

## 2 Background

### 2.1 NSCLC with EGFR ex20ins mutations

Lung cancer is one of the most common types of cancer and is also the most common cause of death from cancer. NSCLC accounts for 85% of lung cancers.<sup>1</sup> Advanced NSCLC is a serious terminal illness and, until recently, had a median overall survival (OS) of approximately 1 year.<sup>2</sup> Fewer than 20% of patients live up to 5 years after being diagnosed with advanced or metastatic NSCLC and many are stigmatized by its association with smoking. EGFR-mutated NSCLC is unique in that two-thirds of patients are never smokers.

Over the past decade, multiple “driver” mutations have been identified that can result in activation of pro-growth signaling pathways. In patients with metastatic disease, driver mutations are observed in approximately 50% to 60% of adenocarcinomas. Among patients with NSCLC adenocarcinoma, driver mutations that result in the activation of EGFR are identified in approximately 15%<sup>3</sup> of Western patients and in up to 40% to 50%<sup>4</sup> of Asian patients. The most frequent of these are ex19del and L858R, which are identified in 80% to 85% of patients with activating EGFR mutations, while ex20ins mutations are identified in up to 10%<sup>5</sup> of those with EGFR mutations.

Many advances in treatment of NSCLC have occurred in recent years. Immune checkpoint inhibitors (ICI) (eg, anti-PD-1 or anti-PD-L1) have improved outcomes in some patients with NSCLC; however, these agents have demonstrated poor outcomes<sup>6-8</sup> in patients with EGFR ex20ins mutations, ex19del, and L858R. As a result, patients with EGFR-mutated NSCLC have been excluded from many frontline immunotherapy phase 3 studies, and frontline indications for approved anti-PD-1/anti-PD-L1 agents in metastatic NSCLC have specifically excluded patients with EGFR-mutated disease, including those with ex20ins.<sup>9,10</sup>

Several EGFR tyrosine kinase inhibitors (TKIs) have been approved for use in front-line therapy of NSCLC patients with tumors characterized by EGFR ex19del and L858R mutations, which has resulted in significantly improved patient outcomes, with improved response rates, prolonged disease control, and an improved median OS of 32 to 39 months.<sup>11</sup> However, these TKIs eventually lead to cancer resistance as new mutations arise. After failure of these TKIs, many patients and physicians have limited options.

In contrast to EGFR ex19del or L858R disease, tumors arising from EGFR ex20ins are known to be insensitive to currently approved EGFR TKI treatments, and patients with EGFR ex20ins have been excluded from the majority of phase 3 clinical trials, including those for immunotherapy. Thus, this population has been relatively understudied in clinical trials. As a result, until recently, there were no approved therapies specifically for the treatment of patients with ex20ins disease and no specific treatment guidelines given by the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) for treatment of this population.

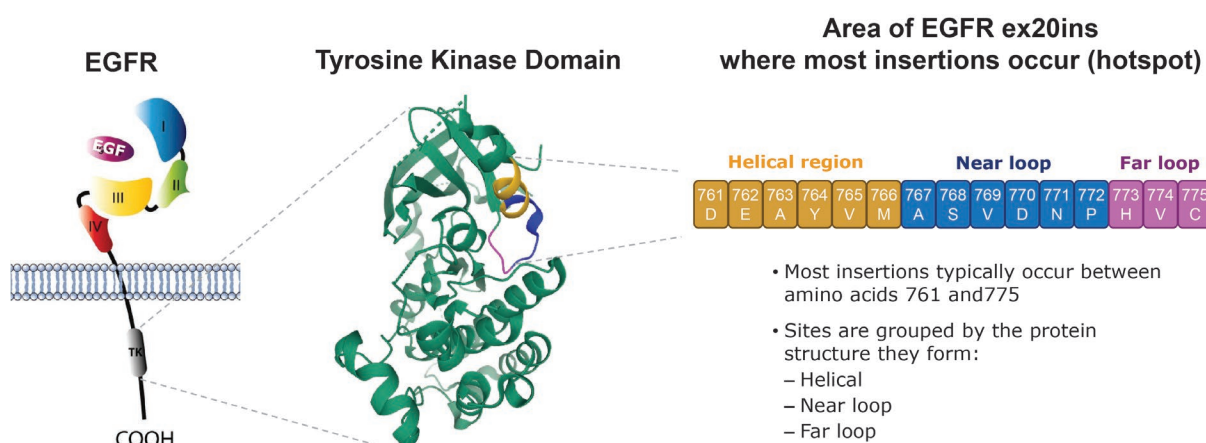
In the absence of effective targeted therapies or immunotherapies, the current standard of care for newly diagnosed patients with EGFR ex20ins NSCLC remains platinum-based chemotherapy.<sup>12</sup> Platinum-based chemotherapy provides transient disease control with an approximate ORR of 30% and a median progression-free survival (PFS) of 4-6 months<sup>12,13</sup> and can be associated with significant morbidity due to neutropenia, anemia, and thrombocytopenia.

Available evidence suggests that, after progression on platinum-based chemotherapy, there is no predominant standard of care for EGFR ex20ins NSCLC and until the FDA approvals of amivantamab and mobocertinib in May and September 2021, respectively, for use in this population, limited treatment options existed for these patients. Given this, outcomes in these patients have been poor. The median OS is 16 months, and fewer than 8% of patients survive for 5 years. Hence, this patient population has a high unmet medical need. Amivantamab, a fully human bispecific antibody with a unique mechanism of action, is expected to address this unmet medical need and represents the first targeted treatment option for patients with EGFR ex20ins.

Amivantamab, the first targeted therapy<sup>14</sup> to be approved for NSCLC patients harboring EGFR ex20ins mutations following progression on chemotherapy, targets the extracellular portion of the EGFR and the mesenchymal-epithelial transition factor (MET) receptor, bypassing intracellular primary or acquired resistance mechanisms. This novel drug was deliberately engineered with differential binding affinities toward the EGFR and MET receptor, increasing cancer selectivity.<sup>15,16</sup> By targeting both the EGFR and the MET receptor, amivantamab can counteract the resistance that develops due to the overlapping signaling pathways of the EGFR and the MET receptor and the compensatory changes that occur in one pathway following inhibition of the other.<sup>17</sup> Moreover, RYBREVANT® also activates macrophages and natural killer cells that can directly attack the cancer.

## **2.2 Pathophysiology of NSCLC with EGFR ex20ins mutations**

Receptor tyrosine kinases (RTKs) are involved in the regulation of many processes in mammalian development, cell function, and tissue homeostasis. Dysregulation of RTKs has been implicated in the development of numerous human cancers, and various RTKs are targets for both approved and experimental anticancer therapies. The EGFR is an RTK that can be activated by 7 ligands, including epidermal growth factor (EGF), and whose signaling pathway induces diverse cellular responses, including differentiation, proliferation, migration, and survival.<sup>18</sup> cMet is also an RTK, and its signaling plays a role in growth and homeostasis, including embryonic development, angiogenesis and wound healing.<sup>19,20</sup> cMet is activated by a single specific ligand, hepatocyte growth factor (HGF), also known as scatter factor. EGFR ex20ins mutations, similar to other EGFR activating mutations, result in a constitutively activated EGFR receptor, leading to abnormal cell proliferation and oncogenesis.



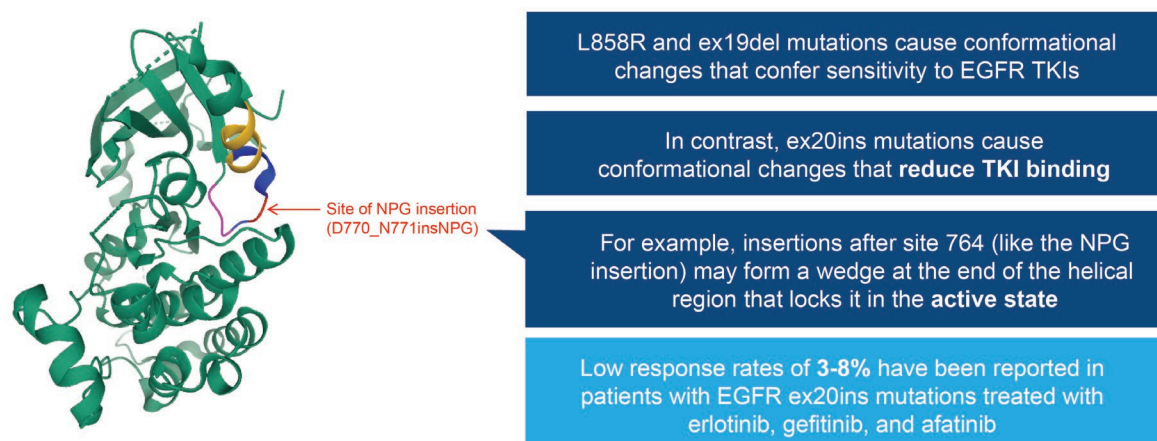
**Figure 1. EGFR ex20ins mutations.**<sup>5,21</sup>

## 2.3 Treatment landscape prior to amivantamab

As discussed above, patients with NSCLC harboring EGFR ex20ins mutations had limited treatment options with no targeted therapies and no standard of care after first-line platinum-based chemotherapy prior to the development and approval of amivantamab and mobocertinib. Although the EGFR TKIs developed prior to the approval of amivantamab were not effective in patients with EGFR ex20ins mutations, primary and acquired resistance to these TKIs led to further research and the eventual development and approval of amivantamab.

### 2.3.1 Insensitivity of EGFR TKIs (first- through third-generation)




EGFR TKIs bind to the intracellular tyrosine kinase domain (the ATP-binding site), inhibiting ATP binding and thus phosphorylation of tyrosine residues and downstream signaling.<sup>22</sup> Three generations of EGFR TKIs have been developed. Although each subsequent generation was designed to combat more primary and resistance mutations and do so more effectively, the change in the ATP-binding site of the protein induced by most ex20ins mutations reduces binding by tyrosine kinase inhibitors and thus limits the efficacy of the TKIs. Site 761 through 775 is the area where most insertions occur, and the mutations are either in-frame insertions or duplications.



**Figure 2. EGFR mutation location and sensitivity to TKI therapy.**<sup>5,23,24</sup>

### 2.3.2 Platinum-based chemotherapy

Due to the insensitivity of tumors with ex20ins to EGFR TKIs, platinum-based chemotherapy is currently the preferred first line of treatment in patients with NSCLC harboring EGFR ex20ins mutations.<sup>25,26</sup> As mentioned, limited other treatment options existed prior to amivantamab's approval, leading to worse outcomes for this patient population. The median OS of patients with NSCLC harboring EGFR ex20ins mutations is 16 months, in contrast to 39 months in patients with NSCLC harboring EGFR TKI-sensitive mutations. This almost 2-year discrepancy in survival highlights the unmet need of this patient population for therapies that can effectively target the constitutively activated EGFR ex20ins mutation.

|      | Patients with EGFR ex20ins |   |  | Patients with EGFR exon 19/21 mutations |   |  |
|------|----------------------------|---|--|---|---|--|
|      | Chemotherapy               |  GIOTRIF <sup>®</sup> (afatinib) tablets |  TAGRISSEO <sup>®</sup> osimertinib | Chemotherapy                            |  GIOTRIF <sup>®</sup> (afatinib) tablets |  TAGRISSEO <sup>®</sup> osimertinib |
| mPFS | 5.7 months                 | 2.7 months  | 3.7 months   | 5.2 months                              | 11.1 months   | 18.9 months  |
| ORR  | 29%                        | 9%  | 6%   | 16%                                     | 50%   | 77%  |

**Figure 3. Responses to therapy in patients with EGFR ex20ins mutations versus common mutations.**<sup>5,27-32</sup>

### 2.3.3 Immunotherapy

Immune checkpoint inhibitors (ICIs) treat cancer by preventing the tumor from inhibiting the body's antitumor cytotoxic T-cell response<sup>33,34</sup> These inhibitors have improved outcomes in patients with NSCLC.<sup>35</sup> However, not all patients with NSCLC will respond to ICIs, and data is limited in patients with ex20ins mutations.<sup>36</sup> Despite this, ICIs are sometimes used in patients with EGFR ex20ins mutations; a significant number of patients in various clinical trials, including those involving amivantamab, had been previously treated with an ICI.<sup>36</sup>