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Review

Novel Combination of Therapeutic Approaches in Advanced NSCLC with EGFR Activating Mutations

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Abstract: The vast majority of advanced NSCLC cases are histologically represented by adenocarcinomas. EGFR activating mutations (exon 19 deletions, exon 21 L858R substitutions, exon 20 insertions) represent one of the most common druggable alterations. Since erlotinib's FDA approval in 2013, EGFR-TKIs have represented a staple of EGFR+ advanced NSCLC treatment, with osimertinib representing the latest major FDA-approved third-generation EGFR-TKI. In recent years, however, several preclinical data have highlighted promising results regarding combination therapies involving EGFR-TKIs plus chemotherapy, and various recent clinical trials have confirmed these results. In addition, in 2021, amivantamab was the first FDA-approved mAb for the treatment of EGFR+ advanced NSCLC patients; according to some extremely up-to-date clinical trials, the combination of amivantamab plus chemotherapy is also associated with superior results. Therefore, this paper aims to provide a comprehensive review of both the bases and the latest evidence of the combination therapies involving EGFR+ advanced NSCLC patients.

Keywords: NSCLC; EGFR; combination treatments; EGFR-TKI; chemotherapy; targeted therapy; monoclonal antibodies

Citation: Rocco, D.; Della Gravara, L.; Boccia, M.C.; Palazzolo, G.; Gridelli, C. Novel Combination of Therapeutic Approaches in Advanced NSCLC with EGFR Activating Mutations. *Targets* **2024**, *2*, 237–249. https://doi.org/10.3390/targets2030014

Academic Editor: Donato Colangelo

Received: 2 July 2024
Revised: 30 August 2024
Accepted: 3 September 2024
Published: 7 September 2024

1. NSCLC Epidemiology and EGFR Mutations

Taking into account the most recent and comprehensive literature data, lung cancer accounts for approximately 2,000,000 new cases each year, and it also accounts for around 1,800,000 deaths every year (50–60% of lung cancers are diagnosed at an advanced stage) [1]. More than 80% of lung cancer cases are described as Non-Small Cell Lung Cancers (NSCLC), the majority of which are histologically defined as adenocarcinomas (more than 50% of NSCLC cases) [2]. Adenocarcinomas can exhibit a number of different druggable and non-druggable genetic alterations; in this vein, EGFR (Epidermal Growth Factor Receptor) mutations represent the most common ones, totaling roughly 15% of adenocarcinomas cases in North American and European patients and roughly 40–50% of adenocarcinomas in Asian patients. With respect to clinical–epidemiological characteristics, EGFR+ NSCLC patients are typically comprised of young female never or light smokers, who present better survival outcomes when compared to non-EGFR+ NSCLC patients [3–5]. Exon 19 in-frame deletions and exon 21 L858R substitutions account for almost 90% of EGFR mutations, while the remaining alterations are categorized as uncommon mutations (among these uncommon alterations, exon 20 insertions constitute a separate subset) [6–8]. EGFR is part of the erbB family of RTKs (Receptor Tyrosine Kinase), and it presents three different regions: an extracellular one, which binds the EGF (Epidermal Growth Factor); a transmembrane one; and an intracellular one, which exhibits tyrosine kinase activity. Upon the EGFR-EGF

binding, EGFR starts a dimerization process (with other EGFRs) or a heterodimerization one (with other erbB family members), leading to autophosphorylation of tyrosine residues and, in conclusion to cell proliferation and/or apoptosis suppression [9]. While this mechanism plays a number of physiological non-pathological roles (e.g., in mammary gland development and function) [10,11], it also is constitutively stimulated in EGFR+ NSCLC, driving cell proliferation and tumorigenesis, on the one hand, while conferring sensitivity to anti-EGFR-specific drugs, on the other [12–14].

2. Current Guidelines

Taking into account the current ESMO (European Society for Medical Oncology) and ASCO (American Society of Clinical Oncology) guidelines on EGFR+ advanced NSCLC treatment, we can note that five different TKIs (Tyrosine Kinase Inhibitors) are currently recommended in a first-line setting for patients presenting exon 19 deletions and exon 21 L858R substitutions: erlotinib (± bevacizumab or ramucirumab); gefitinib (± carboplatin plus pemetrexed); afatinib; dacomitinib; and osimertinib, with osimertinib being associated with the most robust efficacy and survival data; also in this setting, icotinib is only ASCO-recommended and so is the combination of osimertinib plus platinum plus pemetrexed. Osimertinib and afatinib are ESMO and ASCO-recommended for the first-line treatment of EGFR+ NSCLC patients presenting uncommon mutations. With reference to the second line setting, amivantamab (a bispecific EGFR and MET mAb) is ASCO and ESMO-recommended for the treatment of EGFR+ NSCLC patients presenting exon 20 insertions progressing on a platinum doublet-based chemotherapy; lastly, the combination of amivantamab plus carboplatin plus pemetrexed is only ASCO-recommended for the treatment of EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions progressing on osimertinib [15–17].

3. Monotherapy Approaches

Erlotinib was granted approval thanks to the results coming from the EURTAC (European Tarceva vs. Chemotherapy) trial, in which 174 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions were randomized (1:1) to receive erlotinib or standard chemotherapy. At data cutoff, erlotinib performed better in terms of ORR (Overall Response Rate): 58% vs. 15%; in terms of PFS (Progression Free Survival): 9.7 months vs. 5.2 months; HR (Hazard Ratio) for death or progression: 0.37, alongside with a favorable safety profile: grade 3–4 TRAEs (Treatment Related Adverse Events): 6% of treated patients vs. 20% of treated patients [18]. With a later follow-up, PFS data were also confirmed in terms of OS (Overall Survival): 22.9 months vs. 19.6 months; HR for death: 0.86 [19].

Gefitinib was granted approval thanks to the EGFR+ subset of patients from the IPASS study (230 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions randomized (1:1) to receive gefitinib or standard chemotherapy) and thanks to the single-arm IFUM study (106 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions). Gefitinib treatment was associated with favorable results in both trials: PFS: 9.8 months vs. 6.4 months HR for death or progression: 0.48 and OS: 21.6 months vs. 21.9 months HR for death: 1.00 (IPASS study) [20]; PFS: 9.7 months, OS: 19.2 months (IFUM study) [21].

Afatinib approval followed the positive results coming from the LUX-lung 3 and LUX-lung 6 studies. With reference to the first trial, 345 naïve advanced EGFR+ NSCLC patients were randomized (2:1) to receive afatinib or standard chemotherapy with the following results: PFS 11.1 months vs. 6.9 months HR for death or progression 0.58; OS: 28.2 months vs. 28.2 months; HR for death: 0.88. With reference to the second trial, 364 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions were randomized (2:1) to receive afatinib or standard chemotherapy, with similar results: PFS: 11.0 months vs. 5.6 months HR for death or progression 0.28; OS: 23.1 months vs.

23.5 months; HR for death: 0.93. However, both studies found a statistically significant OS benefit associated with afatinib treatment in patients harboring exon 19 deletions [22].

Dacomitinib activity was explored in the phase III randomized ARCHER 1050 trial, which saw the randomization (1:1) of 452 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions to be administered dacomitinib or gefitinib. The recorded results showed a favorable PFS profile: 14.7 months vs. 9.2 months; HR for death or progression: 0.59, alongside a favorable OS one: 34.1 months vs. 27.0 months. It is worth mentioning that this superior OS result could be traced to the uneven distribution of patients between arms; i.e., patients with brain metastases were excluded from enrollment, and more fit patients were allocated to the experimental arm when compared to the control one [23,24].

Icotinib was investigated in the phase III randomized CONVINCE trial. A total of 296 naïve advanced EGFR+ NSCLC patients harboring exon 19 deletions or exon 21 L858R substitutions were randomized (1:1) to be administered icotinib or standard chemotherapy. At data cutoff, icotinib provided sound results when compared to standard chemotherapy with reference to PFS: 11.2 months vs. 7.9 months HR for death or progression 0.61 and to OS: 30.5 vs. 32.1 months [25].

Osimertinib recommendation followed the release of the data from the FLAURA trial, which randomized (1:1) 556 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions to be administered osimertinib or erlotinib/gefitinib according to the investigator's choice. At data collection, osimertinib granted excellent results according to every pre-specified endpoint: ORR: 80% vs. 76%; PFS: 18.9 months vs. 10.2 months; HR for progression or death: 0.46; OS: 38.6 months vs. 31.8 months [26,27].

With specific reference to uncommon mutations, which represent 10% of all EGFR (these are mainly represented by exon 20 insertions), accounting for approximately 1–4% of all EGFR mutations, and by the exon 18 G719X mutation, the exon 21 L861Q mutation, by the exon 20 S768I mutation and by uncommon compound mutations. With reference to non-exon 20 insertions uncommon mutations, as of today, both afatinib and osimertinib are recommended by ESMO and ASCO. Afatinib recommendation is based on post hoc analyses of the LUX-lung 2, LUX-lung 3, and LUX-lung 6 studies involving naïve advanced EGFR+ NSCLC patients presenting non-exon 20 insertions uncommon mutations and reporting positive ORR data: 65.6% with a median time to treatment failure of 10.8 months. These data were also recently strengthened by the ACHILLES trial. A total of 109 naïve advanced EGFR+ NSCLC patients presenting non-exon 20 insertions uncommon mutations were randomized (1:1) to receive afatinib or standard chemotherapy, showing a clear benefit in favor of afatinib: PFS: 10.6 months vs. 5.7 months; ORR: 43% vs. 16% [28–30].

In the KCSG-LU15-09 trial, osimertinib also managed to provide good results in the same subset of patients: ORR: 53%, PFS: 8.2 months, that were further confirmed at a later follow-up: ORR: 50%; PFS: 8.0 months; OS: 27.0 months [31,32]. In the same vein, the UNICORN study, assessing osimertinib in this same subgroup of patients, reported comparable ORR and PFS data: 55% and 9.4 months, respectively [33]. With reference to exon 20 insertions uncommon mutations, on the other hand, amivantamab is the only specific treatment recommended today for the treatment of advanced EGFR+ NSCLC patients progressing on a platinum doublet-based chemotherapy. This approval is based on the CHRYSALIS trial, in which 40 patients with the above-mentioned characteristics received amivantamab, reporting robust results in terms of ORR: 37%, PFS: 6.9 months, and OS: 23.4 months; however, it is worth mentioning that up to 67% of treated patients experienced infusion-related reactions (particularly VTE, i.e., Vascular Thromboembolic Events), with only 3% being $\geq$ grade 3 [34] [Table 1].

Table 1. Selected data from trials assessing monotherapy approaches for the treatment of advanced EGFR+ NSCLC patients.

Trial Name	Subset of Patients	Arm(s)	Efficacy Data	Safety Data
EURTAC	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib vs. chemotherapy	PFS: 9.7 months vs. 5.2 months OS: 22.9 months vs. 19.6 months	Grade 3–4 TRAEs: 6% of treated patients vs. 20% of treated patients
IPASS	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Gefitinib vs. chemotherapy	PFS: 9.8 months vs. 6.4 months OS: 21.6 months vs. 21.9 months	Serious adverse events: 16.3% vs. 15.6% of patients
IFUM	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Gefitinib	PFS: 9.7 months OS: 19.2 months	Grade 3–4 AEs: 15% of patients
LUX-lung 3	Naïve advanced EGFR+ NSCLC patients	Afatinib vs. chemotherapy	PFS: 11.1 months vs. 6.9 months OS: 28.2 months vs. 28.2 months	AEs grade $\geq$ 3: 49% vs. 48% of patients
LUX-lung 6	Naïve advanced EGFR+ NSCLC patients	Afatinib vs. chemotherapy	PFS: 11.0 months vs. 5.6 months OS: 23.1 months vs. 23.5 months	Serious adverse events: 6.3% vs. 8.0% of patients
ARCHER 1050	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Dacomitinib vs. gefitinib	PFS: 14.7 months vs. 9.2 months OS: 34.1 months vs. 27.0 months	Serious adverse events: 9% vs. 4% of patients
CONVINCE	Naïve advanced EGFR+ NSCLC patients harboring exon 19 deletions or exon 21 L858R substitutions	Icotinib vs. chemotherapy	PFS: 11.2 months vs. 7.9 months OS: 30.5 vs. 32.1 months	Grade 3 or 4 TRAEs 4.7% vs. 23.4%
FLAURA	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Osimertinib vs. erlotinib/gefitinib	PFS: 18.9 months vs. 10.2 months OS: 38.6 months vs. 31.8 months	Grade 3–4 TRAEs: 42% vs. 47% of patients
CHRYSALIS	EGFR+ exon 20 insertion NSCLC patients progressing on a platinum doublet-based chemotherapy	Amivantamab	PFS: 6.9 months OS: 23.4 months	Up to 67% of treated patients experienced infusion-related reactions

4. Combo Approaches: The Literature Background

While EGFR mutations represent the chief factor in driving advanced EGFR+ NSCLCs tumorigenesis and proliferation, thus allowing us to specifically target one of their fundamental pathways, it does not represent the only mechanism employed by EGFR+ NSCLC cells to proliferate, grow, and escape immune surveillance [35–37]. In the same vein, after EGFR-TKI treatment, EGFR+ NSCLC cells can also develop (apart from resistance mechanisms exploiting the EGFR pathway, also known as "on-target" resistance mechanisms) resistance mechanisms exploiting EGFR-parallel pathways, also known as "off-target" resistance mechanisms [38,39]. In this sense, a vast amount of the preclinical literature data has shown that combining agents exhibiting different mechanisms of action could represent

an effective approach to target multiple pathways, granting a synergic effect and, thus, possibly boosting efficacy and survival [40,41]. The rationale behind combining an EGFR-TKI with chemotherapy is represented by the fact that EGFR-TKI has been shown to be capable of arresting the cell cycle in a G1/S phase and enhancing DNA damage, therefore boosting chemotherapy's own action in this regard [42,43]. On the other hand, VEGFR-targeting agents can represent useful agents in light of the fact that EGFR and VEGFR share some common downstream effectors whose double blockade can grant enhanced efficacy [44,45]. Lastly, while it is now a well-established fact that EGFR+ advanced NSCLC represent poorly immunogenic tumors, they can, however, express increased levels of Immune Checkpoint Inhibitors members such as PD-1, PD-L1, and CTLA-4, underscoring a possible role for EGFR-TKI plus immunotherapy combinations [46,47]. Naturally, combining two or more agents leads to increased toxicity rates and lower adherence to therapy, which is particularly challenging in elderly patients and/or in frail patients presenting several comorbidities and, thus, concurrent medications [48,49].

5. Combo Approaches: Anti VEGFR mAb + EGFR TKI

The erlotinib plus bevacizumab combo gained its recommendation based on the data from several studies.

In the phase II BELIEF trial, 109 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions received erlotinib + bevacizumab, highlighting interesting PFS results: 13.2 months, with 29% of patients presenting a serious adverse event [50]. In another phase II trial (JO25567), 154 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions were randomized (1:1) to be administered erlotinib + bevacizumab or erlotinib. At the data cutoff, the experimental arm performed better than the control one with reference to PFS: 16.0 months vs. 9.7 months; HR for death or progression: 0.54. At a later follow-up, this benefit was confirmed: PFS: 16.4 months vs. 9.8 months; HR for death or progression: 0.52; however, with respect to OS, no superiority was noted: 47.0 months vs. 47.4 months; HR for death: 0.81; $p = 0.3267$ alongside a complex safety profile: 91% vs. 53% of treated patients experienced grade 3/4 TRAEs [51].

The same combo was also assessed in the same subset of patients in the phase III NEJ026 study, with 228 patients randomized (1:1) to receive erlotinib + bevacizumab or erlotinib alone, with similar results: PFS: 16.9 months vs. 13.3 months HR for death or progression: 0.60, OS: 50.7 months vs. 46.2 months; HR for death: 1.007; $p = 0.97$, grade 3/4 TRAEs: 88% vs. 46% of treated patients, after a median follow-up of 39.2 months [52].

In the same vein, the same conclusion was reached by the phase III BEVERLY trial, in which 160 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions were randomized (1:1) to be administered erlotinib + bevacizumab or erlotinib: PFS: 15.4 months vs. 9.7 months; HR for death or progression: 0.60; OS: 28.4 months vs. 23.0 months (HR for death: 0.70; $p = 0.12$); grade 3/4 TRAEs: 56% vs. 49% of treated patients. At a later follow-up of 36.3 months, the OS data were 33.3 months vs. 22.8 months, and no statistically significant difference was found between the two arms in terms of OS [53,54].

Lastly, the most recent study to investigate this combo (the phase III ARTEMIS-CTONG1509 study) further strengthened these data. After the randomization (1:1) of 311 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions to erlotinib + bevacizumab or erlotinib, the experimental arm once again performed better in terms of PFS: 17.9 months vs. 11.2 months; HR for death or progression: 0.55, but not in terms of OS: 36.2 months vs. 31.6 months; HR for death: 0.92; $p = 0.581$, grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients [55].

On the other hand, the erlotinib plus ramucirumab combo was explored in the phase III RELAY trial, in which 449 naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions were randomized (1:1) to be given erlotinib + ramucirumab or erlotinib. As a result, the former arm performed better than the latter one

with respect to PFS 19.4 months vs. 12.4 months; HR for death or progression: 0.59, while OS results are still not mature; safety data, once again, highlighted a more toxic profile: grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients [56]. On a side note, it is worth mentioning that a post hoc analysis of this trial highlighted interesting results coming from the TP53 mutated subset of patients and from the L858R harboring one. While the literature data on EGFR-TP53 co-mutated patients show that these patients seem to present worse outcomes [57], they seem to greatly benefit from the erlotinib plus ramucirumab combo: PFS: 15.2 months vs. 10.6 months; HR for death or progression: 0.54 [58]; the same robust benefit in terms of efficacy seems to be associated to L858R-presenting patients: PFS: 19.4 months vs. 11.2 months; HR for death or progression: 0.618 [59]. Hoping to build on these promising data, a phase III head-to-head study comparing the erlotinib + ramucirumab combo to osimertinib in naïve EGFR+ L858R advanced NSCLC patients is currently ongoing [60–62]. In light of the different OS data associated with EGFR-TKI plus anti-VEGFR mAb, it is worth mentioning that these trials had different inclusion criteria, different patient distribution, and characteristics, different follow-up times, and also different ethnicities enrolled (Europe vs. Asia).

6. Combo Approaches: IO + EGFR TKI

With reference to immunotherapy plus EGFR-TKI combinations, as of today, no study has ever managed to provide meaningful results since every major assessed combination was burdened by significant reports of grade 3–4 treatment-related adverse events: erlotinib plus nivolumab (19 out of 100 treated patients); erlotinib plus atezolizumab (39 out of 100 treated patients); gefitinib plus durvalumab (40–70 out of 100 treated patients); osimertinib plus durvalumab (38 out of 100 treated patients) [63].

7. Combo Approaches: EGFR mAb + EGFR TKI

The combination of amivantamab plus lazertinib (EGFR-TKI) in naïve or treated with $\leq$2 prior lines advanced EGFR+ NSCLC patients presenting non-exon 20 insertions uncommon mutations was investigated in cohort C of the CHRYSALIS-2 trial. A total of 105 patients received amivantamab plus lazertinib, reporting an ORR of 51% in the intention to treat the population of 55% in the naïve population; however, the most interesting results came from patients progressing on afatinib: ORR: 45%, PFS: 5.7 months. Once again, infusion-related adverse events were heavily reported, with VTE reported in 30% of treated patients [64].

In addition, the same combo was assessed for the treatment of naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions in the phase III MARIPOSA trial. A total of 1074 patients were randomized (2:2:1) to receive amivantamab plus lazertinib or osimertinib or lazertinib, and the most relevant results came from the comparison of the combination arm vs. the osimertinib one. Superior results in terms of PFS (23.7 months vs. 16.6 months; HR for death or progression 0.30) and ORR (80% vs. 76%) were noted; however, grade $\geq$ 3 treatment-related adverse events were far more represented in the experimental arm (75% vs. 43% of treated patients); OS data are still not mature, but a non-statistically significant trend favoring the combo arm has been reported (HR for death 0.80; p = 0.11) [65]. With specific reference to infusion-related adverse events, a combination of subcutaneous (instead of the classic intravenous formulation) amivantamab plus lazertinib was assessed in the same subgroup of patients in cohorts 1 and 6 of the PALOMA-2 study, with a recommended and mandatory prophylactic anticoagulation, respectively. The efficacy and safety data proved to be consistent with those coming from the MARIPOSA trial; however, the rate of VTE was significantly reduced in patients receiving anticoagulation both of every grade (11% vs. 20% of treated patients) and $\geq$ 3 (0% vs. 5% of treated patients) [66]. The PALOMA-3 trial came to the same conclusion but assessed patients progressing after osimertinib and after platinum-based chemotherapy [67].

8. Combo Approaches: CT + EGFR TKI/mAb

Early promising results involving EGFR-TKI plus chemotherapy came from a series of phase II studies exploring the gefitinib plus pemetrexed combination [68–71]. Based on these data, a phase III study was designed (NEJ009), randomizing (1:1) 345 advanced naïve EGFR+ NSCLC patients harboring exon 19 deletions or exon 21 L858R substitutions to be administered gefitinib + carboplatin + pemetrexed or gefitinib. At the pre-specified data cutoff, the combination arm performed consistently better than the control one with respect to ORR: 84% vs. 67%, to PFS: 20.9 months vs. 11.9 months; HR for death or disease progression: 0.490 and to OS: 50.9 months vs. 38.8 months; HR for death: 0.72; it was, however, more prone to grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients. These results led to ESMO and ASCO's recommendations for this combination [72].

As mentioned earlier, two other combinations involving chemotherapy and EGFR-targeted treatments are ASCO recommended: osimertinib plus platinum plus pemetrexed in naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions and amivantamab plus carboplatin plus pemetrexed in advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions progressing on osimertinib.

On the one hand, the first combination was investigated in the phase III FLAURA2 trial, which saw the randomization of 557 patients (1:1) to receive osimertinib plus platinum plus pemetrexed or osimertinib. PFS proved to be longer in the experimental arm: 19.5 months vs. 16.5 months; HR for death or progression 0.62, and ORR proved to be higher: 83% vs. 76%, alongside a higher grade 3/4 TRAEs rates: 54.8% vs. 26.1% of treated patients [73]. In an extremely recent press release, moreover, it was announced that with 41% of data maturity, a beneficial trend in terms of OS was noted [74]; more mature OS data are eagerly awaited.

The second combination, on the other hand, was assessed in the phase III MARIPOSA-2 study, which saw the randomization of 657 patients (2:2:1) to receive amivantamab plus lazertinib plus chemotherapy or standard chemotherapy or amivantamab plus lazertinib. Both the three-drug experimental arm and the two-drug one performed better than the control one: PFS: 8.3 months (HR for death or progression 0.44) vs. 6.3 months (HR for death or progression 0.48) vs. 4.2 months and ORR: 63% vs. 64% vs. 36%. OS data are still immature, but interim data report an HR for death of 0.96 and 0.77 for the three-drug and two-drug experimental arm, respectively; mature OS data are needed in order to clarify these findings. With reference to the safety and tolerability profile, as expected, the rate of grade $\geq$ 3 treatment-related adverse events was markedly more represented in the three-drug and two-drug experimental arms when compared to the control arm: 92% of treated patients vs. 72% of treated patients vs. 48% of treated patients [75].

Lastly, the amivantamab plus chemotherapy combination was explored in the phase III PAPILLON trial for the treatment of naïve advanced EGFR+ NSCLC patients presenting exon 20 insertions. A total of 308 patients were randomized (1:1) to receive amivantamab plus chemotherapy or standard chemotherapy, underscoring superior efficacy results with respect to PFS: 11.4 months vs. 6.7 months and to ORR: 73% vs. 47%; also, in this trial, amivantamab is associated with a higher rate of grade $\geq$ 3 treatment-related adverse events: 75% vs. 54% of treated patients. At 33% of data maturity, interim OS data report a non-statistically significant HR for death of 0.67 associated with the experimental arm [76] [Table 2].

Table 2. Selected data from trials assessing combination approaches for the treatment of advanced EGFR+ NSCLC patients.

Trial Name	Subset of Patients	Arm(s)	Efficacy Data	Safety Data
BELIEF	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + bevacizumab	PFS: 13.2 months	Serious adverse events: 29% of patients
JO25567	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + bevacizumab vs. erlotinib	PFS: 16.4 months vs. 9.8 months OS: 47.0 months vs. 47.4 months	Grade 3/4 TRAEs: 91% vs. 53% of treated patients
NEJ026	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + bevacizumab vs. erlotinib	PFS: 16.9 months vs. 13.3 months OS: 50.7 months vs. 46.2 months	Grade 3/4 TRAEs: 88% vs. 46% of treated patients
BEVERLY	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + bevacizumab vs. erlotinib	PFS: 15.4 months vs. 9.7 months OS data were 33.3 months vs. 22.8 months	Grade 3/4 TRAEs: 56% vs. 49% of treated patients
ARTEMIS-CTONG1509	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + bevacizumab vs. erlotinib	PFS: 17.9 months vs. 11.2 months OS: 36.2 months vs. 31.6 months	Grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients
RELAY	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Erlotinib + ramucirumab or erlotinib	PFS 19.4 months vs. 12.4 months OS: still not mature	Grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients
MARIPOSA	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Amivantamab + lazertinib vs. osimertinib (or lazertinib)	PFS 23.7 months vs. 16.6 months OS: data still not mature	Grade $\geq$ 3 TRAEs: 75% vs. 43% of treated patients
NEJ009	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Gefitinib + carboplatin + pemetrexed vs. gefitinib	PFS: 20.9 months vs. 11.9 months OS: 50.9 months vs. 38.8 months	Grade 3/4 TRAEs: 54.8% vs. 26.1% of treated patients
FLAURA2	Naïve advanced EGFR+ NSCLC patients presenting exon 19 deletions or exon 21 L858R substitutions	Osimertinib + platinum + pemetrexed vs. osimertinib	PFS: 19.5 months vs. 16.5 months OS: data still not mature	Grade 3/4 TRAEs rates: 54.8% vs. 26.1% of treated patients
PAPILLON	Naïve advanced EGFR+ NSCLC patients presenting exon 20 insertions	Amivantamab + chemotherapy vs. chemotherapy	PFS: 11.4 months vs. 6.7 months OS: data still not mature	Grade $\geq$ 3 treatment-related adverse events: 75% vs. 54% of treated patients

9. Conclusions and Perspectives

As the above-mentioned data extensively show, there is a growing interest in combination approaches for the treatment of advanced EGFR+ NSCLC patients, presenting both common and uncommon alterations. In light of international recommendations, no combination can currently offer sound and mature OS data; therefore, while encouraging, these combinations should still be regarded as experimental and not a standard clinical practice. In fact, taking into account the results associated with the EGFR-TKI + anti VEGFR mAbs combinations, i.e., favorable PFS data followed by non-superior OS data, caution is warranted. Moreover, it is worth noting that amivantamab, one of the most extensively investigated drugs in the combo approach, is burdened by heavy toxicity rates; in this vein, the subcutaneous formulation with prophylactic anticoagulation could represent a reasonable solution; once again, long-term data are needed to better clarify this point.

Author Contributions: All the authors contributed to the conceptualization of this paper; writing—original draft preparation D.R., L.D.G.; writing—review and editing, C.G., D.R., L.D.G.; supervision, C.G. All authors have read and agreed to the published version of this manuscript.

Funding: This research received no external funding.

Conflicts of Interest: Cesare Gridelli received honoraria as a speaker bureau and advisory board member from Astra Zeneca, BMS, MSD, and Roche. All the other authors declare no conflicts of interest.

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