Cancer Treatment Reviews 90 (2020) 102105

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins

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ARTICLE INFO

Keywords:
EGFR exon 20 insertions
Poziotinib
TAK-788
Amivantamab
Osimertinib

ABSTRACT

Although targeted therapy is standard of care in a large subset of oncogenic addicted non-small cell lung cancers (NSCLC), until recently, this therapeutic approach has not been feasible for all genomic alterations such as for those tumors harboring Epidermal Growth Factor Receptor (EGFR) exon 20 insertion (ex20ins) mutations. Despite being the third most common *EGFR* mutation, a limited efficacy of first- and second-generation EGFR tyrosine kinase inhibitors (TKI) exists. This is related to the heterogeneity at the molecular level in *EGFR* ex20ins mutation variants and the finding that this mutation promotes active kinase conformation but does not increase the affinity for EGFR TKI. As a result, the prognosis of this population is diminished. Therefore, chemotherapy remained the most suitable strategy in this subset of *EGFR* mutant NSCLC patients. Recently, new treatment strategies have been reported in this landscape, either with new EGFR TKI or bispecific antibodies, which may establish a new standard of care in the coming future for these patients. Future research should focus on elucidating the oncogenic degree of all *EGFR* ex20ins variants, the potential role of combination strategies either with chemotherapy or immune checkpoint inhibitors, and the most appropriate first-line treatment strategy in this subgroup. Finally, the knowledge of mechanisms of acquired resistance to these new agents upon progression is a priority for personalising treatment at that time. It is in this framework, that we provide a thorough overview on this subject.

Introduction

Epidermal Growth Factor Receptor (EGFR) exon 20 insertion (ex20ins) mutations occur in ~2–3% of all non-small cell lung cancer (NSCLC) cases, representing ~10–12% of all cancers with documented *EGFR* mutation [1–4]. These mutations are the third most common *EGFR* mutation subtype after the common sensitizing *EGFR* mutations, i.e. the exon 19 deletions and exon 21 L858R mutation [4].

In contrast to common *EGFR* mutations where frequency varies according to ethnicity (12% Caucasian vs. ~50% in Asian population) [5], there is no clear difference by ethnicity in the frequency of *EGFR* ex20ins mutations [1–4,6,7] (Fig. 1). Indeed, similar to other oncogenic drivers, EGFR ex20ins mutations are found more often in women, non-smokers, and in those with adenocarcinoma histology [1]. The incidence of baseline brain metastases in *EGFR* ex20ins NSCLC patients ranges from 23% to 39% [3,8]. This percentage is similar to patients with common *EGFR* driver mutations [9,10] or other druggable genomic alterations [11,12]. NSCLC patients with *EGFR* ex20ins mutations have a worse prognosis [13,14], either compared with those with common *EGFR* mutations (median overall survival [OS]: 16.5 months versus 33.0 months, $p = 0.06$, respectively) [1] or uncommon *EGFR* mutations (OS 16.8 months versus 22.5 month, $p < 0.001$) [15]. However, outcome is similar to the *EGFR* wild-type population (median OS of 20.0 months, $p = 0.60$) [1].

EGFR ex20ins mutations are located in the tyrosine kinase domain of EGFR. These mutations are heterogeneous at the molecular level but can be characterized as in frame insertions or duplications of between 3 and 21 bp (corresponding to 1–7 amino acids) clustered between amino

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https://doi.org/10.1016/j.ctrv.2020.102105
Received 31 May 2020; Received in revised form 3 September 2020; Accepted 6 September 2020

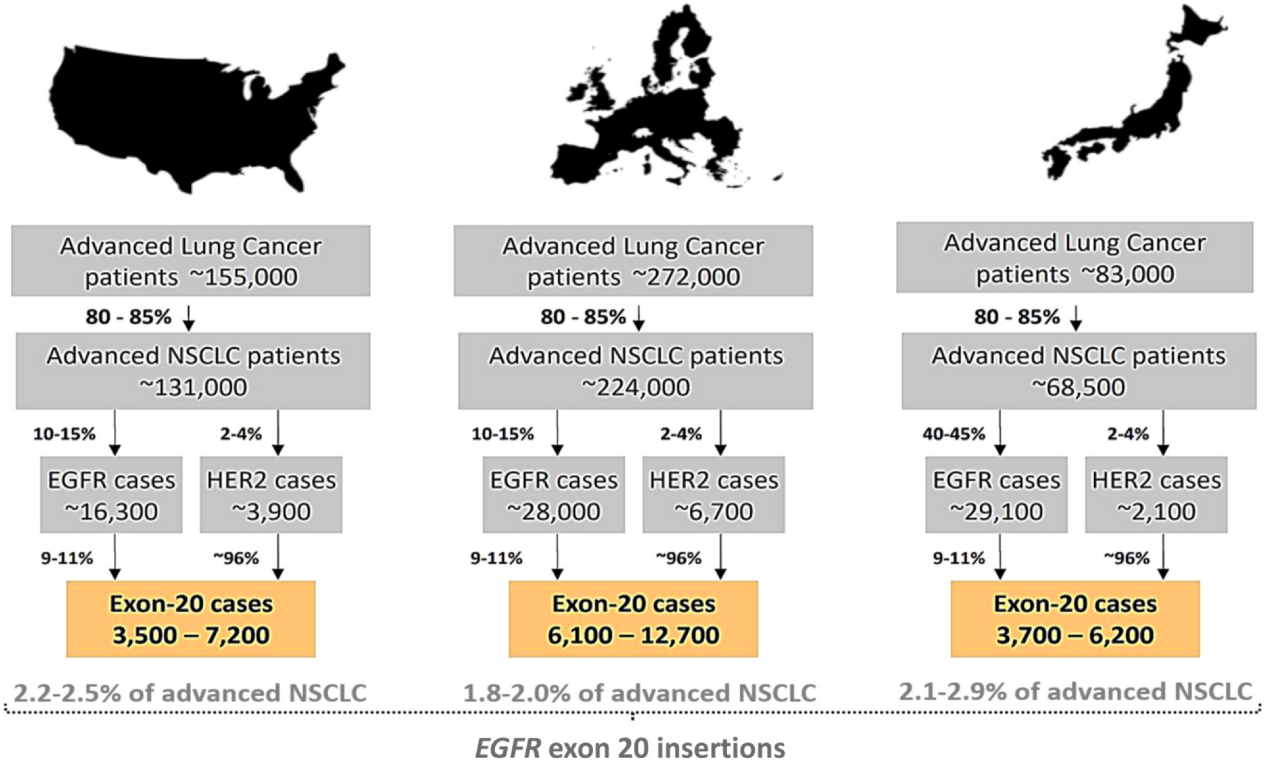

Fig. 1. Non-small cell lung cancer *EGFR* exon 20 insertion mutation population.

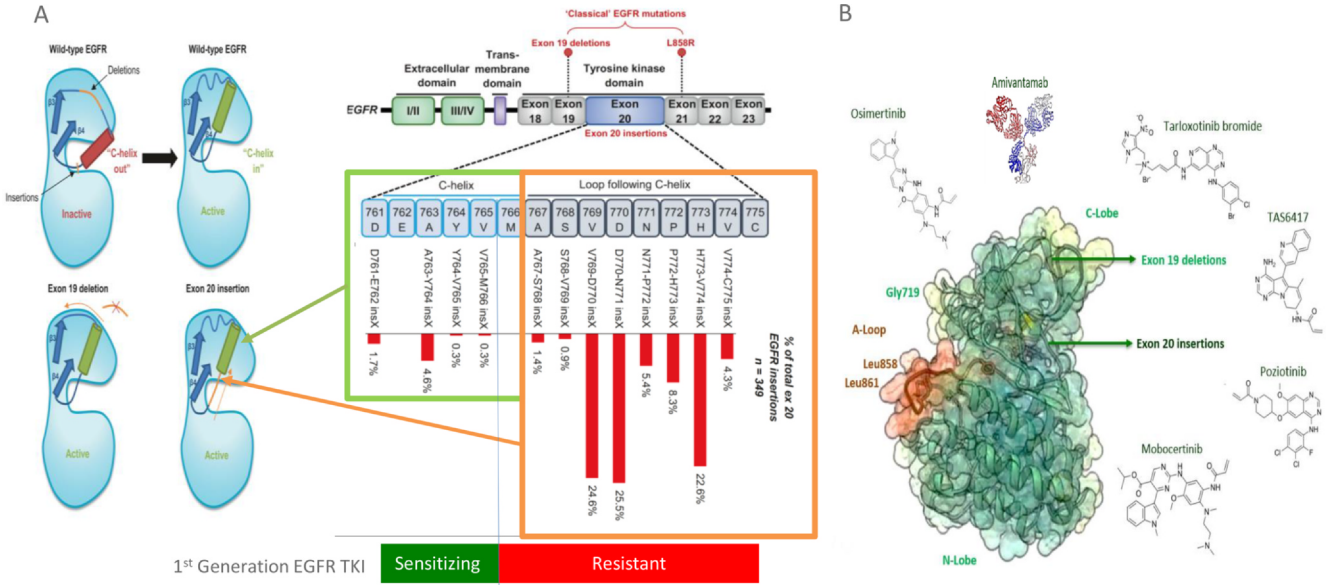

Fig. 2. A) Impact of deletions and insertions on *EGFR* activation, and incidence of *EGFR* exon 20 insertions variants in NSCLC. (modified from Vyse et al. - Signal Transduct Target Ther. 2019); **B)** Potential treatment strategies in *EGFR* exon 20 insertions lung tumors.

acid positions 762 and 774 of the EGFR protein [16], the most common are reported in Fig. 2A. *EGFR* ex20ins are positioned towards the C-terminal of the C-helix (positions 761–766), or in the loop that immediately follows it (positions 767–775, almost 90% of cases), pushing the C-helix into an active conformation [1–3]. The C-helix is a key regulatory element that dictates the activation status of EGFR by rotating from an outward to an inward position, permitting specific interactions with the active site that stabilizes dimerization-competent EGFR [16]. Unlike common *EGFR* mutations, *EGFR* ex20ins mutations do not affect the ATP-binding pocket required for kinase activity but instead form a wedge at the end of the C-helix that promotes active kinase conformation but does not increase the affinity for EGFR tyrosine kinase inhibitors (TKI) [17]. This lack of drug affinity could be caused by steric hindrance secondary to a prominent shift of the C-helix and phosphate-binding loop of EGFR into the drug-binding pocket [18].

Some clinical characteristics have been associated with specific *EGFR* ex20ins variants. In a recent cohort (N = 88), according to age, the V769_D770insASV variant and the A763_Y764insFQEA variant were more prevalent in patients ≥65 years and younger than 65, respectively. Similarly, the V769_D770insASV, H773_V774insNPH, V774_C775insHV and D770_N771insSVD variants were more common in the female population (p = 0.006) and among never smokers

Table 1
Ongoing clinical trials assessing the efficacy of *EGFR* exon 20 insertion inhibitors in non-small cell lung cancer patients.

NCT number	Phase	Population	Treatment	Number of patients needed*	Primary outcome	Status
Afatinib						
NCT03727724 (AFACET)	II	Advanced/metastatic NSCLC with EGFRex20ins	Afatinib 40 mg QD, cetuximab 500 mg/m2 iv Q2W	37	DCR after 18 weeks	Recruiting
Osimertinib						
NCT03414814 (KCSG LU17-19)	II	Pretreated advanced/metastatic NSCLC with EGFRex20ins	Osimertinib 80 mg QD	28	ORR	Active, not recruiting
NCT02496663	I	Previously treated NSCLC with EGFR mutation including EGFRex20ins	Osimertinib 80 mg QD Necitumumab	100	Safety and tolerability	Recruiting
Poziotinib						
NCT04044170	II	Previously treated NSCLC with EGFRex20ins or HER2 ex20ins	Poziotinib orally	114	ORR	Recruiting
Mobocertinib (TAK-788)						
NCT03807778 (Japanese population)	I	Phase II: treatment naive advanced/metastatic NSCLC with EGFRex20ins	TAK-788 orally	63	Phase II: ORR	Recruiting
Pyrotinib						
NCT04063462	II	Previously treated NSCLC with EGFRex20ins or HER2 ex20ins	Pyrotinib 400 mg QD	60	ORR	Not yet recruiting
NCT03574402 (TRUMP)	II	Arm 9: NSCLC with EGFRex20ins	Pyrotinib either 60 mg PO QD or 40 mg PO BID	400	ORR	Recruiting
Tarloxotinib						
NCT03805841 (RAIN)	II	For NSCLC: EGFRex20ins or HER2 activating mutation Other solid tumors: NRG1/EGFR fusion	Tarlaxotinib iv weekly	60	ORR	Recruiting
BDTX-189						
NCT04209465 (MasterKey-01)	I/II	Solid malignancies Phase II part allosteric HER2mut or EGFR/HER2 ex20ins	BDTX-189 orally dosed Phase II based on RP2D	184	Phase II: ORR	Recruiting
DZD9008						
NCT03974022	I/II	Advanced/metastatic NSCLC with EGFR/HER2 mutations, including EGFRex20ins	DZD9008	160	Part B: ORR	Recruiting
TAS6417 (CLN-081)						
NCT04036682	I/II	Recurrent/metastatic NSCLC with EGFRex20ins	CLN-081 QD or BID	80	Dose expansion: ORR	Recruiting

Abbreviations: NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; ex: exon; ins: insertion; HER2: human epidermal growth factor receptor2; mut: mutation; QD: once daily; BID: twice daily; ORR: objective response rate; Q2W: every 2 weeks; DCR: disease control rate; TKI: tyrosine kinase inhibitor; CNS: central nervous system; Q3W: every 3 weeks; mg: milligram; NRG1: neuregulin1; AE: adverse events; DOR: duration of response.

* Numbers for total study given (not specifically for EGFRex20ins cohorts, these data were not available).

(p = 0.04). Finally one-third of patients with brain metastases had the H773_V774insPH variant [3], but other cohorts have reported that the most common *EGFR* ex20ins variant in patients with brain metastases was the V769_D770insASV (21%) [8]. Finally, whether different *EGFR* ex20ins have a different prognostic outcome or major brain tropism merit further evaluation in larger cohorts.

Although almost all *EGFR* ex20ins mutations are mutually exclusive with other mutations, some series have reported co-occurring genomic alterations affecting mutations in *TP53* (in up to 65%) [2,8], cyclin dependent kinase inhibitor 2A and 2B (*CDKN2A* and *CDKN2B*) (22% and 16%, respectively), NK2 homeobox 1 (*NKX2-1*) (14%) RB transcriptional co-repressor 1 (*RB1*) (11%) [2], and *PIK3CA* [3,4,8]. Co-occurring genomic alterations in other known lung cancer drivers were rare (5%) [2], and *EGFR* amplifications were found in up to 22% of cases [2,8]. However, one recent cohort in Hispanic patients has reported that up to one-third of *EGFR* ex20ins NSCLC shared a common *EGFR* sensitizing mutation, which conferred a better prognosis [3]. In contrast, less than 1% of Chinese NSCLC patients harboring an *EGFR* ex20ins mutation had co-occurrence of a common sensitizing *EGFR* mutations [8].

Unlike common *EGFR* mutant NSCLC, currently, there are no approved targeted therapies available for patients whose tumor harbours an *EGFR* ex20ins mutation, and novel treatment approaches are needed. Recently, new treatment opportunities strategies have been reported in this landscape either with new EGFR TKI or bispecific antibodies (Fig. 2B), which may establish a new standard of care in the coming future for these patients. It is in this framework, that we provide a thorough overview on this subject.

Outcome with EGFR tyrosine kinase inhibitors

EGFR ex20ins mutations induce a steric hindrance of the drug-binding pocket, which prevents binding of EGFR TKI. Preclinical models and patient-derived experimental models confirmed that *EGFR* ex20ins in the domain immediately following the C-helix confer poor response to all known first-generation (erlotinib and gefitinib) and second-generation EGFR TKI (afatinib, neratinib and dacomitinib). *EGFR* ex20ins are on average 100 times less sensitive than the common sensitizing *EGFR* mutations [17–19]. However, not all *EGFR* ex20ins mutations have the same degree of resistance, and based on preclinical data, *EGFR* ex20ins A763_Y7764insFQEA is generally considered the unique variant sensitive to first- or second generation EGFR TKI [17,18], which has also been confirmed in the clinic [17,20,21]. Similarly, retrospective clinical data confirmed that NSCLC patients harboring classical *EGFR* mutations (N = 129) had significantly longer median PFS when treated with erlotinib, gefitinib or afatinib compared with patients (N = 9) with *EGFR* ex20ins mutations (14 months versus 2 months, p < 0.0001) [18]. This limited efficacy has also been endorsed by results from other cohorts, reporting a response rate (RR) ranging from 0% to 28%, and median PFS of ~3 months, not supporting first- or second-generation EGFR TKI as the best upfront treatment option for this subset of *EGFR*-mutant tumors [1,3,8,13,14,21–24]. Likewise, at least one study identified that the majority of patients with NSCLC harboring *EGFR*-A763_Y764insFQEA responded to clinical doses of first-, second- and third-generation EGFR TKIs [25]. These data may suggest that knowledge of the specific *EGFR* ex20ins variant may have potential clinical implications for making treatment decisions.

Osimertinib, a third generation EGFR TKI, is the preferred first-line treatment option in NSCLC harboring a common *EGFR* mutation [26], and has also reported clinical activity in uncommon *EGFR* mutations [27]. Although some authors have reported that *EGFR* ex20ins mutations induce large changes within the drug-binding pocket that sterically hinder the binding of third-generation inhibitors, others have reported *in vitro* evidence [28] as well as across xenograft models [29], about the efficacy of osimertinib in this subset of *EGFR* mutant cancers. However, clinical data is scarce and divergent [30]. Among 17 *EGFR* ex20ins NSCLC patients, osimertinib resulted in a RR of 5% and median PFS and OS of 3.6 months and 8.7 months, respectively [31]. In contrast, osimertinib resulted in a RR of 67% (4/6) among Chinese *EGFR* ex20ins NSCLC patients (including one patient with a known sensitizing variant A763_Y764insFQEA and one patient with the variant p.A767_V769dup) [32]. Finally, the phase II ECOG-ACRIN 5162 trial [33] has assessed osimertinib at 160 mg in 21 previously treated *EGFR* ex20ins NSCLC patients. Although the trial did not meet the primary endpoint of a 30% RR, osimertinib reported a confirmed RR of 24% (disease control rate in 85% of cases) and the median PFS was 9.6 months. The RR occurred in *EGFR* ex20ins mutations variants reported as not sensitive to EGFR TKI in preclinical models. Grade ≥ 3 treatment related adverse events (TRAE) included anemia (n = 2), fatigue (n = 2), prolonged QT interval (n = 2) and 1 patient discontinued treatment due to AEs. These data suggest that osimertinib may play a role in the therapeutic strategy of *EGFR* ex20ins. However, the benefit of osimertinib appears lower than in patients with common *EGFR* mutations. The ongoing KCSG-LUG17-19 trial (NCT03414814) is also assessing the efficacy of osimertinib in this population (Table 1). Whether osimertinib at 80 mg daily has the same clinical activity than higher doses, the role of dose escalation as well as correlation between *EGFR* ex20ins variants and osimertinib efficacy and activity of the drug in patients with brain metastases merits further evaluation.

In Ba/F3 cells carrying EGFRA763_Y764insFQEA, Y764_V765insHH, A767_V769dupASV, and D770_N771insNP exon 20 mutations, the combination of afatinib or osimertinib plus cetuximab reported an additive effect and induced a more potent inhibition than either agent alone, with similar IC_{50} with the combination regardless of the EGFR TKI subtype [20]. However, clinical evidence for this combination is limited [34,35]. Two ongoing clinical trials, NCT03727724 (afatinib plus cetuximab) and NCT02496663 (osimertinib plus necitumumab), are exploring this strategy (Table 1). The efficacy/toxicity ratio of the combination of EGFR TKI and cetuximab may limit applicability in daily clinical practice.

Based on the limited efficacy with upfront first- and second-generation EGFR TKI, chemotherapy has been considered the standard upfront treatment in *EGFR* ex20ins NSCLC [13]. Recently, in a retrospective Chinese cohort (N = 165), median PFS was significantly longer in patients who received first-line platinum-based chemotherapy compared with all-generation EGFR TKI (6.4 months versus 2.9 months, p < 0.001) [8]. Indeed, in another retrospective cohort of 84 *EGFR* exon20ins NSCLC patients, first-line pemetrexed-containing regimens compared with regimens without pemetrexed, were associated with significant longer PFS (p < 0.001) and OS (28.0 months versus 15.4 months, p = 0.009) [15]. Whether the upfront combination of EGFR TKI plus either chemotherapy [36,37], or an antiangiogenic agent [10,38,39] may have synergistic effect in this subset of *EGFR* mutant patients, mirroring the data reported among patients with common sensitising *EGFR* mutations remains unknown, as *EGFR* ex20ins tumors were not included in these trials. Only one trial included uncommon *EGFR* mutations (excluding *EGFR* ex20ins) demonstrating that the magnitude of benefit with the combination of gefitinib and chemotherapy occurred regardless of the *EGFR* mutation subtype [37].

Finally, *EGFR* Ex20ins mutant cell lines display sensitivity to heat shock protein (Hsp90) chaperon system inhibition [40]. Luminespib (AUY922) is a highly potent Hsp90 inhibitor. In a phase II trial enrolling 29 *EGFR* ex20ins NSCLC patients previously treated with at least 1 prior line of therapy, luminespib (70 mg/m^2 iv weekly) reported a RR of 17%, and there was no correlation between *EGFR* ex20ins variant and response to luminespib. The median PFS and OS were of 2.9 months and 12.8 months, respectively, and the most common TRAEs included ocular toxicity, diarrhea and fatigue. Grade 3 AEs were very uncommon, but 21% of patients required dose reductions. All study treatment was stopped on 28 February 2017 due to dissolution of study drug availability; 3 patients were on treatment at study termination [41].

New treatment strategies

Poziotinib

Poziotinib is an orally available quinazoline-based EGFR inhibitor. *In vitro*, poziotinib had an average IC_{50} value of 1.0 nM in Ba/F3 cell lines with an *EGFR* ex20ins mutation, making poziotinib approximately 100 times more potent than osimertinib and 40 times more potent than afatinib [18].

In a phase I trial, poziotinib reported encouraging efficacy in *EGFR*-mutant NSCLC and *HER2*-amplified breast or stomach cancers. The most common AEs were diarrhea, skin rash, stomatitis and pruritus. In line with other irreversible EGFR TKI, the dose-limiting toxicity (DLT) was diarrhea. The recommended phase 2 dose (RP2D) was 16 mg daily [42]. Initial data with poziotinib at 16 mg daily among 11 *EGFR* ex20ins NSCLC patients reported a RR of 64%, but 55% of patients required a dose reduction [18]. In a phase II, investigator-initiated single-centre trial (NCT03066206), poziotinib was tested in a cohort of *EGFR* ex20ins or point mutations excluding T790M (N = 50, 92% with *EGFR* ex20ins) and *HER2* ex20ins (N = 13). In the *EGFR* cohort, 70% of patients had already received ≥2 previous treatment lines, including 34% with previous TKI, and 28% had brain metastases. Poziotinib reported a confirmed RR of 44% and median PFS of 5.5 months. Grade 3–4 TRAEs occurred in 56% of patients, mainly skin rash (35%) and diarrhea (18%); with dose reductions and treatment discontinuation in 60% and 3% of patients, respectively [43] (Table 2). This encouraging activity prompted to launch the confirmatory international multicentre phase II ZENITH20 study (NCT03318939). However, this trial did not confirm these previous results. The ZENITH20 study [44] includes four different cohorts of previously treated or untreated *EGFR*- or *HER2*-ex20ins NSCLC patients. In cohort 1, enrolling 115 previously treated *EGFR* ex20ins NSCLC patients; poziotinib reported a RR of 14.8% and disease control rate of 68.7%. Higher RR was observed in *EGFR* ex20ins near the loop (767–772) compared with those insertions far of the loop (773–775), (21% and 9.1%, respectively). Multiple prior lines of therapy did not impair the RR (14.3%, 13.8%, and 16.2% in patients with one, 2, or 3 or more lines of therapy, respectively). The greatest RRs were observed in those without prior EGFR TKI therapy (17.4%), no brain metastases (15.5%), and an ECOG performance status of 0 (18.9%). The median duration of response (DoR) and PFS were 7.4 months and 4.2 months, respectively. Almost all patients enrolled experienced TRAEs at any grade, with the most common being diarrhea (79%), rash (60%), stomatitis (52%), and paronychia (45%). Grade 3 TRAEs occurred in 60% of patients, being again diarrhea (25%) and rash (28%) as the most common. There were two grade 4 TRAEs, one each of diarrhea and dermatitis acneiformis, and no grade 5 TRAEs. The incidence of treatment-related pneumonitis was 4%, however, prior immune checkpoint inhibitors (ICIs) may have confounded some cases. Dose reductions occurred in 68% of patients, with a median relative dose of 72% and a 10% rate of permanent discontinuation due to treatment related AEs (Table 2) [44]. Although the trial did not achieve the primary RR endpoint, the ZENITH20 trial continues enrolment with three new cohorts examining the efficacy of poziotinib in twice-daily dosing or daily low dose (Fig. 3).

The reasons for the differences in RR between both phase II trials remain unknown [43,44]. Both reported similar rates of grade ≥3 TRAE (56% and 60%), and dose reductions (60% and 68%). In the former one there were slightly less treatment discontinuations (3% and 10%, respectively), which may suggest that treatment for potential side effects could be more efficient in the single-centre study with probably better trained physicians for managing these toxicities. However, the safety profile of poziotinib remains a challenge, with especially skin and gastrointestinal toxicities, which may have an impact on patients' quality of life even if these are grade 2 AEs. Evaluation of refined dosing and improved toxicity management to maintain continuous treatment is warranted to assess the potential role of poziotinib in *EGFR* ex20ins related tumors. Although dose reduction and discontinuation with poziotinib rates were similar to those reported with other second-generation EGFR TKI such as afatinib in the LUX-Lung 7 and 6 trials (42–52% and 6–8%) [45,46] and dacomitinib in the ARCHER 1050 trial (66% and 10%, respectively) [47], better dose adjustment of poziotinib may enhance treatment compliance and maximize clinical benefit. For afatinib and dacomitinib, it has been reported that incidence and severity of AEs decreased following dose reductions, and tolerability-guided dose modifications enabled patients to continue on treatment without a negative impact in the outcome [48–50]. Of note, in the ZENITH20 trial responses could be maintained on a lower dose than 16 mg [44]. Therefore, new ongoing cohorts from the ZENITH20 study testing lower doses of poziotinib (10 mg QD, and 6 mg or 8 mg BID, Fig. 3) may improve the tolerability and toxicity ratio of the drug with positive impact on the outcome.

Differences in RR between both phase II trials could also be explained by different activity of poziotinib in the different *EGFR* ex20ins variants. Although the specific *EGFR* ex20ins variants have not been reported in the initial phase II study [43], in the ZENITH20 study, *EGFR* ex20 near-loop insertions were the most prevalent alterations (> 50%) and patients with these near-loop insertions benefited the most from poziotinib. However, in contrast to preclinical models reporting that *EGFR* ex20ins more sensitive to EGFR TKI are those located in the positions 763–765 [17], poziotinib did not report RR in *EGFR* ex20ins in theses positions, but only one patient had this mutation. The specific role of *EGFR* ex20ins variants merit further evaluation as in the ZENITH20 trial poziotinib responses were more common in patients with insertions between M766 to D770 of *EGFR* exon 20 [44] and other EGFR TKI, such as mobocertinib (TAK788), have demonstrated responses in patients with diverse *EGFR* ex20ins variants [51].

Other future challenges with poziotinib are the safety and efficacy of combining the drug either with monoclonal antibodies, such as cetuximab, or Hsp90 inhibitors. Lastly, overall clinical benefit and the mechanisms underlying resistance to poziotinib remain to be determined. In lung cancer models with *EGFR* ex20ins mutation, the secondary mutation encoding either T790M or C797S render tumor cells resistant to poziotinib [18,52]. Indeed, in preclinical models in *EGFR* ex20ins (D770insNPG) genetically engineered mice (GEM), acquired resistance mechanisms to poziotinib were bypass mechanisms such as acquired mutations in *ErbB4* and *KRAS*, as well as reactivation of the MAPK/PI3K pathway. Data coming from matched pre-poziotinib and on-progression samples from 20 out of 50 responding patients revealed acquired *EGFR*-dependent tyrosine kinase domain point mutations in 4 patients (T790M (2), V774A (1), D770A (1)), suggesting that

Table 2
Efficacy of tyrosine kinase inhibitors in *EGFR* exon 20 insertion mutant NSCLC patients.

Drug	Trial	N	RR (%)	PFS (mo.)	Grade 3 TRAE (%)	Dose reductions (%)	Discontinuations (%)
Osimertinib	ECOG-ACRIN 5162 ph II [33]	21	25	9.7	29	NR	5
Poziotinib	Phase II [43]	50	44	5.5	56	60	3
	ZENITH 20 cohort 1 [44]	115	14.3	4.2	60	68	10
Mobocertinib	Phase I/II [51]	43	43	7.3	40	25	14
Amivantamab	Phase I/II [60]	39	36	8.3	6	10	6

N: number. RR: Response Rate. PFS: Progression Free Survival. TRAE: treatment related adverse events. NR: not reported.

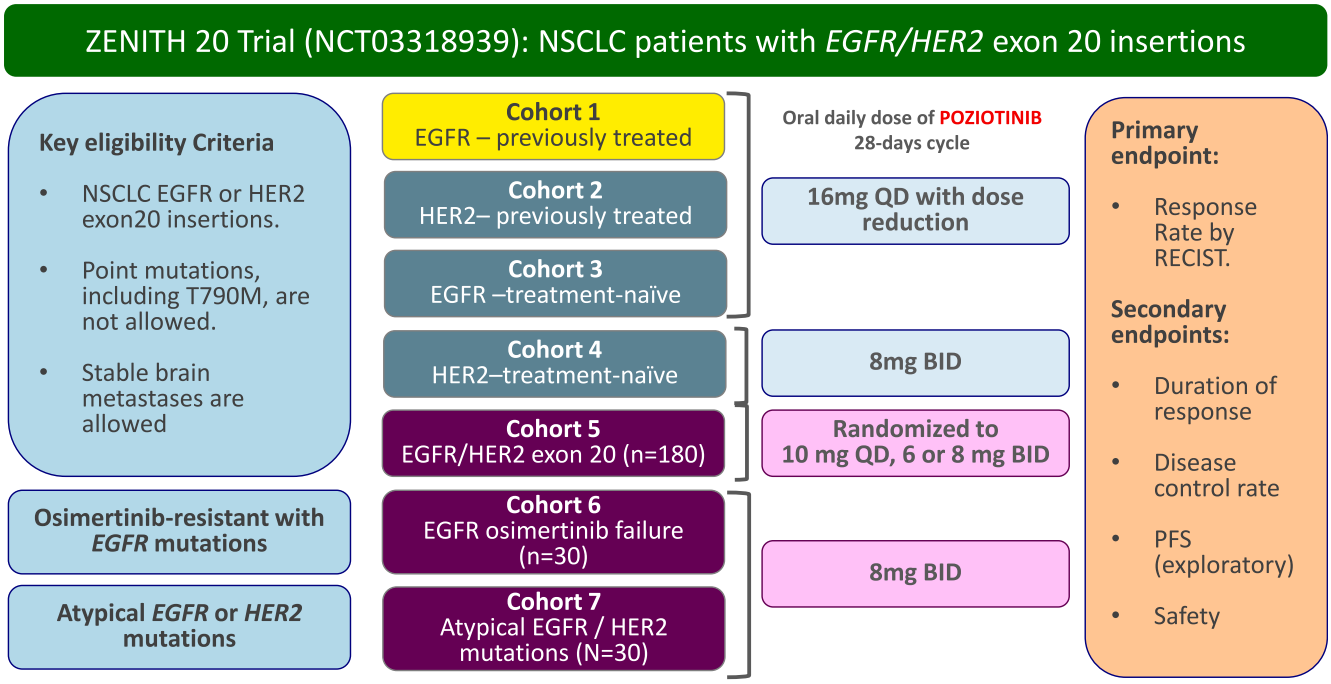

Fig. 3. Figure of ZENITH20 trial cohorts.

T790M is a poziotinib resistance driver. Other mechanisms identified in patients included *MET, EGFR* or *CDK6* amplifications [53]. Whether upfront combination strategies with the aim to delay the onset of resistant mechanisms may increase the efficacy of poziotinib merits further evaluation, with also special attention to additional toxicities.

Mobocertinib

Mobocertinib (TAK-788) is another *EGFR/HER2* ex20ins TKI; it has reported potent and selective preclinical inhibitory activity against *EGFR* ex20ins. Mobocertinib was assessed in a phase I/II trial (NCT02716116). In the phase I dose escalation, 101 patients (median age, 61 years; 70% female; 76% ≥2 prior anticancer therapies; 53% brain metastases) were treated with mobocertinib at 5–180 mg daily. The RP2D was determined to be 160 mg [54], and an expansion multicohort phase II trial is ongoing (Fig. 4).

In total, 28 NSCLC patients with refractory *EGFR* ex20ins were included during the phase I dose escalation or in the phase II expansion cohort 1 with mobocertinib treatment at 160 mg. Out of the patients enrolled, 54% of patients had received ≥3 prior systemic treatments, 61% were previously treated with ICIs, and 43% had brain metastases. Mobocertinib reported a RR of 43% and a median PFS of 7.3 months (Table 2). According to baseline brain metastases status, the RR and PFS were 56% and 8.1 months for those patients without brain metastases (N = 16), whereas among patients with brain metastases (N = 12) the RR and PFS were 25% and 3.7 months, respectively. The antitumor activity of mobocertinib occurred regardless of previous treatment with EGFR TKI or ICI. Of note, there is no clear trend that response to mobocertinib is enriched in specific *EGFR* ex20ins variants (RR of 40% in 769ASV, 50% in 773NPH, 50% in other *EGFR* ex20ins, and 50% in patients with unknown variant). Among all patients treated with mobocertinib at 160 mg (N = 72) Grade ≥ 3 TRAEs were reported in 40% of patients, mainly diarrhea, nausea and rash. Dose reductions and treatment discontinuations occurred in 25% and 14% of cases, respectively [51]. The ongoing EXCLAIM extension cohort searches to validate the efficacy (RR) of mobocertinib in 97 previously treated *EGFR* ex20ins NSCLC patients. While awaiting these results, indirect comparison data from refractory *EGFR* ex20ins NSCLC patients treated with mobocertinib in the trial versus other second-line treatment options used in the real world setting has reported that PFS (7.3 months versus 3.7 months, p = 0.0003) and RR (43% versus 14%, p = 0.0003) were statistically significant improved with mobocertinib compared with other treatment strategies although patients treated with mobocertinib were more heavily pretreated than patients in the real world data [55].

Based on the results of the cohort 1, the FDA granted a Breakthrough therapy designation for mobocertinib in this subset of *EGFR* ex20ins mutant population on 27th April 2020. Likewise, with the aim to validate upfront-personalised treatment approach for this subset of *EGFR* mutant patients, the ongoing phase III EXCLAIM-2 trial (NCT04129502) compares mobocertinib versus platinum-based chemotherapy in 319 treatment naïve *EGFR* ex20ins NSCLC patients. Crossover is allowed and the primary endpoint is PFS by blinded independent radiological review. Patients are stratified according to baseline brain metastases status and race.

Amivantamab (JNJ-61186372)

Amivantamab is a novel, fully humanized anti-EGFR-MET bispecific IgG1 antibody whose mechanism of action can target both *EGFR*- and *MET*-driven disease. Amivantamab inhibits tumor growth and progression by three distinct mechanisms. Two of these mechanisms involve inhibition of *EGFR* and c*Met* signaling, first by inhibition of ligand-induced activation via blocking ligand binding to each receptor and second by receptor inactivation via degradation. The third mechanism utilizes Fc effector-mediated killing of *EGFR*- and *cMet*-expressing tumor cells by antibody-dependent cellular cytotoxicity. Through these mechanisms of action, amivantamab showed activity in multiple xenograft models [56] and BaF3 cells [57] harboring diverse *EGFR* mutations (Del19, L858R, T790M, ex20ins, C797S) and *MET* amplification. In BaF3 cells with multiple ex20ins viability decreased when treated with amivantamab. In contrast, treatment with gefitinib and osimertinib showed limited antiproliferative activity compared to amivantamab. Importantly, *in vivo*, efficacy of amivantamab was superior to cetuximab or poziotinib [57]. In a first-in-human CHRYSALIS phase I trial [58] (NCT02609776) patients received amivantamab at 140–1400 mg iv weekly for the first 28-day cycle and biweekly thereafter. Amivantamab displayed manageable safety profile with no DLTs during dose escalation up through the 1400 mg dose cohort. Infusion-

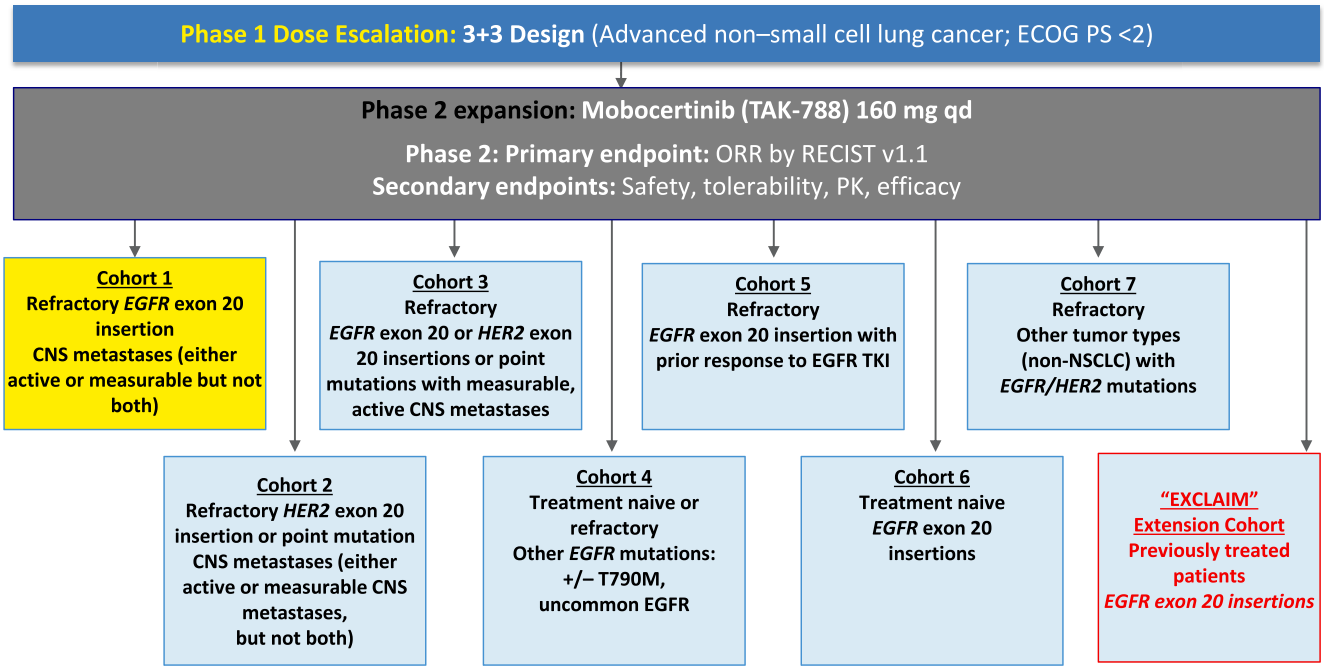

Fig. 4. Design of the Phase 1/2, Open-Label, Multicenter Trial (NCT02716116) with mobocertinib (TAK-788) (CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER, human epidermal growth factor receptor; MRI, magnetic resonance imaging; ORR, objective response rate; PS, performance status; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours. Yellow box, results reported). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

related reaction, which was mainly limited to the first infusion, and rash (mainly grade 1–2) were the most common AEs. TRAEs grade ≥3 occurred in 9% of patients. The RP2D was 1050 mg (1400 mg for patients ≥80 Kg), and preliminary but clinically significant efficacy was observed in patients with *EGFR*-mutant NSCLC (N = 108, RR 30%) including *EGFR* ex20ins mutant NSCLC patients (N = 27, RR 30%) [58,59]. A recent analysis reported the data including all 50 enrolled patients with *EGFR* ex20ins disease who received amivantamab at the RP2D. Among the 39 response-evaluable patients (74% previously treated with platinum-based chemotherapy, median age 61 years, and 51% female), the RR was 36% (41% in previously treated patients) with a median DoR of 10 months. The median PFS was 8.3 months (8.6 months in previously treated). The most common AEs reported were rash (72%), infusion related reaction (60%), and paronychia (34%), stomatitis (16%), pruritus (14%), and diarrhea (6%). Grade ≥ 3 AEs were reported in 36% of patients; and 6% were TRAEs. Dose reductions and discontinuations occurred in 6% and 10%, respectively [60]. These data support amivantamab as a potential treatment strategy and on March 10th 2020 FDA granted a breakthrough therapy designation for amivantamab in this subset of *EGFR* mutant patients.

Other evaluated drugs

TAS6417 is a robust inhibitor against the most common *EGFR* mutations (Del19, L858R, T790M). It has as well activity in cells driven by the less common *EGFR*-G719X, L861Q, and S768I mutations [61]. Indeed, TAS6417 targets *EGFR* ex20ins mutations while sparing wild-type [62], and selectivity indexes (wild-type EGFR/mutant EGFR ratio of inhibition) favored TAS6417 in comparison with poziotinib and osimertinib, indicating a wider therapeutic window [61]. A phase I/II clinical trial (NCT04036682) is ongoing in previously treated *EGFR* ex20ins mutant NSCLC patients.

Tarloxotinib is a prodrug that releases an irreversible EGFR/HER2 TKI under physiologically hypoxic conditions. In cell lines, tarloxotinib can overcome intrinsic EGFR ex20ins resistance to standard EGFR TKIs [63]. The ongoing RAIN phase II study (NCT03805841) is assessing the RR of tarloxotinib in *EGFR/HER2* ex20ins mutant NSCLC patients and in other solid tumors with *NRG1* fusions (Table 1).

Other ongoing clinical trials with other EGFR/HER2 ex20ins TKI such as pyrotinib [64], BDTX-189 and DZD9008 [65] are summarized in Table 1.

Immune checkpoint inhibitors

Average tumor mutational burden (TMB) in *EGFR*ex20ins NSCLC is low (mean 4.3, range 0 to 40.3 mutations/Mb) [2,66] similar to common sensitizing *EGFR* mutations [67]. However, low TMB in the presence of oncogenic driver mutations should not preclude ICI efficacy [68]. The programmed death ligand-1 (PD-L1) expression in *EGFR* ex20ins lung tumors ranges from 37% to 80% [3,66,67]. High PD-L1 expression (≥50%) occurs in 10% of cases (N = 9/88) [3], and PD-L1 expression may vary according to different *EGFR* ex20ins variants [3]. Evidence about the efficacy of ICI in this subset population is scarce [8]. Compared to common sensitizing *EGFR*-mutant NSCLC (N = 36) the *EGFR* ex20ins NSCLC patients (N = 30) significantly achieved longer PFS (2.9 months versus 1.9 months, HR 0.45, p = 0.002) and OS (NR versus 11.5 months, HR 0.2, p < 0.001), as well as a higher RR (25% versus 0%) with ICI [69]. These results may suggest that patients with alterations in this particular region have distinct tumor behaviour more suitable to be treated with ICI. However, the limited number of patients included and lack of information about PD-L1 expression and TMB in this cohort does not lead to firm conclusions. Indeed it remains unknown whether ICI monotherapy or in combination with chemotherapy could be suitable in this subset of patients as *EGFR* mutant tumors were excluded from randomized phase III clinical trials assessing the role of ICI in first-line setting of advanced NSCLC patients [70–72]. However, the IMpower130 and IMpower150 phase III clinical trials allowed to enrol tumors with sensitizing common *EGFR* mutations and other *EGFR* mutations [73,74]. Although chemo-immunotherapy did not improve the outcome compared with chemotherapy alone [73,74], the four-drug combination of bevacizumab plus atezolizumab plus chemotherapy improved the outcome compared with the bevacizumab and

chemotherapy combination [74]. Whether these results can be translated to *EGFR* ex20ins mutant tumors remains unknown. In the IMpower 150 trial only 12 patients with this mutation were included, not allowing to obtain firm conclusions.

Future perspective

Oncogenic addicted *EGFR* ex20ins mutant NSCLC remains a tumor with poor prognosis despite being potentially druggable with personalised approaches. However, the conformation of the mutation limits the efficacy of conventional TKI and even the selective EGFR ex20ins TKI have reported more limited efficacy than other EGFR TKI targeting common sensitizing EGFR mutations. Indeed, in some cases the toxicity profile linked to EGFR wild type cells such as diarrhea or rash limits their clinical utility. Therefore, there is a clinical need to identify new therapies for patients with *EGFR* ex20ins mutation.

Whether different *EGFR* ex20ins variants may achieve different benefit from these selective TKI remains controversial. Likewise, most of these selective *EGFR* ex20ins TKI have been tested in previously treated populations, with no data in the first-line setting. Similarly, half of the *EGFR* ex20ins tumors have a *TP53* co-mutation. In NSCLC patients with concomitant *EGFR* and *TP53* mutation, the efficacy of EGFR TKI is decreased compared with those without *TP53* mutation [75]. Although in preclinical models the antitumor activity with amivantamab occurred regardless of this co-mutation [57], the role of co-mutations in the treatment efficacy of EGFR ex20ins TKI merits also further evaluation.

Despite these limitations, results from clinical trials with selective EGFR ex20ins TKI have been eagerly awaited and they represent an important progress towards the identification of an effective therapeutic option for NSCLC patients with *EGFR* ex20ins, an area of high unmet medical need. Evaluation of refined dosing of selective *EGFR* ex20ins TKI and improved toxicity management to maintain continuous treatment with these new agents may improve the outcome. However, evidence is still scarce and based on the limited number of patients included in the phase I/II clinical trials. Indirect trial comparisons report similar efficacy, but different toxicity profiles, without head to head comparison for assessing the best treatment option. Whether EGFR TKIs are more suitable than bi-specific antibodies remains unknown. Indeed, the best place of ICI in this therapeutic strategy is also relevant. Although previous studies in sensitizing *EGFR*-mutant [76] or *ALK*-positive [77,78] NSCLC patients have reported that concurrent or sequential ICI and TKI may increase the risk of pneumonitis or hepatotoxicity, clinical trials with TKI in EGFR ex20ins NSCLC have not reported increased pulmonary or hepatic toxicity, despite a high proportion of patients enrolled in the trials had previously received ICI.

In the close future, the ongoing phase III clinical trials will hopefully confirm the efficacy of a personalised treatment approach in the first-line setting compared with chemotherapy, and potential trials assessing the efficacy of combination strategies either with chemotherapy or antiangiogenics merit also further evaluation in EGFR ex20ins tumors. This potential synergism must be clearly balanced with toxicity for not hampering treatment compliance.

As almost one-third of *EGFR* ex20ins mutant patients may have brain metastases at baseline, intracranial efficacy of these drugs is relevant for this population. Finally, the knowledge of the mechanisms of acquired resistance for personalising treatment upon progression is relevant and may help to enhance the outcome of this population. Finally, the best place of ICI in the therapeutic strategy is also relevant.

Conclusions

Although rare and initially thought not targetable, promising treatments for *EGFR* ex20ins with either new EGFR-TKI or anti-EGFR-MET bispecific antibodies have launched a new treatment approach in this subset of the lung cancer population. Special attention should be paid to the balance of toxicity and survival, and the role of the specific *EGFR* ex20ins mutation variants, as well as intracranial activity. Based on the availability of new drugs, physicians should be aware of treatment opportunities and patients should be tested for *EGFR* ex20ins mutations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2020.102105.

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