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DRUG EVALUATION

Is there a role for dacomitinib, a second-generation irreversible inhibitor of the epidermal-growth factor receptor tyrosine kinase, in advanced non-small cell lung cancer?

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ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) is a highly lethal disease. During the past 20 years, the epidermal growth factor receptor (EGFR) has been a relevant target for anticancer drug-design, and a large family of EGFR tyrosine kinase inhibitors (TKI) were designed, which improved therapeutic outcomes compared to conventional chemotherapy in NSCLC patients with specific EGFR mutations. However, resistance to these inhibitors occurs; therefore, the debate on which inhibitor should be used first is still open. Dacomitinib was approved in 2018 for the first-line treatment of NSCLC with EGFR activating mutations.

Areas covered: This manuscript reviews the properties of dacomitinib, including the current information from clinical trials and its potential application as stand-alone therapy, or in combination.

Expert opinion: Dacomitinib is a second-generation EGFR-TKI that has demonstrated significant improvement in overall survival in a phase III randomized study compared with gefitinib, a first-generation TKI. However, the rapid development and approval of a new generation of TKIs (osimertinib), with better clinical profiles, raises the question of which role can dacomitinib play in NSCLC. Further studies are required to evaluate the efficacy of this drug on brain metastases, as a second-line treatment after third-generation TKIs, or in combination with other types of treatments.

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KEYWORDS
Dacomitinib; EGFR; irreversible inhibition; non-small cell lung cancer (NSCLC); tyrosine kinase inhibitors

1. Introduction

Lung cancer is one of the most commonly diagnosed cancers (11.6% of the cases), and also the main cause of cancer death (18.5% of cancer cases) worldwide [1]. Patients diagnosed with lung cancer have one of the worst prognoses, with a 5-years-survival rate of 18%, partially caused by the lateness of diagnosis, which occurs in more than one-half of the cases at advanced stages [2].

Lung cancers can be divided into two main types: small cell lung cancer and non-small cell lung cancer (NSCLC), the latter being the most frequently occurring (85% of lung cancer cases). NSCLC is divided into three main subcategories: adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma. Current treatment options include surgery, when the tumor is resectable, combined with adjuvant/neoadjuvant therapy in selected cases in order to reduce the risk of lung cancer relapse. When patients are not suitable for surgery, radiation therapy can be beneficial. However, for patients with advanced disease, systemic treatment is usually envisaged, and when patients are not responsive to surgery or medical treatment, radiotherapy is used to improve the quality of life [3].

The undesirable side effects associated with conventional chemotherapy led researchers to focus on novel therapies, targeting new molecular markers specific for cancer cells. These therapies have been and are being developed against a number of receptor tyrosine kinases (RTK), which are mutated in NSCLC cells and lead to uncontrolled amplified RTK signaling, which will often activate downstream signaling that stimulates tumorigenesis. One of the most popular targets is epithelial growth factor receptor (EGFR) because specific mutations in this receptor drive cancer cells proliferation and sensitize cancer cells to treatment with RTK inhibitors.

2. EGFR signaling

2.1. EGFR mutations

EGFR is a RTK, member of the ErbB family together with HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4). ErbB receptors are single-chain transmembrane glycoproteins composed of an extracellular ligand-binding domain, a transmembrane domain, a short juxtamembrane section, a TK domain, and a tyrosine-containing C-terminal tail. Binding of their ligands promotes a conformational change that leads to homo- and hetero-

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Article highlights

- Dacomitinib is a second generation irreversible EGFR tyrosine kinase inhibitor, which has also activity against ErbB family members and can thus be considered as a pan-ErbB inhibitor.
- Dacomitinib has a good bioavailability of >50% and a long half-life (> 12 hr), but is somewhat more toxic than first-generation EGFR inhibitors.
- Dacomitinib has been registered for first-line treatment of NSCLC patients with activating mutations in the EGFR, since it showed a significant improvement in comparison with gefitinib.
- Dacomitinib may have a role in combinations with either conventional chemotherapy or in particular monoclonal antibodies directed against the EGFR receptor.
- Dacomitinib has shown brain penetration in preclinical models and should therefore be investigated in patients with CNS metastases.
- Dacomitinib is being evaluated a second-line therapy in patients resistant to first line therapy with osimertinib.

dimerization between receptors of the family, which is essential for the phosphorylation of the tyrosines in the cytoplasmic C-terminal tail, carried out by the TK domain. Phosphotyrosine residues are then able to activate downstream components of signaling pathways including Ras/MAPK, PLCγ1/PKC, PI (3) kinase/Akt and STAT [4]. Those pathways are associated with cell growth, cell survival, and proliferation (Figure 1).

EGFR overexpression is frequent and negatively correlated with prognosis in many types of human malignancies, including NSCLC, in which it is overexpressed in 40-80% of the cases, depending on the ethnicity (higher in Asians). In addition, in NSCLC, the *EGFR* gene can be subject of peculiar mutations that confer the 'oncogene-addiction' to the tumor, meaning a condition in which the growth and survival of the tumor are dependent on constitutively active oncogenes signaling. The most common *EGFR* mutations are the short in-frame deletions in exon 19 (ex19del), or point mutations in exon 21, the latter resulting in arginine replacing a leucine in codon 858 (L858 R). These genetic aberrations are typically clustered around the ATP-binding pocket of the enzyme (coded by exons 18–24) and cause a constitutive activation of signal transduction pathways, unrelated to the presence of ligands, and therefore lead to uncontrolled cell proliferation or evasion from apoptosis. For this reason, EGFR has become such an interesting target for cancer therapy [5,6].

2.2. EGFR-TKI

The discovery of the role of EGFR in cancer formed the impetus to develop EGFR-specific tyrosine kinase inhibitors (EGFR-TKIs) (Table 1). In patients with sensitizing mutations, this increased the overall survival (OS) to nearly 30 months, which was not possible with conventional cytotoxic chemotherapy [7,8].

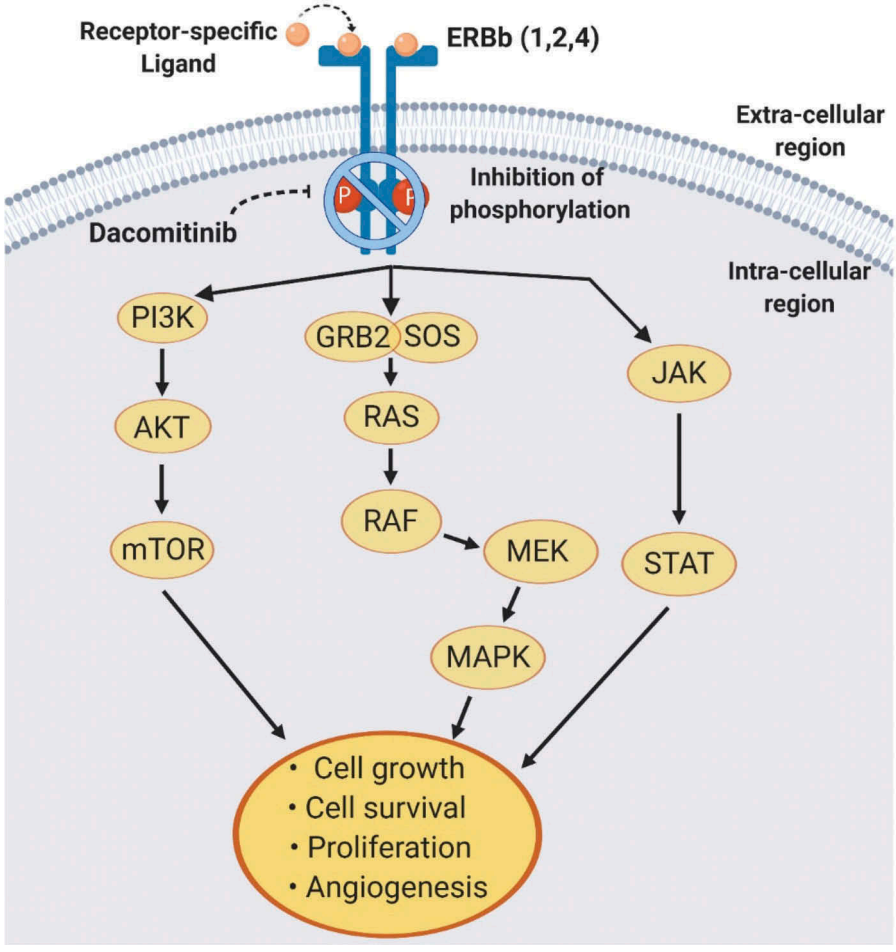


Figure 1. Schematic representation of the mechanism of action of Dacomitinib (Created with BioRender.com).

Table 1. Overview of molecular properties and application of EGFR-TKIs approved for clinical use.

Drug	Specificity	IC_{50}	Company	Dose	FDA indication
I generation					
Gefitinib	EGFR inhibitor	15.5 nM ($EGFR^{wt}$) 823.3 nM ($EGFR^{L858\ R/T790\ M}$)	AstraZeneca	250 mg/day	First-line treatment in metastatic NSCLC: • Exon 19 deletions • Exon 21 (L858 R) substitution (2015)
Erlotinib (OSI-744)	EGFR inhibitor	2 nM EGFR	Roche	150 mg/day	NSCLC: • Exon 19 deletion • Exon 21 (L858 R) substitution
II generation					
Afatinib	Irreversible EGFR/ErbB inhibitor	0.5 nM $EGFR^{wt}$ 0.4 nM $EGFR^{L858\ R}$ 10 nM $EGFR^{L858\ R/T790\ M}$ 14 nM ErbB2 (HER2) 1 nM ErbB4 (HER4)	Boehringer Ingelheim Pharmaceuticals	40 mg/day	Metastatic NSCLC (first-line): • Exon 19 deletions • Exon 21 (L858 R) substitution • nonresistant epidermal growth factor receptor (EGFR) mutations (S768I, L861Q, and/or G719X) Metastatic and squamous NSCLC progressing after platinum-based chemotherapy
Dacomitinib	Irreversible pan-ErbB inhibitor	6.0 nM EGFR 45.7 nM ErbB2 73.7 nM ErbB4	Pfizer	45 mg/day	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) • exon 19 deletion • exon 21 L858 R substitution mutations (2018)
III generation					
Osimertinib	Irreversible and mutant-selective EGFR inhibitor	12.92 nM Exon 19 deletion EGFR 11.44 nM $EGFR^{L858\ R/T790\ M}$ 493.8 nM $EGFR^{wt}$	AstraZeneca	80 mg/day	First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) • exon 19 deletions • exon 21 L858 R mutations (2018) Treatment of patients with metastatic EGFR T790 M mutation-positive NSCLC, whose disease has progressed on or after EGFR-TKI therapy

IC50 values represent the concentration that can inhibit the phosphorylation of the depicted EGFR-TKI variant by 50%.

The first-generation EGFR-TKIs was designed to mimic the binding site of the ATP molecule; the drugs bind reversibly to the ATP-binding site preventing receptor autophosphorylation and downstream signaling. Two orally bioavailable drugs that are still widely used in clinic are gefitinib (Iressa®, AstraZeneca, Wilmington, DE, USA) and erlotinib (Tarceva®, Hoffman-La Roche, Basel, Switzerland). Gefitinib was initially approved in 2003 as monotherapy treatment for patients with locally advanced or metastatic NSCLC after the failure of both platinum-based and docetaxel chemotherapies. Erlotinib was initially approved in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after the failure of at least one prior chemotherapy regimen. They were developed before knowing the mutations occurring in *EGFR* gene, so their efficacy was not 'impressively' higher compared to the standard chemotherapy. The turning point was reached in 2004 when Lynch et al. [9] and Paez et al. [10] demonstrated that patients responding to gefitinib harbored the previously mentioned *EGFR* activating mutations, and this led to a change in the design of further clinical trials. The initial indication for erlotinib and gefitinib was subsequently extended for the first-line treatment of metastatic ex19del or L858 R *EGFR*-mutated NSCLC patients.

Despite the initial encouraging clinical response, eventually, almost all patients developed resistance to first-generation inhibitors over time. This resistance was mainly caused by a point mutation in the kinase domain of EGFR, in particular mutation T790 M, which increased the ATP affinity for its binding site [11]. It should be noted that the T790 M mutation has been detected, in a small percentage of cases, as primary mutation in EGFR-TKI naïve patients [12]. Additionally, D761Y, T854A, and L747 S are rare *EGFR* mutations that confer acquired resistance to first-generation TKIs [11]. Acquired resistance can be also caused by the activation of bypassing pathways, such as amplification of *c-Met*, overexpression of receptors FGFR1 and FGFR2 or of their ligands FGF2 and FGF9, loss of *PTEN* and over-expression of the Yes-associated protein (YAP) [11]. Consequently, a second generation of TKIs was designed, including afatinib (Giotrif®, Boehringer Ingelheim; Ingelheim, Germany) and dacomitinib (VIZIMPRO®, Pfizer Inc., New York, NY, USA), the latter being the main subject of this review.

The second-generation TKIs were designed to bind covalently and irreversibly to EGFR, targeting the Cys797 in the entrance of the ATP-binding site, but these drugs also have less selective activity and inhibit ErbB2 and ErB4 as well. Evaluation in preclinical models showed notable advantages: such as increased affinity and irreversible blockade of the receptor, inhibition of other ErbB family members, such as HER2 and HER4, and lastly, partial *in vitro* efficacy against T790 M mutation, and other rarer genetic alterations connected with primary resistance to first-generation inhibitors [13,14]. However, inhibition of T790 M mutated EGFR was only possible at concentrations not clinically achievable without having considerable skin and gastrointestinal toxicity. It should be noted that the prevalence of T790 M mutations may be different depending on the assay used to detect this mutation (e.g. CAST-PCR, digital PCR, sequencing, etc.). Obviously, a validated PCR should be used to stratify patients.

To overcome the resistance due to the T790 M mutation, the third generation of TKIs was developed, and among them, osimertinib (Tagrisso®, AstraZeneca Pharmaceuticals LP) is the only one that has been approved for clinical use by FDA and EMA, so far. Its approval as front-line EGFR-mutant NSCLC treatment was based on the results of FLAURA trial [15]. Next to its activity against the T790 M mutation, osimertinib is also active against ex19del and exon 21 mutations. It is preferentially selective for mutated EGFR, and therefore toxicity at therapeutic doses is lower than for first- and second-generation agents. Notably, osimertinib is able to cross the blood-brain barrier to some extent, making it active against disease in the CNS [16].

2.3. Market analysis for EGFR-TKIs

The market for drugs for the treatment of lung cancer has become rather diversified; next to surgery and radiation, platinum-based chemotherapy, or an EGFR-TKI is given to most patients, while novel immunotherapy is limited to a subgroup, often in combination with a platinum-based regimen. Lung cancer is the most common cancer worldwide with more than 2 million cases in 2018. In the USA lung cancer is the 2nd common cancer with 234,030 new cases in 2018 (https://seer.cancer.gov). NSCLC is the most common (85%) subtype and adenocarcinoma the most common histology. At diagnosis, approximately 75% are metastatic with a 5-year survival of less than 5% in stage IV. Among the adenocarcinoma patients, 12–47% have EGFR activating mutations, depending on the geographic area, with 22% in the US patients (https://seer.cancer.gov). This means that the majority is still not eligible for treatment with one of the EGFR directed drugs, either one of the first-generation EGFR inhibitors, erlotinib, and gefitinib (www.accessdata.fda.gov/drugsatfda_docs/nda) or the second-generation EGFR inhibitor afatinib, which is intended for the same (or a smaller) part of this group of patients. With the approval of osimertinib for this group of first-line patients, this market has become more crowded. Obviously, dacomitinib will be a drug of choice (as outlined later in this review) for a subgroup of patients. The market will, however, become different for first- and second-line treatment, since second line is not dependent on the presence of activating mutations. The sales of dacomitinib at its launch in 2014 were 1.83 USD million and are expected to increase to 181.66 USD million in 2022, with the major markets being the USA and China (together about 80%) (https://www.marketresearch.com/product/).

3. Dacomitinib

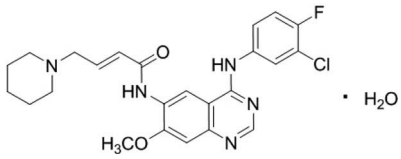
3.1. Introduction to the compound

Dacomitinib belongs to the second generation of EGFR-TKIs, it is a pan-ErbB inhibitor, which covalently binds to the cysteine residue in the ATP-binding pocket, inhibiting the activity of the receptors [17]. (Box 1). It has been approved for the front-line treatment of mutated NSCLC but is currently being evaluated in other settings and combinations that will be discussed in the paper.

3.2. Chemistry

Dacomitinib is a member of the class of quinazolines that is 7-methoxyquinazoline-4,6-diamine in which the amino group

Box 1. Drug summary box

Drug name	Dacomitinib
Phase	Approved
Indication	First-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as verified by an FDA approved test
Pharmacology description	Irreversible inhibition of the activity of the EGFR family (EGFR/HER1, HER2, and HER4) tyrosine kinases via covalent binding to the cysteine residues in the catalytic domains of the HER receptors
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	ARCHER 1050 [20]

at position 4 is substituted by a 3-chloro-4-fluorophenyl group and the amino group at position 6 is substituted by an (E)-4-(piperidin-1-yl)but-2-enoyl group. Its relative molecular mass is 487.95 Daltons.

3.3. Pharmacokinetics and Phase I dose-finding studies

In preclinical assessments on rat, monkey, and dog models, dacomitinib showed a high bioavailability, over 50%, a $t_{1/2}$ longer than 12 h and a volume distribution greater than 17 L/kg [17]. In healthy volunteers, the absolute bioavailability after a 45 mg dose (oral administration) was estimated to be 80.01% (90% CI: 74.90%, 85.47%) [18].

The first-in-human clinical trial (NCT00225121 [19]) assessed the safety, tolerability, and pharmacokinetic parameters in patients with advanced malignant solid tumors. Dacomitinib was generally safe and well-tolerated, with a maximum tolerated dose (MTD) of 45 mg daily. The maximum plasma concentration (C_{max}), was 104 ng/mL on day 4 of the first cycle. In addition, drug exposure at steady state showed a linear increase with increasing dose. Also in humans, a long half-life (59 to 85 h) and a large volume of distribution were found, as well as an efficient tissue penetration ability. The geometric mean apparent plasma clearance of dacomitinib was 24.9 L/h. There was evidence of accumulation after multiple doses, although the maximal accumulation appeared during the first cycle. Therefore, it does not cause an increase in toxicity when the treatment requires more than one cycle.

In the ARCHER 1050 study, the trough concentration (C_{trough}) varied from 70.2 to 61.7 ng/mL between cycles 2 and 6 measured at every first day of the cycle, in NSCLC patients taking 45 mg/day doses without dose modifications, or interruptions [20].

In addition, pharmacokinetics was not altered by the administration of a high-fat, high-calorie meal, whereas its exposure, after the administration of acid-reducing proton pump inhibitors (PPI), was reduced. Therefore, dacomitinib could be taken both in fasted or fed state, but the use of PPI with long-lasting effects should be avoided, when possible [21].

Dacomitinib metabolism occurs mainly in the liver, with oxidative and conjugative reactions, catalyzed predominantly by cytochrome P450 2D6 (CYP2D6) and by CYP3A4. For this reason, the effect of hepatic impairment on drug exposure (AUC_{inf} and C_{max}) was studied, after a single oral dose of 30 mg. Patients with mild and moderate hepatic impairment did not experience a clinically significant decrease in dacomitinib exposure, compared to the healthy subjects [22].

Following a single 45 mg oral dose of radiolabelled dacomitinib, 79% of radioactivity was recovered in the feces and 3% in urine [23].

3.4. Phase II and III clinical studies

Dacomitinib was tested for its efficacy as second- and third-line therapy. In the phase II and III clinical trials ARCHER 1028 [24] and ARCHER 1009 [25], it was compared to erlotinib in patients with advanced NSCLC previously treated with one or two lines of chemotherapy, non-selected for *EGFR* mutations (Table 2). When results were analyzed retrospectively to identify the effect of *EGFR*-mutations on the outcome of the treatment, differences in median progression-free survival (mPFS) between treatment with dacomitinib or erlotinib did not emerge (7.44 months for both dacomitinib and erlotinib, HR = 0.46; 95% CI 0.18–1.18; two-sided $P = 0.098$). In addition, dacomitinib was associated with more severe adverse events (AE) [24,25]. Regarding its efficacy on unselected NSCLC, again when compared to erlotinib it did not show a difference in mPFS, 2.6 months (95% CI 1.9–2.8) in both groups

Table 2. Clinical studies with dacomitinib in patients with lung cancer.

Identifier	Study population	Clinical Phase	Drugs	Status
ARCHER 1042	236 (132 evaluable)	Phase II	Dacomitinib	Completed
ARCHER 1028	188	Phase II	Erlotinib vs. Dacomitinib	Completed
ARCHER 1009	878	Phase III	Dacomitinib vs. Erlotinib	Completed
BR.26	720	Phase III	Dacomitinib vs. Placebo	Completed
Archer 1050	452	Phase III	Dacomitinib vs. Gefitinib	Active, not recruiting
NCT03810807	34	Phase I	Dacomitinib and Osimertinib	Recruiting
NCT03755102	24	Early phase I	Dacomitinib (After osimertinib)	Recruiting

(HR 0.941, 95% CI 0.802–1.104), one-sided log-rank $p = 0.229$ (ARCHER 1009).

In the multicentre randomized phase III study BR.26 [26], the efficacy of dacomitinib vs. placebo was assessed in patients who had received up to three previous lines of conventional chemotherapy, and at least one of gefitinib or erlotinib. In patients retrospectively grouped for bearing the *EGFR* activating mutation, dacomitinib slightly improved the PFS from 0.95 to 3.52 months, but the OS was unchanged, 7.23 months for the dacomitinib group (95% CI 6.08–8.61) and 7.52 months for the placebo group (95% CI 4.99–9.49) (HR 0.98, 95% CI 0.67–1.44, $P = 0.46$).

Therefore, the use of this drug as second-line treatment in patients who have progressed after first-generation TKIs, or after conventional cytotoxic chemotherapy, does not appear to be beneficial [25,26].

The turning point was the major clinical trial ARCHER 1050, which was a phase III randomized, multicentre, open-label, active-controlled trial with the aim of comparing the safety and efficacy of dacomitinib with gefitinib in 452 treatment-naïve patients with unresectable, metastatic NSCLC, bearing the sensitizing mutations (Table 2) [20]. Treatment with dacomitinib showed an improvement of PFS (14.7 months vs 9.2 months; HR 0.59; 95% CI 0.47–0.74). Upon this evidence, FDA approved dacomitinib tablets for the first-line treatment of patients with metastatic NSCLC.

Recently, Mok et al. [27] presented the mature results from OS analysis of ARCHER 1050 patient population, after a 30-month follow-up: OS in the dacomitinib group was significantly improved compared to gefitinib (HR 0.760, 95% CI 0.582–0.993, two-sided $P = 0.0438$), with median OS of 34.1 months with dacomitinib and 26.8 months with gefitinib. It should be noted that this study demonstrated for the first time an improvement in OS, comparing a second-generation EGFR-TKI to a standard of care EGFR-TKI.

3.5. Problems with tolerability and adverse effects (AE)

EGFR-TKIs are often associated with AE such as rash, paronychia, stomatitis, diarrhea, and changes in liver enzymes [28]. This occurs because of the wide expression of EGFR especially in cells of epithelial origin, such as cells of the skin and gastrointestinal tract.

Indeed, in the phase I trial NCT00225121, grade 1 to 3 AEs were observed, including diarrhea (66.7%), rash (45%), fatigue (38%) and nausea (36%). In the ARCHER 1042 [29] phase II trial, the effect on dermatologic and gastrointestinal AE in NSCLC patients was investigated, by treating them with doxycycline against placebo in one cohort and with a probiotic plus topical aclometasone against placebo in the other. The results showed that doxycycline treatment significantly reduced the select dermatologic adverse events of interest (SDAEI) of grade ≥ 2 by 50% ($P = 0.016$) compared to the placebo. However, doxycycline was not able to reduce SDAEI of all grade in a statistically significant way. Aclometasone reduced SDAEI of all grades but not with statistical significance. Finally, the probiotic was ineffective in reducing gastrointestinal AEs.

In the ARCHER 1009 trial dacomitinib showed a higher toxicity compared to gefitinib and erlotinib. This finding was confirmed by the ARCHER 1050 trial, in which, focusing on grade 3 AEs, dermatitis acneiform occurred in 13.7% of dacomitinib patients as opposed to none of gefitinib patients, paronychia in the 7.5% of dacomitinib arm and 1.3% of gefitinib arm, and finally the most frequent AE overall, diarrhea, which occurred in 8.8% of dacomitinib patients and only in the 0.9% of gefitinib patients. However, this was expected to happen with second-generation inhibitors because their binding mode is irreversible, so they have a stronger and longer-lasting effect, also on normal cells.

However, management of toxicity can be obtained with dose reduction (DR) and standard co-medication. In particular, Corral et al. [30] analyzed the outcomes of DR on efficacy, safety, and PK in patients of the ARCHER 1050 trial. They reported that the median PFS was similar in all the patients who received dacomitinib, 14.7 (95% CI: 11.1–16.6) months for patients without DR and 16.6 (95% CI: 14.6–18.6) months with DR. The median OS was retained as well: 34.1 (29.5–37.7) months without DR and 36.7 (32.6 – not reached [NR]) months with DR. Regarding the safety, no grade 4 adverse events were experienced by patients who had DR, and the incidence of the grade 3 events that lead to DR decreased, for example, grade 3 diarrhea incidence was reduced from 15.3% (n = 23) to 6.7% (n = 10). Finally, the C_{trough} of dacomitinib at cycle 2, day 1, was lower in patients receiving the highest dose (45 mg) than those with DR. Therefore, DR can allow patients to benefit from dacomitinib treatment for longer, without having to discontinue the therapy. In addition, during phase III studies, dacomitinib appeared to be more effective in reducing lung cancer-related symptoms and chest pain, when compared to erlotinib and gefitinib [20].

3.6. Dacomitinib and brain metastases

From preclinical models, dacomitinib showed good brain penetration, with measurable concentrations in cerebrospinal fluid [31]. However, patients with a history of brain metastases or leptomeningeal disease were excluded in the ARCHER1050. Therefore, data on its efficacy on brain metastasis are not available, but the incidence of CNS metastasis could be evaluated in patients receiving dacomitinib compared to gefitinib. Interestingly, only one patient of the dacomitinib group progressed in the brain compared to eleven patients in the gefitinib group (0.44% vs 4.9%).

A recent study investigated the brain distribution of a panel of EGFR-TKIs using cassette dosing in mice. This study included first-generation TKIs, afatinib, dacomitinib and osimertinib, and showed that dacomitinib and osimertinib can be classified as brain penetrant EGFR inhibitors, as opposed to afatinib, erlotinib, and gefitinib, which were categorized in the low brain penetration group [32].

On the other hand, both preclinical and clinical studies showed that afatinib is active against brain metastasis and that it might be able to delay their development [33]. The same applies to osimertinib, which has been proven to be effective in controlling brain metastasis in AURA3 and FLAURA clinical trials, after prior EGFR-TKI treatment and as first-line treatment, respectively [15,34–36].

Combining the previous evidence, it could be speculated that dacomitinib might be active as well in brain, given the higher brain penetration compared to afatinib, observed in mice, providing a new therapeutic option for NSCLC patients with CNS lesions. However, clinical studies are warranted to verify this hypothesis.

Interestingly, in the cassette-dose study, it was also shown that dacomitinib is a substrate for both/either P-glycoprotein (P-gp) and/or breast cancer resistance protein (BCRP). Both efflux transporters are located in the blood-brain barrier and are able to reduce the concentration of their substrates in the CNS. In mice knock-out for these transporters, dacomitinib and osimertinib had the highest concentrations in the brain, compared to the other TKIs investigated. Therefore, dacomitinib might be evaluated in combination with an efflux transporter inhibitor, to improve its efficacy on CNS metastasis.

3.7. Combination with cetuximab

Given the outstanding performance of osimertinib as first-line treatment, with 18.9 months of PFS, it is likely that it will be chosen over second-generation TKIs. However, dacomitinib should be further evaluated in combination with other drugs, for example, cetuximab, a human-mouse chimeric antibody that binds the extracellular domain of EGFR.

In the phase Ib open-label clinical trial NCT01090011 [37], the combination of afatinib with cetuximab was evaluated in patients with NSCLC who had progressed after erlotinib or gefitinib. With this trial, the combination of the two drugs showed promising results, conferring robust clinical responses in patients with *EGFR*-mutant NSCLC with acquired resistance to gefitinib or erlotinib, mediated either by T790 M mutation or differently.

Furthermore, Oashi and collaborators [38] performed a study with different EGFR inhibitors administered in combination with cetuximab, showing that only afatinib and dacomitinib act synergistically with the monoclonal antibody. Notably, osimertinib and first-generation TKIs did not show a synergistic effect. They proposed that the mechanism behind it is a monomer preference of EGFR-TKIs, and since cetuximab directs the monomer-dimer equilibrium toward monomer dominance, the result is a synergistic activity. As a confirmation of this, the IC_{50} values of afatinib and dacomitinib for Ba/F3 cells expressing dimerization-impaired EGFR were approximately 30–1000 lower than those for cells with dimerization-competent *EGFR* mutations. Synergistic activity of afatinib and cetuximab was also found *in vivo* on mouse xenografts. When given as monotherapy, the two drugs did not affect the tumor volumes, however, combination therapy induced statistically significant regression of tumors. Finally, after the crosslinking of harvested tumors, immunoblotting showed that afatinib alone promoted dimerization of EGFR compared with the control group, but this effect was contrasted by cetuximab in the combination treatment group. Given these data, a combination of dacomitinib with cetuximab is warranted, even if the potential addictive toxicity could be a limitation in clinical practice.

3.8. Other combinations and cancers

Dacomitinib has been evaluated in combination with several other agents. In preclinical gastric cancers model *in vitro* and *in vivo*, dacomitinib showed synergistic activity when combined with trastuzumab, IGF1 R inhibitors, ERK1/2 inhibitors, and PI3 K/mTOR inhibitors [39]. Dacomitinib showed additive anti-tumor efficacy *in vivo*, in combination with ionizing radiation (IR) against head and neck squamous cell carcinoma (SCCHN), apparently without additional toxicity on normal tissue [40].

In a phase I clinical trial (NCT01121575 [41]), dacomitinib was evaluated in combination with a c-Met inhibitor in patients with advanced NSCLC after failure of previous systemic conventional chemotherapy or various types of TKI directed targeted therapy (both small molecules and monoclonal antibodies). An increased toxicity compared to each of the separate agents was found; 94% of the patients showed at least one AE with diarrhea (74%) as the most occurring and most concerning toxicity. These AEs necessitated the permanent discontinuation of 26% of the patients. The study showed a minimal antitumor activity with no objective response (OR), although 61% of the patients had a stable disease (SD). In the expansion phase, just one patient had partial response (PR), and 32% had SD. Therefore, the investigation on this combination was not continued.

Dacomitinib was also studied in combination with figitumumab (CP-751,871), a monoclonal antibody against IGF-1 receptor, in patients with advanced solid tumors (NCT00728390 [42]). AEs were similar to those observed with the agents given as monotherapies, but since the grade of these AEs was increased, a reduction of dosage of figitumumab was required. However, the higher toxicity was not caused by an interaction of dacomitinib with figitumumab that would have led to increased exposure to the former, since they observed that the clearance of dacomitinib was higher, resulting in an even lower plasma exposure to dacomitinib than expected. Preliminary data on the efficacy of this treatment showed that 3 out of 61 (4.9%) patients had PR as the best overall response (BOR), and 22 (36%) had SD as BOR. The three patients with the PR had ovarian carcinoma, adenoid cystic carcinoma, and salivary gland carcinoma, while 8 of the 22 patients with SD had NSCLC [43].

Another combination that was evaluated was with chemo-radiotherapy, in particular with radiotherapy and cisplatin, in a phase I study on 12 patients with loco-regionally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). At 15 mg and 30 mg of dacomitinib, there were no dose-limiting toxicities (DLT), and at 45 mg, one of four patients reported a DLT caused by a grade 2 diarrhea. Only 10 patients were evaluable for efficacy, who were all alive at 1 year, not yet reaching a median PFS and OS. The study was terminated early since other studies evaluating HER inhibitors in combination with platinum-based chemo-radiotherapy in LA-SCCHN did not show improvement in the outcomes, while the toxicity was increased [44].

Currently, the phase I/II NCT02039336 [45] is recruiting patients to assess the combination of dacomitinib with the MEK inhibitor PD-0325901, against *KRAS* mutant NSCLC, while in the NCT01920061 [46] study, dacomitinib will be evaluated

in patients with advanced cancers in combination with gedatolisib, a PI3 K/mTOR inhibitor. Dacomitinib is also being evaluated in skin squamous carcinoma (NCT02268747 [47]) and advanced/metastatic squamous cell carcinoma of the penis (NCT01728233 [48]).

3.9. Regulatory affairs

Dacomitinib was first approved in the US on the 27th of September 2018, for the treatment of NSCLC with *EGFR* ex19del or ex21 L858 R substitution mutations as detected by an FDA-approved test, in Canada has been approved with the same indications, as well. After that, dacomitinib received the marketing authorization by the European Medicine Agency on the 2nd of April 2019. In addition, dacomitinib has been approved in Japan for the treatment of NSCLC positive to *EGFR* mutation, recurrent, or inoperable.

4. Expert opinion

Given the current information on dacomitinib, it is still not clear what should be its place in clinical practice, because during its process of approval the third generation of TKIs (osimertinib) was introduced into the clinic. Initially, osimertinib was approved in 2015 for treatment of patients with metastatic NSCLC positive for EGFR T790 M who had progressed during or after prior first-generation EGFR-TKI therapy. Then, in the FLAURA trial, the efficacy of osimertinib in front-line treatment in NSCLC was compared to that of erlotinib and gefitinib, which resulted in a longer PFS and OS [15,49]. Thereafter, osimertinib was also approved in April 2018 as first-line treatment for patients with metastatic *EGFR*-mutated NSCLC, regardless of T790 M status. These data led to speculations on the future of second-generation EGFR-TKIs.

In addition, recent clinical trials tested the efficacy of the combination of first-generation EGFR-TKIs with platinum-based chemotherapy or with monoclonal antibodies, such as bevacizumab and ramucirumab, and compared the combination to TKI alone or TKI with placebo. The results from these studies suggest that first-generation TKIs should not be completely set aside. Indeed, combination of gefitinib, pemetrexed and carboplatin led to a mPFS of 16 months (95% CI, 13.5 to 18.5 months), significantly longer than gefitinib alone, with a mPFS of 8 months (95% CI, 7.0 to 9.0 months), as first-line treatment in advanced NSCLC and EGFR sensitizing mutation [50]. The study RELAY evaluated the combination of erlotinib with ramucirumab in metastatic EGFR-mutated NSCLC, and the initial analysis reported a PFS of 19.4 months (95% CI 15.4–21 · 6) in the combination group compared to 12.4 months (11 · 0–13 · 5) in the group treated with erlotinib plus placebo, a remarkable result, considering that it is very similar to that obtained by osimertinib first-line treatment in FLAURA trial [15,51].

In the ARCHER 1050 phase III trial, dacomitinib demonstrated an overall survival benefit compared to a first-generation TKI, as first-line treatment. However, this trial excluded patients with brain metastasis, failing to provide fundamental information in the drug evaluation process, especially for NSCLC that often progresses in the brain. It can only be hypothesized, considering preclinical data and clinical observations, that dacomitinib could reach the CNS and exert its activity, while for osimertinib and afatinib, the brain penetration has been evaluated in clinical trials.

Since the most common resistance mechanism to second-generation TKIs is the T790 M mutation, osimertinib, which has been developed especially against this mutation, could be spared and used as second-line treatment. In addition, according to the updated results of FLAURA trial, osimertinib was effective also on T790 M negative patients. However, new drugs are being evaluated for their efficacy against rare de novo mutations, acquired after EGFR-TKIs treatment. For example, poziotinib showed interesting results in a clinical trial against rare exon 20 insertions, which might occur after first- and second-generation TKI treatment [52]. Poziotinib also showed activity against a novel exon 20 mutation (M766Q), acquired after third-line treatment with osimertinib [53]. In addition, fourth-generation TKIs are being developed to specifically overcome the C797 S mutation, which is the most common mechanism of acquired resistance to osimertinib [54].

It could be desirable to have results on a head-to-head comparison of second- and third-generation TKIs because the only information currently available comes from the comparison of each generation with first-generation TKIs. This would better facilitate the choice between one drug and the other, or the sequence of administration to achieve the best OS. Currently, it is only possible to do a retrospective analysis of the results from ARCHER1050 trial, in which a fraction of patients that discontinued the treatment with dacomitinib or gefitinib was given a subsequent therapy, such as chemotherapy, third-generation or other type of EGFR-TKI. The 22 (9.7%) patients treated with osimertinib as second-line agent after dacomitinib showed a median OS of 36.7 months (30.1 to NR), result that was better compared to the median OS reached with chemotherapy as second-line option. However, this result should be interpreted with caution since the number of patients in this group was small [27]. Another retrospective study on the efficacy of second-line osimertinib is the GioTag study [55], a global observational study, assessing as first end-point the time on treatment. They observed that subsequent use of afatinib and osimertinib, in patients who had developed T790 M mutation, led to a median overall survival of 41.3 months (90% CI: 36.8–46.3) overall and 45.7 months (90% CI: 45.3–51.5) in patients with Del19-positive tumors (n = 149). Such a study has not been performed on dacomitinib trials; however, it shows the potential benefit of the use of osimertinib as second-line treatment after second-generation TKI. Notably, the phase I NCT03810807 [56] new clinical trial is recruiting patients to assess the safety and, if any, the effects of the combination of dacomitinib with osimertinib in metastatic EGFR-mutant lung cancers that have not been treated with an EGFR-TKI.

Dacomitinib is currently being evaluated as second-line agent for patients previously treated with first-line osimertinib. Indeed, an early phase I clinical trial (NCT03755102 [57]) is currently recruiting patients in order to assess whether dacomitinib after osimertinib is effective in patients with metastatic EGFR-mutant lung cancers, and patients will be divided in 2 arms: those with reported C797 S mutation and those without. Indeed, Kobayashi and collaborators [58,59] showed that cells

carrying L858 R and C797 S mutations are moderately sensitive to dacomitinib, they are more sensitive to erlotinib and gefitinib instead. This superior activity of first-generation EGFR-TKIs was also reported by Rangachari and collaborators [60]. However, Kobayashi and collaborators also demonstrated that dacomitinib was most effective on cells with Del18 and L792 F mutations, the latter being a rare mutation that confers resistance against afatinib and osimertinib. Future studies should include selection based on these mutations. On the topic of uncommon mutations, in ARCHER 1001 trial there were five NSCLC patients (evaluable) harboring exon 20 insertion, and one of them had a PR, two had SD and two had PD, therefore dacomitinib could also be active on this type of mutation [61]. Moreover, second-generation EGFR-TKIs appeared to be more active against exon 18 mutations [62] compared to first- and third-generations. In addition, osimertinib appears to be less effective in patient with uncommon mutations, compared to patients with the common ones (mPFS of 8.2 months – 95% CI, 5.9 to 10.5 months) [63], and since uncommon mutations represent 10% to 18% of EGFR-mutated patients, dacomitinib could be exploited in this type of setting.

In conclusion, until new drugs will show an improved outcome as second-line treatment after osimertinib, dacomitinib could provide a valuable therapeutic option, especially as first-line treatment for NSCLC, sparing osimertinib treatment for subsequent therapy. However, new TKIs are being approved and developed, with better clinical profiles. Therefore, dacomitinib should be evaluated for its brain penetrance, which has not yet been tested in clinical trials, and for its efficacy as second-line treatment after third-generation TKIs. In addition, combinatorial approaches (e.g. dacomitinib combined with osimertinib or cetuximab) should be explored in clinical setting as they could provide new potential therapeutic options in addition to the single treatment approach.

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