**Abstract**

*EGFR* exon 20 insertion mutations (Ex20ins) and *HER2* mutations characterize an oncogene-addicted subtype of non-small-cell lung cancer (NSCLC) typically associated with a never or light smoking history, female sex, and adenocarcinoma histology. Nevertheless, Ex20ins-mutant and HER2-mutant advanced NSCLCs are still difficult to treat for various reasons. First, there is a need for sophisticated diagnostic tools (e.g. next-generation sequencing) that could allow the identification of these relatively rare molecular drivers. Second, highly active targeted drugs that might support a significant change in patients’ prognosis when used as first-line therapy are required. In fact, although a few targeted drugs have so far demonstrated antitumour activity for these patients, mainly selective human epidermal receptor-tyrosine kinase inhibitors such as poziotinib and mobocertinib (for both molecular alterations), monoclonal antibodies such as amivantamab (for Ex20ins), and antibody–drug conjugates such as trastuzumab deruxtecan (for HER2 mutants), they are mostly confined for clinical use in pretreated patients. Finally, Ex20ins-targeted or HER2-targeted drugs might be difficult to access in different countries or regions worldwide.

In the present review, we provide a concise but comprehensive summary of the challenges that lie ahead as we move towards personalized treatment of Ex20ins-mutant and HER2-mutant advanced NSCLC, also suggesting a treatment algorithm that could be followed for patients with these genetic aberrations. This article is part of the *Treatment of advanced non-small-cell lung cancer: one size does not fit all* Special Issue: [https://www.drugsincontext.com/special_issues/treatment-of-advanced-non-small-cell-lung-cancer-one-size-does-not-fit-all/](https://www.drugsincontext.com/special_issues/treatment-of-advanced-non-small-cell-lung-cancer-one-size-does-not-fit-all/)

**Keywords:** amivantamab, *EGFR* exon 20 insertion mutations, HER2 mutation, mobocertinib, non-small-cell lung cancer, poziotinib, trastuzumab deruxtecan.

**Citation**

Metro G, De Giglio A, Ricciuti B, Siringo M, Marinelli D, Gelibter A, Pecci F, Berardi R, Cantini L, Di Federico A, Andrini E, Mosca M, Lamberti G, Brambilla M, Mountzios G. Advanced non-small-cell lung cancer: how to manage *EGFR* and *HER2* exon 20 insertion mutation-positive disease. *Drugs Context.* 2022;11:2022-3-9. [https://doi.org/10.7573/dic.2022-3-9](https://doi.org/10.7573/dic.2022-3-9)

**Introduction**

Lung cancer still represents the primary cause of cancer-related deaths worldwide despite recent advances allowing the personalization of treatment for most patients affected by non-small-cell lung cancer (NSCLC). In particular, tyrosine kinase inhibitors (TKIs) have revolutionized the therapeutic algorithm and the prognosis of patients harbouring actionable molecular alterations. *EGFR* mutations and *ALK* and *ROS1* rearrangements were the first genomic alterations in NSCLC to be targeted by TKIs; however, following the recent development of new TKIs, the spectrum of susceptible alterations widened to include other oncogenes such as *BRAF, MET, HER2, KRAS, RET* and *NTRK*. *EGFR* alterations can be found in 10–40% of patients with NSCLC, with higher prevalence amongst Asian patients. Of these alterations, approximately 90% are represented by exon 19 deletions and exon 21 L858R point mutation, so-called ‘common’ *EGFR* mutations. The remaining 10% of...
‘uncommon’ alterations mainly constitute mutations involving exons 18–21 and exon 20 insertions. On the contrary, HER2 mutations have a significantly lower prevalence in patients with NSCLC than EGFR mutations but most occur in exon 20 as codon 776 insertions or duplications of YVMA amino acids. Herein, we provide a practical but comprehensive review of the literature regarding the clinical management of patients with NSCLC harbouring EGFR and HER2 exon 20 insertions.

**EGFR exon 20 insertion mutations**

**Introduction and biology**

Epidermal growth factor receptor (EGFR or HER1) is part of the human epidermal receptor (HER) superfamily that exerts an essential role in cell proliferation, metabolic functions and evasion of apoptosis. In the last 20 years, EGFR has emerged as an important therapeutic target across a variety of solid tumours, with the larger clinical implementation seen in advanced NSCLC.

EGFR consists of three main structural elements. The extracellular part, which serves as the membrane receptor for extracellular ligands, including epidermal growth factor (EGF), the transmembrane domain, which functions as an anchor, and the intracellular domain, which possesses tyrosine kinase activity, potentially leading to proliferative signal transduction to the nucleus when activated by phosphorylation from ATP. EGFR-TKIs, such as gefitinib, erlotinib, afatinib and osimertinib, are active molecular targeted therapies predictive of antitumour response to ‘classic’ EGFR-activating exon 19 deletions and exon 21 point L858R mutations. Besides common EGFR mutations, rare mutations of the EGFR gene with a variable degree of sensitivity to the aforementioned EGFR-TKIs include the point mutations S768I (exon 20) (~1%), L861Q (exon 21) (~2%), G719X (exon 18) (~4%), the osimertinib-sensitive T790M mutation (exon 20; de novo incidence <1%) and compound mutations (<1%).

Notwithstanding, other EGFR mutations, such as insertions of exon 20 (Ex20ins), have a completely different structure and biology and are considered resistant mutations to commonly administered EGFR-TKIs. These mutations account for approximately 12% of EGFR mutations, thus configuring 0.8–1.2% of all genetic aberrations amongst patients with NSCLC. EGFR exon 20 insertions can be further grouped into two main categories: in-frame insertions, usually comprising up to 4 amino acids or 3–21-bp duplications. The vast majority of these mutations (up to 90%) occur in the region encoding amino acids 766–775, which form the far loop between the αC-helix and β4 strand of the kinase domain, whereas other less frequent insertions occur within amino acids 761–768 that comprise the ‘near loop’ of the αC-helix. All Ex20ins trigger the conversion of the αC-helix into an active conformation, resulting in independent and continuous transduction of proliferative signals to the nucleus. Unlike the classic EGFR mutations, Ex20ins do not directly affect the ATP-binding pocket but provoke constitutive activation of the kinase domain through the ‘tail’ of amino acid residues that shift into the pocket of the αC-helix.

Ex20ins are most common in women, never or light smokers, and in tumours of adenocarcinoma histology. Tumours with Ex20ins are characterized by a high incidence of baseline brain metastases (reported in up to 39% of new cases) and a propensity for skeletal metastases (25% of new cases) in a way similar to EGFR-activating mutations. These patients represent a highly unmet medical need because commonly administered EGFR-TKIs that act in the ATP-binding pocket have limited activity against Ex20ins, including the newer-generation drug osimertinib. Even the doubling dose of osimertinib from 80 to 160 mg QD attempted in 21 patients with Ex20ins treated in a phase II study resulted in poor activity, with a confirmed objective response rate (ORR) of 25%, a median progression-free survival (PFS) of 9.7 months and median duration of response of 5.7 months. Out of clinical trials, this subgroup of patients is treated with standard chemotherapy, immunotherapy or combination strategies according to PD-L1 expression. Platinum-based chemotherapy represents the most efficacious first-line treatment, with a median overall survival (OS) of 17 months and ORR of 19.5%. Notably, immunotherapy evidenced dismal results either as a first-line or subsequent line of treatment. Moreover, adding immunotherapy to chemotherapy as a first-line combination did not improve the efficacy of chemotherapy.

On this basis, there is a desperate need for new active treatments that might be beneficial for patients with Ex20ins NSCLC. Table 1 presents the relevant studies evaluating novel drugs in this context. Amongst them, novel EGFR exon 20-TKIs as well as monoclonal bi-specific antibodies are the most actively investigated drugs.

**EGFR exon 20-targeted TKIs**

To date, over 60 different Ex20ins have been reported in advanced NSCLC, the majority composed of 1–4 amino acid insertions or duplications within the loop following the αC-helix. Following this notion, several molecular targeted agents have been developed to specifically target the protein product of these mutations. Of note, a small portion of these mutations, namely the insertions of the four amino acids FQEA between the A763 and Y764 residues, remain highly sensitive to gefitinib, erlotinib, afatinib and osimertinib because they involve the loop edge, which lies within the ATP-binding pocket.

Poziotinib is a pan-HER-TKI directly targeting the protein product of Ex20ins. In the phase II ZENITH20-1 trial, involving 115 patients with platinum chemotherapy-pretreated Ex20ins, poziotinib at the dose of 16 mg QD exhibited modest antitumour activity, with ORR of 14.8% and median PFS of only 4.2 months. Moreover, poziotinib was associated with substantial class-specific toxicity, mainly grade 3 diarrhoea and...
Table 1. Selected studies examining the activity of HER-TKIs for NSCLC with HER2 mutation or a de novo HER2 amplification.

| Author and year       | Treatment               | Type of study | Number of patients | PR (%)  | DCRa (%) | Median PFS (months) | Median OS (months) |
|-----------------------|-------------------------|---------------|--------------------|---------|----------|--------------------|--------------------|
| Le et al. 2020 (ref.17) | Poziotinib              | Phase II      | 115                | 14.9b (by IRC) | 68.7c (by IRC) | 4.2                | NR                 |
| Zhou et al. 2021 (ref.19) | Mobocertinib           | Phase I/II PPP cohort | 114              | 28 (by IRC)   | 78 (by IRC) | 7.3                | NR                 |
|                       |                         | Phase II EXCLAIM cohort | 96             | 25 (by IRC)   | 76 (by IRC) | 7.3                | NR                 |
| van Veggel et al. 2021 (ref.20) | Afatinib + cetuximab   | Phase II      | 17                 | 47         | 59        | 5.5                | NR                 |
| Park et al. 2021 (ref.23) | Amivantamab            | Phase I/II    | 81d               | 40              | 74        | 8.3                | 22.8               |

aComplete or partial response + stable disease; b 19.3% in the evaluable for response population; c 80.7% in the evaluable for response population; dEfficacy population.

DCR, disease control rate; IRC, independent review committee; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response.

rash, observed in 25% and 28% of patients, respectively. Even though a modification of drug uptake to 8 mg BID is generally associated with improved tolerability, the modest activity of poziotinib and toxicity concerns have limited further clinical development to date. Nevertheless, poziotinib was the first agent specifically targeting Ex20ins, and provided the proof of concept for this class of agents.

Mobocertinib is another newer-generation EGFR-TKI specifically and non-reversibly targeting Ex20ins in the EGFR gene. Mobocertinib 160 mg QD was evaluated in prior platinum-based chemotherapy-pretreated patients (PPP cohort) and in an extension cohort of pretreated patients (EXCLAIM cohort). In the PPP cohort involving 114 patients, ORRs were observed in 28% of patients, with a median PFS of 7.3 months and median OS of 24 months. In the EXCLAIM cohort, ORR was 25%, with comparable results in terms of median PFS (7.3 months) and a median OS (not reached). Notably, the median duration of response was 17.5 months in the PPP cohort and not reached in the EXCLAIM cohort, which indicates the long-lasting activity of mobocertinib in responders. Of note, these encouraging outcomes were accompanied by an acceptable toxicity profile, with grade ≥3 diarrhea occurring in 21% and 16% of patients in the PPP and EXCLAIM cohorts, respectively, whereas no grade ≥3 rash was reported in either cohort. Treatment discontinuation related to toxicity was observed in 17% of the PPP cohort and in 10% of the EXCLAIM cohort. These favourable outcomes led to first-line evaluation of mobocertinib in the phase III EXCLAIM-2 clinical trial of patients with untreated Ex20ins advanced NSCLC, which is currently enrolling patients (NCT04129502).

In addition, two novel EGFR-TKIs, CLN-081 and DZD9008, demonstrated an acceptable toxicity profile and promising antitumour activity in patients previously treated with standard chemotherapy.

Interestingly, another therapeutic strategy consists of combining the monoclonal antibody against EGFR cetuximab with an ‘old’ irreversible dual EGFR/HER2-TKI, named afatinib, to induce a more complete EGFR blockade. This regimen was tested in a small phase II study and produced encouraging signs of efficacy with an ORR of 40%.

Bi-specific monoclonal antibodies

MET amplification is an acknowledged resistance mechanism in patients with EGFR-mutant tumours harbouring the classic activating mutations in exons 19 and 21. In recent years, targeting MET gene amplification has been an area of intense research activity and molecular targeted agents directed against MET have been developed, including crizotinib, capmatinib and tepotinib. More recently, advances in biotechnology allowed the development of bi-specific monoclonal antibodies, which have the ability to target two different molecular epitopes in parallel. Amivantamab is a fully human bi-specific IgG1 antibody targeting both EGFR and MET. This agent blocks the interaction between these receptors and their corresponding ligands, thus promoting receptor degradation and, more importantly, inducing antibody-dependent cytotoxicity through its Fc domain. Due to its unique properties, amivantamab showed preclinical antitumour activity not only against the known EGFR-activating mutations but also against the Ex20ins. Consequently, amivantamab was first studied in the phase I/II CHRYSALIS study. Amongst 81 patients with platinum-pretreated, Ex20ins advanced NSCLC, treatment with...
HER2 exon 20 insertion mutations

Introduction and biology

Human epidermal growth factor receptor 2 (HER2) is another receptor of the HER superfamily. In cancer cells, HER2 signalling promotes cancer cell proliferation and survival via homodimerization and heterodimerization with other HER family receptors activating the Raf–mitogen-activated protein kinase (MAPK) and phosphatidylinositol-4,5-biphosphate 3-kinase (P3K)–AKT pathways. No ligand has been found for HER2, which acts as a dimerization partner for other receptors of the HER family. Generally, the mechanisms that lead to HER2 deregulation in NSCLC include somatic gene mutation, amplification and protein overexpression either alone or in combination. Nevertheless, these three situations should be considered distinct biological phenomena as they infrequently overlap, especially regarding HER2 gene mutation and gene amplification. Scientific evidence suggests that patients with HER2-mutated advanced NSCLC benefit from anti-HER2 therapies such as small molecule HER-TKIs, monoclonal antibodies and antibody–drug conjugates. Therefore, we will briefly discuss HER2 mutation in NSCLC in the context of the therapeutic approach that physicians should adopt in case this molecular aberration is detected.

In terms of frequency, HER2 mutations occur in 1–2% of patients with lung adenocarcinoma, and more frequently in women, and never or light smokers. HER2 mutations occur predominantly in exon 20 of the HER2 gene located at the long arm of human chromosome 17 (17q12) and consist of approximately 80% of cases of insertion of 12 base pairs (bp) that leads to the A775_G776insYVMA mutation. Of note, HER2 mutation is mutually exclusive with other actionable genetic mutations that may occur in NSCLC (e.g. EGFR mutation, ALK rearrangement, BRAF mutation), which supports the fact that this molecular aberration may act as a genetic driver itself in lung adenocarcinoma. With regard to testing, reverse-transcription PCR or next-generation sequencing are affordable.
methods of detection. Conversely, HER2 protein expression analysis may fail to detect HER2 mutations.66

Currently, data on the prognostic role of HER2 mutation in NSCLC cancer are scarce. In an old series of 504 Japanese patients with resected NSCLC, 2.6% were found to carry HER2 mutation.42 Patients with HER2 mutations, those harbouring EGFR mutations, and patients who were wild type for both EGFR and HER2 did not experience any survival differences. However, molecular tests have greatly evolved in the last decade, and new studies employing novel next-generation sequencing techniques are essential to address the prognostic role of HER2 mutation in NSCLC. A more recent Japanese study suggested that the presence of a HER2 aberration (mutation, amplification or overexpression) in patients with advanced NSCLC might be linked to poor prognosis as compared to the presence of other genetic drivers (that is, EGFR mutation or ALK rearrangement), which might be due to the limited access to anti-HER2 therapies by patients with HER2-deregulated disease.37

**HER-TKIs**

In recent years, novel and more selective HER-TKIs have been clinically evaluated for the treatment of patients with HER2-mutated advanced NSCLC (Table 2). Poziotinib is an oral irreversible pan-HER-TKI with a relevant in vitro activity against cell lines harbouring HER2 exon 20 insertion mutations.43 Clinically, poziotinib was active in HER2-mutated NSCLC, with an overall response rate of 27% in pretreated patients44–46 and 41.7% in untreated patients.46 Of note, an overall reduction in tumour diameters was noted in 74% and 88% of cases, respectively. Unfortunately, despite its convenient oral administration, a major limitation of poziotinib administration is the high rate of treatment-related toxicities observed at the commonly employed dose of 16 mg QD, which leads to frequent dose interruptions, reductions and discontinuation.44–46 In fact, at this dose, any grade diarrhoea and skin rash were observed in roughly 80% and 70% of patients, respectively.45,46 Consistently, the results of an expanded access programme of poziotinib administered in clinical practice showed that as much as 76% of patients underwent dose reduction.47 However, an alternative dosing of 8 mg BID was recently reported to be associated with an overall reduction of 14% in the incidence of treatment-related adverse events greater than or equal to grade 3, including diarrhoea and rash.46 This improvement with a modified dosing schedule of 8 mg BID results in a lower rate of dose interruptions and reductions, of 32% and 36%, respectively.46

Given the activity demonstrated by poziotinib in HER2-mutated NSCLC, a submission for new drug authorization was submitted to the FDA for the treatment of pretreated patients with HER2-mutated NSCLC.49

Amongst novel HER-TKIs other than poziotinib, pyrotinib and mobocertinib showed preclinical activity in HER2-mutated lung cancer.50,51 Pyrotinib also showed signs of important antitumour activity in patients with HER2-mutated advanced NSCLC.50,52 Currently, both drugs are being evaluated in clinical trials (NCT04447118; NCT02716116).

Tarloxotinib is a prodrug whose active metabolite, tarloxotinib-E, is formed through fragmentation occurring preferentially under hypoxic conditions in malignant tissues.53 Tarloxotinib-E is a pan-HER-TKI, preliminary tested in the RAIN-701 trial in which tarloxotinib induced an objective response in 2 out of 8 patients with HER2-mutated NSCLC who were

| Author and year (ref.) | Treatment | Type of study | HER2 alteration | Number of patients | PR (%) | DCR (%) | Median PFS (months) | Median OS (months) |
|------------------------|-----------|---------------|----------------|--------------------|--------|---------|--------------------|--------------------|
| Elamin et al. 2022     | Poziotinib| Phase II      | Mutation       | 35                 | 43b    | 73b     | 5.5b               | 15b                |
| Le et al. 2020         | Poziotinib| Phase II      | Mutation       | 90                 | 35.1%c | 82.4%c  | 5.5                | NR                 |
| Cornelissem et al. 2021| Poziotinib| Phase II      | Mutation       | 48                 | 43.8%  | 75.0%   | 5.6                | NR                 |
| Wang et al. 2019       | Pyrotinib | Phase II      | Mutation       | 15                 | 53.3%  | 73.3%   | 6.4                | NR                 |
| Zhou et al. 2020       | Pyrotinib | Phase II      | Mutation       | 60                 | 30%    | 88%     | 6.9                | 14.4               |
| Liu et al. 2020        | Tarloxotinib| Phase II      | Mutation       | 11                 | 25.0%d | 75.0%d  | NR                 | NR                 |

*Partial response + stable disease; a30 treated patients; b74 evaluable for response; dOut of 8 evaluable for response. DCR, disease control rate; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response.
Table 3. Select studies examining the activity of HER2-targeted monoclonal antibodies or antibody–drug conjugates for NSCLC with HER2 mutation.

| Author and year | Treatment | Type of study | HER2 alteration | Number of patients | PR (%) | DCRa (%) | Median PFS (months) | Median OS (months) |
|-----------------|-----------|---------------|-----------------|--------------------|--------|----------|--------------------|--------------------|
| Hainswort et al. 2018 (ref.49) | Trastuzumab + pertuzumab | Phase II basket | HER2 mutation | 14 | 21 | NR | NR | NR |
| Mazeries et al. 2022 (ref.50) | Trastuzumab + pertuzumab + docetaxel | Phase II | HER2 mutation | 45 | 29b | 87b | 6.8 | 17.6 |
| Hotta et al. 2018 (ref.52) | T-DM1 | Phase II | HER2 mutation | 7 | 14.3 | 71.4 | 2c | 10.9c |
| Li et al. 2018 (ref.51) | T-DM1 | Phase II basket | HER2 mutation | 18 | 44 | 83 | 5 | NR |
| Li et al. 2020 (ref.53) | T-DM1 | Phase II basket | HER2 mutation | 32 | 34.3 | 87.5 | 5.0 | NR |
| Tsurutani et al. 2020 (ref.54) | Trastuzumab-deruxtecan | Phase I | HER2 mutation | 11 | 72.7 | 90.9 | 11.3 | NR |
| Li et al. 2021 (ref.55) | Trastuzumab-deruxtecan | Phase II | HER2 mutation | 42 | 61.9 | 90.5 | 14.0 | Not reached |

Partial response + stable disease; a44 evaluable for response; bIncludes 5 patients HER2 immunohistochemistry 3+; c7 patients had concomitant HER2 mutations. DCR, disease control rate; NR, not reported; OS, overall survival; PFS, progression-free survival; PR, partial response; T-DM1, ado-trastuzumab-emtansine.

Table 3: Select studies examining the activity of HER2-targeted monoclonal antibodies or antibody–drug conjugates for NSCLC with HER2 mutation.

- **HER2-targeted monoclonal antibodies**: Following its consolidated efficacy for HER2-amplified or HER2-overexpressing metastatic breast and gastric cancers, the monoclonal antibody trastuzumab also attracted consideration for the treatment of HER2-mutated advanced NSCLC. In a small retrospective study, the addition of trastuzumab to chemotherapy provided a response rate of 50% and a median PFS of 5.1 months. More recently, trastuzumab has been evaluated in combination with another anti-HER2 monoclonal antibody, pertuzumab, with or without docetaxel, in two separate phase II studies. Unfortunately, the results in terms of activity were dismal, with response rates below 30% in both trials (Table 2). On this basis, HER2-targeted monoclonal antibodies with or without chemotherapy appear to have a minor role in treating HER2-mutated advanced NSCLC, and their use cannot be recommended in clinical practice.

- **HER2-targeted antibody–drug conjugates**: Ado-trastuzumab-emtansine (T-DM1) conjugates trastuzumab with a payload consisting of the anti-microtubule agent emtansine. T-DM1 is currently approved for the treatment of patients with HER2-amplified or HER2-overexpressing metastatic breast cancers whilst it is still an investigational agent for NSCLC. A phase II study evaluated T-DM1 for the treatment of HER2-mutated NSCLC. Although T-DM1 provided a response rate of 44% (8 out of 18 patients), the median duration of response was only 4 months, which suggested that this agent had an unsatisfactory antitumour activity in this context. Analogously, another phase II trial was suspended early due to limited clinical efficacy with a 6.7% of ORR (1 out of 16 patients).

Trastuzumab deruxtecan (T-dx) is an antibody–drug conjugate linking trastuzumab to a topoisomerase I inhibitor payload. The drug has been recently shown to be active against HER2-mutated NSCLC. Destiny-Lung01 was a multicentre, open-label, phase II study exploring the antitumour activity of T-dx in 91 patients with advanced NSCLC who had been pretreated...
with at least one prior therapy\textsuperscript{63}; the primary endpoint was ORR. Overall, 50 patients had an objective response (55%), whilst 84 patients obtained disease control (84%). The median PFS and OS were 8.2 and 17.8 months, respectively.\textsuperscript{63} Grade ≥3 drug-related adverse events occurred in 46% of patients (n=42), with neutropenia and anaemia occurring in 19% (n=18) and 10% (n=10) of cases, respectively. Of note, this drug was associated with interstitial lung disease in 24% (n=24) of patients, of whom 29% (n=7) consisted in grade ≥3 events. Based on this peculiar event, caution is required on the dose that should be employed in patients with NSCLC with HER2-mutated disease; therefore, a randomized phase II study is being run in order to compare the Destiny-Lung01 dose of 6.4 mg/kg to a lower dose of 5.4 mg/kg (NCT04644237). However, beyond dose optimization and management of interstitial lung disease, there are other questions that need to be addressed regarding the use of T-dx in NSCLC: particularly, it is not known whether this drug is superior to chemo-immunotherapy as a first-line treatment of HER2-mutated NSCLC. On this basis, the Destiny-Lung04 trial is being conducted to address this issue (NCT05048797).

In Table 3, we summarized the studies investigating the activity of HER2-targeted monoclonal antibodies or antibody–drug conjugates for NSCLC with HER2 mutation.

### Conclusions and treatment algorithm

**HER2** mutation in NSCLC identifies a group of patients with a driver genetic alteration that is generally mutually exclusive with other driver mutations (e.g. **EGFR** and **ALK**). However, current evidence is not strong enough to recommend the use of a HER2-targeted agent in the first-line setting. Figure 1 shows our proposed treatment algorithm for HER2-mutated advanced NSCLC. Chemotherapy with or without ICI treatment appears to be the preferred therapeutic option in the upfront setting. Consistently, a recent study suggested that first-line chemo-immunotherapy for HER2-mutated NSCLC may achieve response rates comparable to those of unselected patients with NSCLC, with an ORR of 52.4% and a median PFS of 6.0 months.\textsuperscript{64} At the time of progressive disease, these patients should receive a HER2-targeted drug as second-line therapy, which has been demonstrated to achieve better outcomes when compared to historical data of second-line chemotherapy used for unselected patients with NSCLC. On the other hand, ICI as monotherapy (in case of no prior immune-checkpoint inhibition) should be reserved as third-line treatment given the response rate lower than 10% that has been generally observed in retrospective studies.\textsuperscript{32,65,66}

**Contributions:** GM and ADG: conceptualization, writing of original draft. BR, MS, DM, AG, FP, RB, LC, ADF, EA, MM, GL and MB: writing, review and editing. GM: methodology and supervision. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

**Disclosure and potential conflicts of interest:** RB declares Data Safety Monitoring Board or Advisory Board participation for AstraZeneca, Boehringer Ingelheim, Novartis, Amgen, Eisai, MSD, Eli Lilly, Roche, GSK and BMS. The authors declare that they have no other conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2022/07/dic.2022-3-9-COI.pdf

**Acknowledgements:** None.

**Funding declaration:** There was no funding associated with the preparation of this article.

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**Article URL:** https://www.drugsincontext.com/advanced-non-small-cell-lung-cancer-how-to-manage-egfr-and-her2-exon-20-insertion-mutation-positive-disease

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**Provenance:** Invited; externally peer reviewed.

**Submitted:** 26 March 2022; **Accepted:** 4 July 2022; **Publication date:** 29 July 2022.

**Drugs in Context** is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

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