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Resistance to epidermal growth factor receptor tyrosine kinase inhibitors in mutated non-small cell lung cancer: new avenues and strategies to overcome resistance

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Summary The most common driver mutation in non-small cell lung cancer (NSCLC) is found within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). It commonly affects younger, female, and non-smoking patients. To date, there are five approved tyrosine kinase inhibitors (TKIs) for the treatment of EGFR-mutated NSCLC: erlotinib, gefitinib, the second-generation TKI afatinib and dacomitinib, and the third-generation TKI osimertinib. Sequencing TKI treatment or starting with osimertinib first are reasonable treatment strategies. Nevertheless, patients develop resistance to these TKIs, which can be primary or acquired. Primary resistance includes resistance mutations such as EGFR insertion 20, acquired resistance comprises the development of resistance mutations, activation of bypass signaling, or histological transformation into small cell lung cancer.
This article summarizes the current landscape of treatment in EGFR-mutated lung cancer and discusses the different resistance mechanisms. It gives a perspective on novel EGFR TKIs and potential combination strategies to overcome resistance.

Keywords Lung cancer · Driver mutation · Epidermal growth factor receptor · Tyrosine kinase inhibitor · Resistance

Introduction and current landscape of treatment

Lung cancer with molecular oncogenic driver mutations is an exciting field of activity for physicians. The possibility of treating patients with targeted therapy instead of chemotherapy—or even with the better-tolerated immunotherapy—offers high and long response rates and very few side effects.

Tumors with molecular drivers are much more common in never-smokers, long-time ex-smokers (>10 years), or light smokers (<15 pack-years), in younger and female patients [1]. The vast majority of oncogene-addicted lung cancers are adenocarcinomas, and the different mutations are generally mutually exclusive [1].

The most common driver mutations are found within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). The continuous activation of the intracellular domain of the EGF receptor via driver mutations leads to an activation of downstream pathways and finally to cell survival. The prevalence is around 10–20% in the Caucasian population with adenocarcinoma and much higher (about 40%) in the Asian population [1]. They can occur within exon 18–21 of the EGFR gene and about 90% of the alterations comprise exon 19 deletions and the L858R point mutation in exon 21 [2]. Beside these common mutations of the EGFR there are also uncommon mutations accounting for about 10% of EGFR mutations (Fig. 1; [2]).

International guidelines recommend testing all patients with advanced non-small cell lung cancer (NSCLC) that contains adenocarcinoma for oncogenic driver mutations. In very small biopsies or in cases of never/light smokers, molecular testing is recommended regardless of histology [1, 3].

To date, the European Medical Agency (EMA) has approved four tyrosine kinase inhibitors (TKIs) for the treatment of EGFR-mutated NSCLC: the first-generation TKIs erlotinib and gefitinib, the second-generation TKI afatinib, and the third-generation TKI osimertinib.

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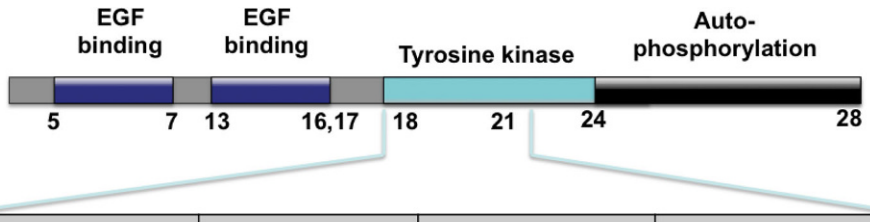

Exon 18	Exon 19	Exon 20	Exon 21
G719A[a)]	Deletion 19 (48%)	S768I (1%)	L858R (43%)
G719C[a)]	Insertion 19 (1%)	V765A (<1%)	L861Q (2%)
G719D[a)]	L747S (<1%)	T783A (<1%)	T854A (<1%)
G719V[a)]	D761Y (<1%)	V774A (<1%)	A871E (<1%)
E709X[b) c)]		S784P (<1%)	
delE709-T710insD[b)]		T790M [d)]	
		C797S [e)]	
		Insertion 20 (4%)	

Fig. 1 Common and uncommon EGFR mutations; *green*: typically sensitive to TKIs, *red*: resistant to TKIs. (T790M as resistant mutation is sensitive to osimertinib). *Parentheses*: frequency of occurrence in treatment-naïve patients. (Adapted from [44]). [a]G719X mutation 3–4%. [b]E709X approx. 1.5%. [c]RR 50% of complex E709X mutation (in combination with another EGFR mutation). [d]T790M: approx. 5% in TKI-naive; approx. 65% after TKI treatment. [e]C797S: 40–69% after treatment with osimertinib). *EGFR* epidermal growth factor receptor, *TKI* tyrosin kinase inhibitor

The first-generation drugs, including erlotinib and gefitinib, are reversible inhibitors of the EGFR and were primarily designed against the wild-type EGFR [2]. The second- and third-generation inhibitors, including afatinib, dacomitinib (currently not EMA approved), and osimertinib, are irreversible inhibitors that covalently bind to EGFR.

Phase III clinical trials have shown that patients with EGFR-mutant tumors have about 70% response rates (RRs) and a statistically significant improved progression-free survival (PFS) when treated with first- or second-generation EGFR TKIs compared with platinum-based chemotherapy [4–7].

At present, there are three phase III trials that directly compare TKIs. The Lux lung 7 was a head-to-head trial of afatinib versus gefitinib in the first-line setting and showed better PFS (HR: 0.73, 95% CI: 0.58–0.92) and a higher RR (70% vs. 56%; $p = 0.0083$) for afatinib. There was no statistically significant difference in OS (HR: 0.86, 95% CI: 0.66–1.12; [8]).

Dacomitinib is a second-generation TKI that was recently approved by the EMA for the first-line treatment of metastatic EGFR-mutated NSCLC (exon 19 deletion or exon 21 L858R mutation). The phase III ARCHER trial compared dacomitinib with the first-generation TKI gefitinib and enrolled 452 patients with EGFR-mutant NSCLC. Dacomitinib improved PFS compared with gefitinib (14.7 vs. 9.2 months; HR: 0.59, 95% CI: 0.47–0.74;). Overall survival was presented after a median follow-up of 31 months. Patients treated with dacomitinib had a significant longer OS than patients treated with gefitinib (HR: 0.760; 95% CI: 0.582–0.993); the median OS was 34.1 months with dacomitinib versus 26.8 months with gefitinib. A main limitation of this trial was the exclusion of patients with cerebral metastases, since brain metastases are very frequent in NSCLC patients with driver mutations. Toxicity was higher with dacomitinib; 66% of patients required a dose reduction, compared with 8% for those who received gefitinib. The most commonly reported adverse events (of any grade) in patients given dacomitinib were diarrhea (87%), paronychia (62%), dermatitis acneiform (49%), and stomatitis (44%). The most common adverse events in patients given gefitinib were diarrhea (56%), alanine aminotransferase increase (39%), and aspartate aminotransferase increase (36%; [9, 10]).

The FLAURA Trial compared first-generation TKIs erlotinib and gefitinib with osimertinib in the first-line setting and showed a statistically significant PFS benefit for osimertinib (18.9 months) versus standard-of-care TKI (10.2 months, HR: 0.46, 95% CI: 0.37–0.57) The benefit was independent of CNS metastases, but the OS data is currently imature [11].

The approval of osimertinib in the front-line setting is based on the FLAURA trial. This leads to the discussion of sequencing TKI treatment or starting front-line treatment with the most potent drug. From my point of view, both treatment algorithms are plausible. Starting with afatinib and switching to osimertinib at the time of progression and detection of T790M can lead to treatment durations of 27 months [12]. Nevertheless, this sequence would be relevant only for 50–60% of cases. By contrast, osimertinib in the first-line setting ensures that the patients get the currently best drug independent of the detection of a resistance mutation.

Resistance to TKI

Despite meaningful improvement in treatment of EGFR-mutated lung cancer, sooner or later all patients develop resistance to TKI treatment.

There are two main types of resistance to target therapy in patients with NSCLC and driver mutations: primary (i.e., intrinsic) and secondary (i.e., acquired) resistance [13, 14]. Primary resistance describes a de novo resistance to the targeted therapy, whereas acquired resistance occurs when progressive disease develops after an initial response. Mechanisms of acquired resistance to TKI treatment in EGFR-mutated NSCLC include the development of resistance mutations, activation of bypass signaling, or histological transformation [13, 15].

Intrinsic resistance

As mentioned, beside the most common EGFR mutations (exon 19 deletion and L858R mutation) uncommon mutations also occur in about 10% of adenocarcinoma patients. While, for example, the mutations G719X, L861Q, and S768I are sensitive to afatinib [16] or osimertinib [17], the exon 20 insertions or duplications that account for about 4% are associated with resistance to all currently approved EGFR inhibitors. Recently, at the World Lung Cancer Conference (WCLC) in Toronto in 2018, the TKI poziotinib showed promising results in this difficult-to-treat mutation. Poziotinib is a potent inhibitor of exon 20 insertions in EGFR and HER2. In an open-label phase II trial, it showed overall response rates (ORR) of 55% in 44 patients with EGFR exon 20 mutated who were heavily pre-treated. Also, durable responses of >1 year were seen in six patients. Treatment-related adverse events were typical for EGFR TKIs with diarrhea (69%), oral mucositis (69.8%), paronychia (60.3%), and skin rash (55.6%; [18]). TAK788 is another selective TKI with activity against EGFR and HER2 exon 20 insertions. In a phase I dose-escalation trial presented at WCLC 2018, promising results were seen in pretreated EGFR-mutated patients; the most common adverse events were diarrhea (47%), nausea (26%), and fatigue (21%). A phase II trial is planned after determination of the recommended phase II dose for TAK788 [19].

Acquired resistance

Development of resistance mutations

While various mechanisms can lead to TKI resistance, the EGFR T790M mutation is the most common mechanism of acquired resistance to first- and second-generation EGFR TKIs. It occurs in about 50–60% of the cases [20]. T790M resistance mutation is located within the ATP-binding pocket of the EGFR protein and leads to TKI resistance by increasing protein affinity for ATP [21]. Evaluating EGFR T790M status is necessary in the setting of acquired resistance to first- or second-generation TKIs. Liquid biopsy uses blood samples for the isolation and analysis of circulating cell-free tumor DNA or circulating tumor cells (CTCs) to detect both EGFR sensitizing and resistance mutations. It is less invasive with improved patient safety. However, depending on the detection method used (Cobas, ARMS; ddPCR, BEAMing, NGS), although specificity is rather high (reaching 58–100%), sensitivity is still low (around 29–71%; [22]). A liquid biopsy negative for T790M and positive for the initial sensitizing mutation indicates the presence of the circulating tumor DNA, without a resistance mutation, whereas double-negative results do not exclude the presence of T790M, since there is no confirmation that any tumor DNA was in the sample, and these results are more likely to be false negative. Nevertheless, the case of a negative liquid biopsy is an indication for tumor tissue biopsy.

With osimertinib moving to the first-line setting for treatment of EGFR-mutated NSCLC, further resistance mutations will challenge us in the future. Oxnard et al. [23] investigated resistance mechanisms in 143 patients with T790M-positiv lung cancer who developed acquired resistance to osimertinib. They found mainly two groups of patients: Patients who maintained the T790M at the time of resistance had a high frequency of the C797S mutation. On the other hand, those patients who lost T790M had a broad range of competing resistance mechanisms including MET amplifications, BRAF mutations, and small cell lung cancer (SCLC) transformation. Time to treatment discontinuation (TTD) was shorter in patients with T790M loss (6.1 vs. 15.2 month). In their conclusions, the authors suggested that patients who develop early resistance to osimertinib likely have competing resistance mechanisms in other tumor subclones, whereas patients who develop late resistance are more likely to have maintained T790M and acquired C797S and that these findings may have clinical relevance in the future [23]. Fourth-generation TKIs targeting C797S are currently under development [24]. Case reports also showed sensitivity of C797S to gefitinib and erlotinib [25–27]. Niederst et al. demonstrated that the allelic context in which C797S was acquired might predict responsiveness to TKI treatment. If the C797S and T790M mutations are in *trans*, cells will be resistant to third-generation EGFR TKIs, but will be sensitive to a combination of first- and third-generation TKIs. If the mutations are in *cis*, no EGFR TKIs alone or in combination can suppress activity [28].

Activation of bypass signaling pathways

Acquired resistance to EGFR treatment can also occur through reactivation of downstream signaling pathways. There are multiple mechanisms of resistance via bypass pathways as, for example, MET amplifi-

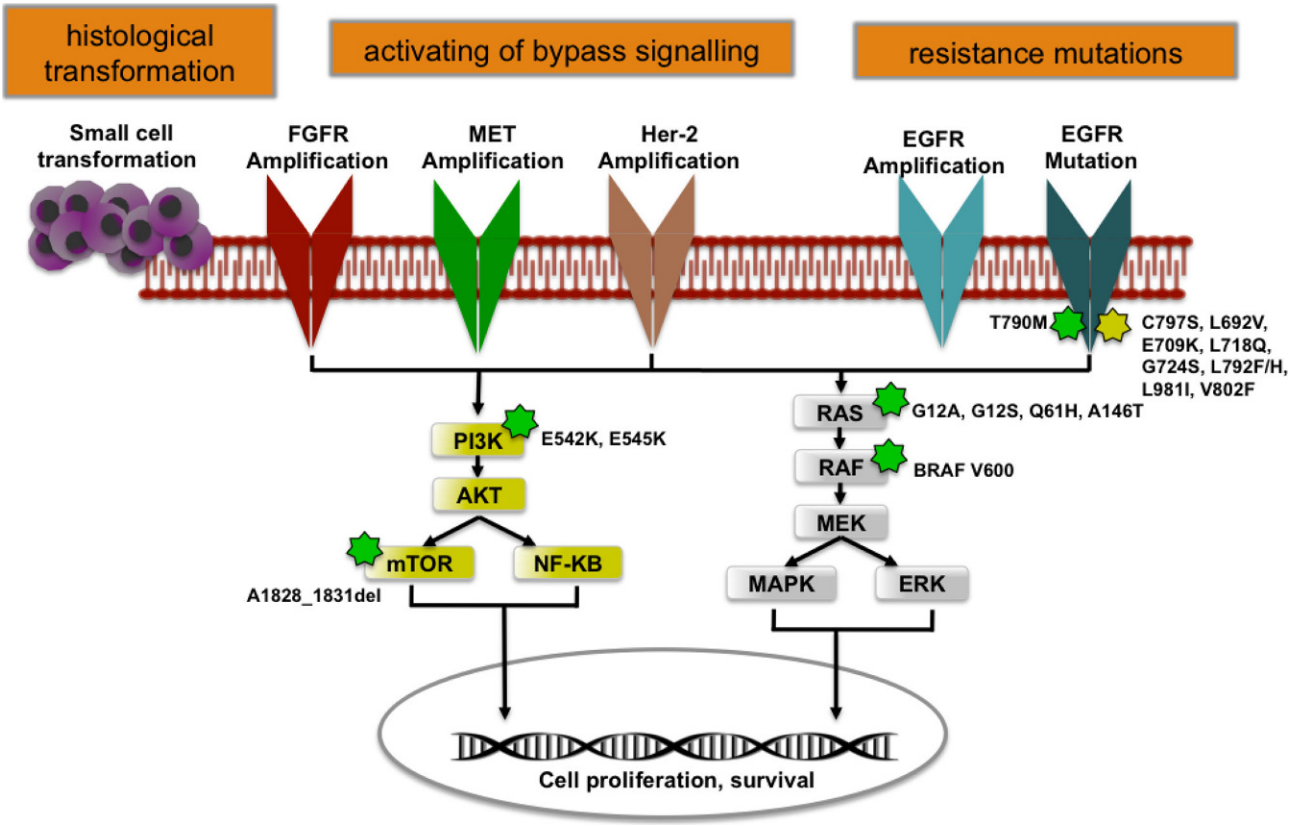

Fig. 2 Mechanisms of acquired resistance to tyrosine kinase inhibitor treatment in epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer. (Adapted from [14])

cation, HER 2 amplification, PIK3CA mutations, and BRAF mutation (Fig. 2).

MET and Her2 amplifications have been reported in both preclinical and clinical studies [15]. The MET oncogene encodes for the transmembrane tyrosine kinase c-MET. The binding of its ligand leads to activation of downstream signaling pathways including those involved in proliferation [15]. Crizotinib showed activity in NSCLC with MET amplifications and in those with c-MET mutation [29–33]. Multiple trials are currently evaluating the combination of EGFR and MET inhibitor (NCT01866410, NCT02468661, NCT01982955, NCT02374645).

Her2 amplification is mutually exclusive with the T790M mutation [34]. It also activates downstream signaling pathways and is found in about 12% of EGFR-resistant NSCLC [35]. Ado-trastuzumab, which showed promising results in Her2 mutated NSCLC, could be a therapeutic option [36].

Histological transformation to SCLC

Histological transformation from NSCLC to SCLC is more common in lung cancer with EGFR mutations than EGFR wild-type tumors, with the frequency ranging between 5 and 14% [37]. Nevertheless, this finding could be biased by a greater number of re-biopsies in EGFR-mutated lung cancer. The mechanism of histological transformation is not fully understood. One hypothetical model is based on the fact that a subtype of lung cancer cells of origin, the type II alveolar cells, have the potential to become both EGFR-mutated adenocarcinoma cells and SCLC cells. The development of SCLC depends on the presence and absence of oncogenes and tumor suppressor genes (e.g., TP53, Retinoblastoma gene 1, RB1; [38]). On the other hand, the well-differentiated type II alveolar cells have a high expression of EGFR family members (EGFR, Erbb2) and activation of EGFR signaling leads to proliferation and EGFR-mutated adenocarcinoma cells. The TKIs against EGFR block this proliferation and an additional genetic event such as the loss of RB1 and/or TP53 can lead to small cell transformation [38].

New avenues: third-generation TKIs nazartinib and lazertinib

Nazartinib (EGF816) is a new third-generation EGFR TKI that selectively targets EGFR ex19del and L858R mutations as well as the T790M resistance mutation while sparing wild-type EGFR. A phase I/II trial in pretreated patients (≤3 lines) showed a promising ORR of 44% and a DCR of 91% [39]. At the ESMO 2018 meeting in Munich, first-line data from nazartinib were presented: 29 of 45 patients demonstrated a response

Table 1 Ongoing trials investigating third-generation EGFR TKIs in combination with other drugs

EGFR TKI	Combination	Line	Phase	*N* (planned)	Trial number	Status
Osimertinib	+ Selumetinib	1st	II	98	NCT03392246	Recruiting
Osimertinib	± Bevacizumab	1st	II	154	NCT02971501	Recruiting
Osimertinib	+ Necitumumab or Ramucirumab	2nd	I	74	NCT02789345	Active, not recruiting
Osimertinib	+ Necitumumab	2nd	I	82	NCT02496663	Recruiting
Osimertinib	+ multi-DARPin®[a]	1st	I/II	40	NCT03418532	Recruiting
Osimertinib	+ Dasatinib	1st	I/II	38	NCT02954523	Recruiting
Osimertinib	+ Gefitinib	1st	I	64	NCT03122717	Recruiting
Osimertinib	+ T-DM1	2nd	II	58	NCT03784599	Recruiting
Osimertinib	+ Savolitinib	2nd	II	172	NCT03778229	Planned
Rociletinib	+ Trametinib	2nd	I/II	7	NCT02580708	Stopped enrolment
Nazartinib	+ Trametinib	2nd	I	24	NCT03516214	Recruiting
Nazartinib	+ Nivolumab	1st + 2nd	II	68	NCT02323126	Recruiting
Nazartinib	+ Gefitinib	1st	II	36	NCT03292133	Recruiting
Nazartinib	+ Capmatinib (INC280)	1st	I/II	117	NCT02335944	Recruiting

DARPin designed ankyrin repeat proteins, *EGFR* epidermal growth factor receptor, *T-DM1* trastuzumab-emtansine, *TKI* tyrosine kinase inhibitor
[a]Protein able to simultaneously neutralize the activities of vascular endothelial growth factor (*VEGF*) and hepatocyte growth factor (*HGF*) and also to bind to human serum albumin (*HSA*)

to nazartinib (ORR: 64%, 95% CI: 49–78%), and DCR was 93%. At data cut-off in March 2018, responses were ongoing in 27 of the 29 responding patients. In addition, nazartinib showed meaningful CNS activity and was well tolerated; only one patient discontinued owing to an adverse event [40].

Another promising third-generation EGFR TKI with activity against common mutations and T790M is lazertinib. In a phase I/II trial of 115 patients with acquired resistance to EGFR TKIs, lazertinib showed an ORR of 61% and a DCR of 81%. A phase III trial is planned for this year [41].

Strategies to overcome resistance: combination?

Checkpoint blockade and TKIs

Immunotherapy with a PD1 or PD-L1 checkpoint inhibitor (IO) has revolutionized treatment of medical oncology in general, especially in lung cancer. Nevertheless, we learned that patients with driver mutations respond poorly to IO and therefore have been excluded from further IO trials. It seems logical that the combination of EGFR TKI and IO should solve this problem, but a high incidence of severe side effects was found. A phase I trial evaluating the combination of erlotinib and nivolumab in 21 patients with EGFR-mutated NSCLC who progressed under prior TKI showed a promising RR of 20% and the PFS rate at 24 weeks was 47% [42]. The toxicity profile was manageable with four patients experiencing toxicity of grade 3–4. The TATTON trial investigated osimertinib plus durvalumab in 23 pre-treated and 11 treatment-naive patients. The ORR was 67% in T790M-positive and 21% in T790M-negative patients. Unfortunately, this combination was associated with a high incidence of interstitial lung disease (ILD; (38% of the whole study population; [43]). Gefitinib plus durvalumab was investigated in the dose expansion phase of a phase Ib study. Despite an ORR of 77–80%, a high incidence of grade 3/4 liver enzyme elevation (40–70%) was observed [44].

Chemotherapy and TKIs

The open-label phase III NEJ009 study tested the combination of chemotherapy (carboplatin/pemetrexed) with gefitinib versus gefitinib alone in 344 previously untreated EGFR-positive NSCLC patients. Patients who received the combination had a significantly prolonged PFS compared with patients treated with gefitinib alone (20.9 vs. 11.2 months; HR: 0.49, 95% CI: 0.391–0.625). The OS was also increased in the combination arm with 50.9 months versus 38.8 months (HR: 0.72). No significant difference was seen in PFS2; median PFS2 in the gefitinib monotherapy arm was 20.7 months versus 20.9 months in the experimental arm (HR: 0.966, 95% CI: 0.766–1.220; [45]).

Anti-angiogenesis and TKIs

Based on the positive PFS results of the JO25567 phase II trial evaluating erlotinib plus bevacizumab versus erlotinib alone [46], a phase III NEJ026 was conducted [46]. Results were presented at ASCO 2018. The trial met its primary endpoint. Erlotinib and bevacizumab prolonged PFS compared with erlotinib alone (HR: 0.605, 95% CI: 0.417–0.877). The median PFS was 16.9 months for the combination versus 13.3 months among patients who received monotherapy. As expected, the rate of side effects was higher in

the combination with hypertension, proteinuria, and hemorrhage [47].

The approval of osimertinib in the first-line setting for EGFR-mutated NSCLC redefines the results of these trials. The control arm with first-generation TKIs is the exception rather than the rule. Nevertheless, many clinical trials investigating the combination of third-generation TKIs with anti-angiogenesis and/or other TKIs are currently ongoing (Table 1).

At present, patients with EGFR mutation who progress under one or more lines of TKIs are often treated on the basis of the Impower150 trial [48]. This trial compared the quadruple combination of chemotherapy, bevacizumab, and the PD-L1 checkpoint inhibitor atezolizumab with chemotherapy and bevacizumab and enrolled wild-type and EGFR/ALK-mutated NSCLC patients. It demonstrated a significant PFS (8.3 months vs. 6.8 months; HR: 0.62, 95% CI: 0.52–0.74) and OS (19.2 months vs. 14.7 months; HR: 0.78, 95% CI: 0.64–0.96) benefit for the quadruple regimen in the wild-type population. Nevertheless, IMpower 150 is the only IO trial that demonstrated also a PFS benefit in the EGFR/ALK-positive subset (median 9.7 months vs. 6.1 months; HR: 0.59, 95% CI: 0.37–0.94; [48]). Despite this benefit, the combination is toxic with a high rate of adverse events. Treatment-related serious adverse events were noted in 25.4% of the patients in the quadruple group and in 19.3% of those in the chemotherapy and bevacizumab group [48].

Another IO-trial that enrolled EGFR and ALK-positive patients was the IMpower 130. This study compared atezolizumab plus carboplatin and nab-paclitaxel with carboplatin and nab-paclitaxel in patients with stage IV NSCLC. The trial demonstrated a statistically significant benefit of 4.7-month OS (and 1.5-month PFS) for atezolizumab plus chemotherapy in the ITT-WT population. Nevertheless, patients with EGFR or ALK genomic alterations had no benefit [49].

The treatment of NSCLC patients with EGFR mutation significantly improved in the past few years. Hopefully, we will have further opportunities with new potent TKIs or less toxic treatment combinations for patients with EGFR-mutated NSCLC in the near future.

Conflict of interest G. Absenger declares that she has no competing interests.

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