pérol.⁶⁵

This novel therapeutic approach, along with shared decision making, has expanded possibilities for patients with *EGFR*-mutated advanced NSCLC. "These outcomes lead me to advocate for an alternative standard of care with ramucirumab plus erlotinib as first-line therapy in appropriate patients with *EGFR*-mutated NSCLC. This would potentially enable a longer survival benefit, by delaying subsequent osimertinib," Prof Garassino explained.

CONCLUSION

Patients with advanced *EGFR*-mutated NSCLC have an unmet need for additional first-line treatment options that provide clinically meaningful benefits, including delaying

disease progression and the emergence of acquired resistance. Increasing the selection of first-line treatment options for patients with *EGFR*-mutated advanced NSCLC provides clinicians with greater strategic choices. These include how to use the available drugs to limit toxicity, provide the best chance of long-term PFS, potentially prolong time on targeted therapy, and delay time to chemotherapy. Furthermore, recent data suggest therapeutic additivity, if not synergy, for the concurrent use of monoclonal antibodies targeting angiogenesis with EGFR-TKI. PFS now exceeds 19 months with front-line combination ramucirumab and erlotinib therapy, and with appropriate sequencing, this approach could potentially prolong time on targeted therapy and delay chemotherapy, resulting in improved patient outcomes.

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