Pemetrexed for the treatment of non-small cell lung cancer

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EXPERT OPINION

Pemetrexed for the treatment of non-small cell lung cancer

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Introduction: Non-small cell lung cancer (NSCLC) is a major cause of cancer-related death worldwide. Although advanced NSCLC is still incurable, various anti-neoplastic agents have become available for the treatment of this disease. Pemetrexed, a multi-target folate antagonist, has improved the survival of non-squamous NSCLC patients. Currently, pemetrexed is approved for first-line treatment in combination with a platinum derivate, for second-line treatment as a single agent and, more recently, as maintenance treatment after first-line chemotherapy.

Areas covered: The authors analyzed the state of the art of pemetrexed through a review of the literature. Clinical trials and meta-analyses involving pemetrexed in NSCLC were evaluated. Pemetrexed improved survival of non-squamous NSCLC in first-line, maintenance, and second-line treatments; this benefit is limited to non-squamous histology. Because pemetrexed has become part of the standard of care, current clinical trials are designed to compare it to other investigational combinations. Limited data on resectable disease are available, and additional clinical trials are being conducted.

Expert opinion: Pemetrexed has shown effectiveness and a favorable toxicity profile. Histology-driven indications and the relationship of pemetrexed with thymidylate synthase expression suggest that a more precise definition of predictive biomarkers could be further investigated.

Keywords: chemotherapy, non-small cell lung cancer, pemetrexed, thymidylate synthase

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1. Introduction

Non-small cell lung cancer (NSCLC) represents the main cause of cancer-related death worldwide, with approximately 900,000 deaths every year [1]. For years, platinum-based combinations have represented the main pharmacologic approach to advanced NSCLC in first line, and various compounds have been combined with cisplatin or carboplatin.

Pemetrexed (**Box 1**) (Alimta®, MTA, LY231514) is a multi-targeted anti-folate agent, developed by Eli-Lilly and registered for the treatment of malignant pleural mesothelioma and advanced non-squamous NSCLC [2]. Currently, pemetrexed is employed in combination with platinum derivates for first-line treatment and as single agent for subsequent lines; moreover, it can be administered as maintenance treatment after first line. Due to its effectiveness and its mild toxicity, pemetrexed is widely employed; additionally, its specific action against the non-squamous histotype makes it a useful example of a histology-driven approach in oncology. The aim of this review is to evaluate the role of pemetrexed in NSCLC treatment. The state of the art was explored though a review of the literature. The keywords "pemetrexed," "lung neoplasms," and "thymidylate synthase" were searched on PubMed, and abstracts from the ASCO, ESMO, and WCLC congresses

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Box 1. Drug summary.

Drug name	Pemetrexed
Phase	On market
Indication	Non-small cell lung cancer, malignant pleural mesothelioma
Pharmacology description	Antimetabolite
Route of administration	Intravenous
Chemical structure	Disodium salt ($C_{20}H_{21}N_5O_6$)
Pivotal trial(s)	[22,33,43,85]

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were analyzed. Pertinent clinical trials and meta-analyses were evaluated. Data from relevant randomized trials and meta-analyses were reported in **Tables 1-4**.

2. Pharmacology

2.1 Pharmacodynamics

Pemetrexed is a folate analog belonging to the antimetabolites class. The drug interferes with the synthesis of nucleic acids, resulting in a cytotoxic effect on neoplastic cells. Pemetrexed competes with reduced folate, thereby significantly inhibiting the activity of multiple folate-requiring enzymes: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT) [3,4]. Additionally, another folate-dependent enzyme involved in purine synthesis, aminoimidazolecarboxamide ribonucleotide formyltransferase (AICART), has been reported to be a target for pemetrexed [5]. The mechanism of action of pemetrexed is shown in **Figure 1**. The primary pharmacologic target of pemetrexed is TS: as the *de novo* source of thymidylate synthesis, it is an essential enzyme involved in DNA replication and cell growth. It converts deoxyuridylate (dUMP) to deoxythymidylate (dTMP), which is essential for the synthesis of DNA [6]. The inhibition of TS reduces dTMP and increases dUTP in cells, causing DNA strand breakage and apoptosis. Some data suggest that low expression of TS could predict responsiveness to pemetrexed in NSCLC patients [7]; in contrast, other data, collected from patients affected by malignant pleural mesothelioma, indicate that the expression of TS lack sufficient predictive value for response to pemetrexed [8].

Recent data show that, in addition to the aforementioned DNA damage, pemetrexed is also able to induce caspase 2, 3, 8, and 9 activation in NSCLC cell lines, resulting in caspase-dependent apoptosis. This mechanism was associated with the activation of ataxia-telangiectasia mutated (ATM)/p53-dependent and (ATM)/p53-independent signaling pathways, leading to activation of the caspase signaling cascade and apoptosis [9].

Other targets of pemetrexed are DHFR, which catalyses the reduction of dihydrofolate to tetrahydrofolate, an essential cofactor in the synthesis of thymidine and purines, and the enzymes GARFT and AICART, involved in *de novo* purine synthesis. AICART inhibition has also been demonstrated to block the mTOR signaling pathway, resulting in cell death [5]. Pemetrexed is transported into the tumor cell by either the reduced folate carrier (RFC) or proton-coupled folate transporter (PCFT); then, in the intracellular environment, it undergoes polyglutamation, and this form of the drug enhances inhibition on target enzymes compared to the monoglutamate form [3]. Several mechanisms of resistance to pemetrexed have been reported including: increased intracellular expression of TS, modification in the binding site of TS for the drug, decreased expression of the transporting proteins RFC and PCFT, and reduced polyglutamation of the drug [3,4].

2.2 Pharmacokinetics

Pemetrexed is administered by the intravenous route only; the drug is rapidly distributed within the body and peak plasmatic levels are reached within 30 min. Pemetrexed is 81% bound to plasma proteins. Pemetrexed is rapidly eliminated (half-life: 3.5 h; total systemic clearance: 91.8 mL/min), mainly via the kidneys through glomerular filtration and active tubular secretion. Approximately 90% of pemetrexed is excreted in the urine within 24 h after administration. Only a limited amount of the drug is metabolized by the liver. Preclinical data suggest that pemetrexed does not interfere significantly with the metabolism of other drugs carried out by cytochrome P450 isozymes [10].

2.3 Toxicity

Pemetrexed is a well-tolerated drug. Its main adverse events involve bone marrow function: myelosuppression, represented in particular by neutropenia and thrombocytopenia, is the dose-limiting toxicity of the drug. An elevated pre-treatment level of plasma homocysteine (a surrogate marker for functional folate deficiency) predicts severe, potentially life-threatening thrombocytopenia and neutropenia, with or without associated severe diarrhea and mucositis, while a high pre-treatment level of methylmalonic acid (a marker of vitamin B12 deficiency) is an independent predictor of severe diarrhea and mucositis. It has been reported that vitamin supplementation with folic acid and B12 leads to a substantial reduction of pemetrexed-related toxicity without reducing efficacy [11]. According to these findings, folic acid by mouth (350 µg/day) and vitamin B12 SC (1000 µg every 9 weeks) have become mandatory supplementations for patients receiving pemetrexed. According to the current indications, vitamin administration should start at least 1 week before the first cycle of pemetrexed and last until at least 3 weeks after the last cycle of treatment [2]. Recently, data collected from a trial of pemetrexed in patients with relapsed small cell lung cancer (SCLC) have suggested that a shorter interval between the

Table 1. Relevant published randomized clinical trials of pemetrexed in first line for NSCLC.

First author	Phase	Regimens	Pts	Results
Scagliotti GV [21]	II	PemOx vs CarboPem	41	PFS: 5.5 m (PemOx) vs 5.7 m (CarboPem) OS: 10.5 m (both arms)
Scagliotti GV [22]	III	CisPem vs CisGem	1725	Globally: PFS: 4.8 m (CisPem) vs 5.1 m (CisGem); HR = 1.04 OS: 10.3 m (CisPem) vs 10.3 m (CisGem); HR = 0.94 Non-squamous (including adenocarcinoma and large cell carcinoma): PFS: 5.3 m (CisPem) vs 4.7 m (CisGem); HR = 0.90 OS: 11.8 m (CisPem) vs 10.4 m (CisGem);HR = 0.81; p = 0.005 Squamous: PFS: 4.4 m (CisPem) vs 5.5 m (CisGem); HR = 1.36 OS: 9.4 m (CisPem) vs 10.8 m (CisGem); HR = 1.23; p =0.005
Grønberg BH [26]	III	CarboPem vs CarboGem	436	HrQoL similar between the two arms OS: 7.3 m (CarboPem) vs 7.0 m (CarboGem); p = 0.63
Rodriguez-Pereira J [27]	III	CarboPem vs DocPem	260	Survival without grade 3 – 4 toxicity: 3.2 m (CarboPem) vs 0.7 m (DocPem); HR = 0.45 OS: 14.9 m (CarboPem) vs 14.7 m (DocPem); HR = 0.93; p = 0.934
Yang JC [28]	III	Afatinib vs CisPem	345	PFS: 11.1 m (Afatinib) vs 6.9 m (CisPem); HR = 0.58; p < 0.0001
Gridelli C [65]	II	Pem vs sequential Pem- > Gem	87	TTP: 4.5 m (Pem- > Gem) vs 4.1 m (Pem) PFS: 3.3 m (both arms) OS: 5.4 m (Pem- > Gem) vs 4.7 m (Pem)
Lilembaum [69]	III	CarboPem vs Pem	217	PFS: 5.9 m (CarboPem) vs 3.0 m (Pem); HR = 0.46; p < 0.001 OS: 9.1 m (CarboPem) vs 5.6 m (Pem); HR = 0.57; p = 0.001

Hazard ratio and p value were reported where available.
CarboPem: Carboplatin–pemetrexed; CarboGem: Carboplatin–gemcitabine; CisGem: Cisplatin–gemcitabine; CisPem: Cisplatin–pemetrexed; DocPem: Docetaxel–gemcitabine; Gem: Gemcitabine; m: Months; OS: Overall survival; Pem: Pemetrexed; PemOx: Pemetrexed–oxaliplatin; PFS: Progression-free survival; Pts: Patients; TTP: Time to progression.

first administration of B12 and the administration of pemetrexed could prove to be as safe as the standard interval [12].

Nausea and vomiting have been described; however, pemetrexed is classified as an agent with low emetic risk [13]. Because pemetrexed can be administered in combination with more emetogenic agents, such as cisplatin, the emetic risk of the combination should be taken into account to provide an adequate anti-emetic prophylaxis.

Skin rash has been observed, but it may be prevented through prophylactic use of PO steroids; the equivalent dose of 4 mg BID of dexamethasone can be administered for 3 days, starting on the day before infusion of pemetrexed [2]. The elevation of transaminases and/or bilirubin has been reported in 10 – 15% of treated patients; however, this elevation is usually transitory and asymptomatic. Because pemetrexed is mostly eliminated through the kidneys, creatinine clearance (ClCr) should be evaluated (using the Cockroft and Gault formula): patients with ClCr ≥ 45 ml/min require no dose adjustment; an insufficient number of patients with ClCr < 45 ml/min has received pemetrexed; therefore, this drug should be avoided in this case. In addition, non-steroidal anti-inflammatory drugs and aspirin may reduce the renal excretion of pemetrexed, potentially causing increased toxicity; therefore, administration of such drugs should be interrupted at least 2 days before pemetrexed and should not be restarted until at least 2 days after its administration [2,9]. While methotrexate, similar to pemetrexed in structure and pharmacokinetics, is associated with increased toxicity in patients with third-space fluid (such as pleural effusions or ascites), pemetrexed is well tolerated in such patients, and no specific precautions are required [14].

3. Pemetrexed in advanced NSCLC

3.1 First line

Advanced NSCLC is currently considered incurable, and the treatment of choice is systemic therapy, usually consisting of platinum-based combinations for first-line treatment [15]. Pemetrexed was employed as a single agent [16,17] and in combination with cisplatin [18,19] and carboplatin [20] in several non-randomized, Phase II trials. Pemetrexed showed activity as measured by the response rate (RR) and time to progression (TTP) with a favorable toxicity profile. Such findings were consistent between the aforementioned trials. In particular, pemetrexed combined with cisplatin produced an overall RR ranging from 26% to 64%, while median survival ranged from 8.9 to 10.9 months within the different non-randomized trials. Pemetrexed combined with carboplatin resulted in a partial RR of 24% and a median survival of 13.5 months in the aforementioned trial.

In a multicentre, randomized Phase II trial, pemetrexed was administered with carboplatin (PemCb; 39 patients) or with oxaliplatin (PemOx; 41 patients) to compare the two different platinum derivates. Objective RRs were 26.8% for PemOx

Table 2. Relevant published randomized clinical trials of pemetrexed as maintenance and in second line for NSCLC.

First author	Phase	Line	Regimens	Pts	Results
Ciuleanu T [30] Belani CP [31]	III	Maintenance	Pem vs Plac	663	PFS: 4.3 m (Pem) vs 2.6 m (Plac); HR = 0.50; p < 0.0001 OS: 13.4 m (Pem) vs 10.6 m (Plac); HR = 0.79; p = 0.012
Paz-Ares L [33]	III	Maintenance	Pem vs Plac	1022	PFS: 4.1 m (Pem) vs 2.8 m (Plac); HR = 0.62; p < 0.0001 OS: 13.9 m (Pem) vs 11.0 (Plac); HR = 0.78; p = 0.0195
Barlesi F [35]	III	Maintenance	PemBev vs Bev	376	PFS: 10.2 m (PemBev) vs 6.6 m (Pem); HR = 0.5; p < 0.001 OS: not available yet
Patel JD [38]	III	Maintenance	PemBev after CarboPemBev vs Bev after CarboPacBev	939	PFS: 6 m (PemBev) vs 5.6 m (Bev); HR = 0.83; p = 0.012 OS: 12.6 m (PemBev) vs 13.4 m (Bev); HR = 1.0; p = 0.949
Hanna N [43] Peterson P [45]	III	Second Line	Pem vs Doc	571	Globally: -PFS: 2.9 m (both arms) -OS: 8.3 m (Pem) vs 7.9 m (Doc); p = non significant Squamous cell -OS: 6.2 m (Pem) vs 7.4 m (Doc); HR = 1.563 Non-squamous -OS: 9.3 m (Pem) vs 8.0 m (Doc); HR = 0.778
Cullen MH [47]	III	Second Line	Pem500 vs Pem900	588	PFS: 2.6 m (Pem500) vs 2.8 m (Pem900); HR = 0.9681; p = 0.708 OS: 6.7 m (Pem500) vs 6.9 m (Pem900); HR = 1.013; p = 0.893
Ohe Y [48]	II	Second Line	Pem500 vs Pem1000	216	PFS: 3.0 m (Pem500) vs 2.5 m (Pem1000); p = 0.7139 OS: 16.0 m (Pem500) vs 12.6 m (Pem1000); p = 0.1463
Smit EF [52]	II	Second Line	CarboPem vs Pem	240	PFS: 4.2 m (CarboPem) vs 2.8 m (Pem); HR = 0.67; p = 0.005 OS: 8.0 m (CarboPem) vs 7.6 m (Pem); HR = 0.85; p = non significant
Ardizzoni A [53]	II	Second Line	Pem vs CarboPem	239	-PFS: 3.5 m (CarboPem) vs 3.6 m (Pem); HR = 1.05; p = non significant -OS:8.8 m (CarboPem) vs 9.2 m (Pem); p = non significant. Pooled analysis with NVALT7 trial for OS: HR = 0.90; p = 0.316
De Boer RH [77]	III	Second Line	VanPem vs Pem	534	PFS: 17.6 weeks (VanPem) vs 11.9 weeks (Pem); HR = 0.86; p = 0.108 OS: 10.5 m (VanPem) vs 9.2 m (Pem); HR = 0.86; p = 0.662
Schiller JH [78]	II	Second Line	MatPem q7 vs MatPem q21 Pem	148	PFS: 2.3 m (MatPem q7) vs 2.5 m(MatPem q21) vs 2.7 m (Pem); HR = 0.96 (MatPem q7); HR = 1.46 (MatPem q21) OS: 12.4 m (MatPem q7) vs 5.9 m (MatPem q21) vs 7.9 m (Pem); HR = 0.67 (MatPem q7); HR = 1.66 (MatPem q21)
Chiappori A [79]	II	Second Line	EnzPem vs Pem	160	PFS: 3.0 m (both arms); p = 0.544 OS: 9.6 m (EnzPem) vs 7.4 m (Pem); p = 0.171
Scagliotti GV [80]	II	Second Line	BorPem vs Pem vs Bor	155	TTP: 4.0 m (BorPem) vs 2.9 m (Pem) vs 1.4 m (Bor) PFS: 3.6 m (BorPem) vs 2.8 m (Pem) vs 1.5 m (Bor) OS: 8.6 m (BorPem) vs 12.7 m (Pem) vs 7.8 m (Bor)

Hazard ratio and p value were reported where available.
Bor: Bortezomib; BorPem: Bortezomib–pemetrexed; CarboPem: Carboplatin–pemetrexed; CarboPemBev: Carboplatin–pemetrexed–bevacizumab; Carbopacbev: Carboplatin–paclitaxel–bevacizumab; CisPem: Cisplatin–pemetrexed; Doc: Docetaxel; EnzPem: Enzastaurin–pemetrexed; m: Months; MatPem: Matuzumab–pemetrexed; OS: Overall survival; Pem: Pemetrexed; Pem500: Pemetrexed at 500 mg/m^2; Pem900: Pemetrexed at 900 mg/m^2; Pem1000: Pemetrexed at 1000 mg/m^2; PemBev: Pemetrexed–bevacizumab; Plac: Placebo; PFS: Progression-free survival; Pts: Patients; q7: weekly; q21: every 21 days TTP: Time to progression; VanPem: Vandetanib–pemetrexed.

and 31.6% for PemCb. Median TTP was 5.5 months for PemOx and 5.7 months for PemCb. A median overall survival (OS) of 10.5 months was observed with both schedules. Hematologic toxicity was higher in the PemCb arm [21].

A large, randomized Phase III trial comparing cisplatin–pemetrexed with cisplatin–gemcitabine (a standard regimen at the time) was conducted by Scagliotti *et al.* [22]. Taking into account the mild toxicity of pemetrexed, the study was designed as a non-inferiority trial. Globally, 1725 eligible patients were randomized to receive cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2, both on day 1, every 3 weeks (with prophylactic use of folic acid and B12) or cisplatin 75 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8. A maximum of six cycles was allowed for both arms, and dose reductions for treatment-related toxicity were permitted. Median OS (the primary end-point) was non-inferior in the pemetrexed arm (10.3 vs 10.3 months; HR = 0.94; 95% CI 0.84 – 1.05). One-year survival rates were 43.5% in the cisplatin–pemetrexed arm and 41.9% in the cisplatin–gemcitabine arm, while 2-year survival rates were 18.9% in the cisplatin–pemetrexed arm and 14.0% in the cisplatin–gemcitabine arm. Median progression-free survival (PFS) was 4.8 months

Table 3. Relevant published randomized clinical trials of pemetrexed for early and locally advanced NSCLC.

First author	Phase	Line	Regimens	Pts	Results
Schmid-Bindert G [55]	II	Adjuvant	CisPem vs CarboPem	118	FR: 59.4% (CisPem) vs 50.0% (CarboPem)
Kreuter M [56]	II	Adjuvant	CisPem vs CisVin	132	FR: 95.5% (CisPem) vs 75.4% (CisVin); p = 0.001
Choy H [63]	II	CT-RT	CarboPem-RT vs CisPem-RT	98	TTP: 8.8 m (CarboPem) vs 13.1 m (CisPem); p = 0.057 OS: 18.7 m (CarboPem) vs N/A CisPem

Hazard ratio and p value were reported where available.

CarboPem: Carboplatin–pemetrexed; CisPem: Cisplatin–pemetrexed; CisVin: cisplatin–vinorelbine; CT-RT: Chemo-radiation; FR: Feasibility rate; N/A: Not available; OS: Overall survival; Pem: Pemetrexed; Pts: Patients; RT: Radiation; TTP: Time to progression.

Table 4. Relevant published meta-analyses of pemetrexed for NSCLC.

First author	Line	No of trials	Regimens	Pts	Results
Li M [74]	First line	4	CisPem vs PBR	2518	Global PFS similar (HR = 1.03; p = 0.57) Global OS favors CisPem (HR = 0.91; p = 0.04) Non-squamous: OS favors CisPem (HR = 0.87; p = 0.02)
Al-Saleh K [76]	First line Second line Maintenance	5	Pem vs other treatments or placebo	3541	Global OS favors Pem (HR = 0.89 in first line; HR = 0.88 in second line) Non-squamous OS favors Pem (HR = 0.82) Squamous OS has a trend towards inferiority with Pem (HR = 1.19)
Qi WX [81]	Second line	5	PBD vs Pem alone	1186	PFS favors PBD (HR = 0.89; p = 0.007) OS does not favor PBD (HR = 0.89; p = 0.129)

Hazard ratio and p value were reported where available.

CarboPem: Carboplatin–pemetrexed; CisPem: Cisplatin–pemetrexed; HR: Hazard ratio; OS: Overall survival; PBD: Pemetrexed-based doublets; PBR: Other platinum-based regimens (non containing pemetrexed); Pts: Patients; Pem: Pemetrexed; PFS: Progression-free survival.

in the cisplatin–pemetrexed arm and 5.1 months in the cisplatin–gemcitabine arm (HR = 1.04; 95% CI 0.94 – 1.15). Pre-planned subgroup analysis showed significant differences between histologic sub-types. Patients affected by non-squamous NSCLC achieved better OS in the investigational arm: for large-cell carcinomas, median OS was 10.4 months in the cisplatin–pemetrexed arm and 6.7 months in the cisplatin–gemcitabine arm (HR = 0.67%; 95% CI 0.48 – 0.96; p = 0.03), while for adenocarcinoma, median OS was 12.6 months in the cisplatin–pemetrexed arm and 10.9 months in the cisplatin–gemcitabine arm (HR = 0.84; 95% CI 0.71 – 0.99; p = 0.03). By contrast, patients with squamous carcinoma had a worse median OS in the cisplatin–pemetrexed arm than in the cisplatin–gemcitabine arm (9.4 vs 10.8 months; HR = 1.23; 95% CI 1.0 – 1.5; p = 0.05). Patients whose diagnosis was generic, not otherwise specified NSCLC achieved similar survival results with cisplatin–pemetrexed or with cisplatin–gemcitabine with a median OS of 8.6 vs 9.2 months (HR = 1.08; 95% CI 0.81 – 1.45; p = 0.586). The cisplatin–pemetrexed combination was better tolerated, with a lower incidence of grade 3 – 4 hematologic toxicity (febrile and non-febrile neutropenia, thrombocytopenia, anemia) and alopecia; by contrast, drug-related nausea was more common. Toxicity was consistent between the sub-groups. This trial demonstrated the superiority of the cisplatin–pemetrexed combination compared to cisplatin–gemcitabine in non-squamous NSCLC; moreover, cisplatin–pemetrexed was associated with a more manageable safety profile. The histology-specific benefit is likely related to data showing that squamous NSCLC expresses higher levels of TS than adenocarcinoma of the lung [23] and that overexpression of TS is related to a reduced sensitivity to pemetrexed [24]. This trial led to the approval of a cisplatin–pemetrexed doublet in chemo-naïve patients affected by non-squamous NSCLC in the U.S. [3].; similarly, the European Medicines Agency (EMEA) published a regulatory approval, valid for the European Union countries, with the same indications [25].

Because carboplatin can be used in patients that are unable to receive cisplatin [15] and due to the encouraging data on the carboplatin–pemetrexed combination that have been published [20], the Norwegian Lung Cancer Study Group enrolled 436 patients in a Phase III trial, designed to compare carboplatin–pemetrexed and carboplatin–gemcitabine as first-line treatments for advanced NSCLC [26]. The primary end-point was health-related quality of life (HRQoL), while secondary end-points were OS and toxicity. The two regimens achieved similar results in terms of HRQoL and OS (7.3 months for carboplatin–pemetrexed vs 7.0 months for carboplatin–gemcitabine; p = 0.63). A higher incidence of hematologic toxicity was reported in the carboplatin–gemcitabine

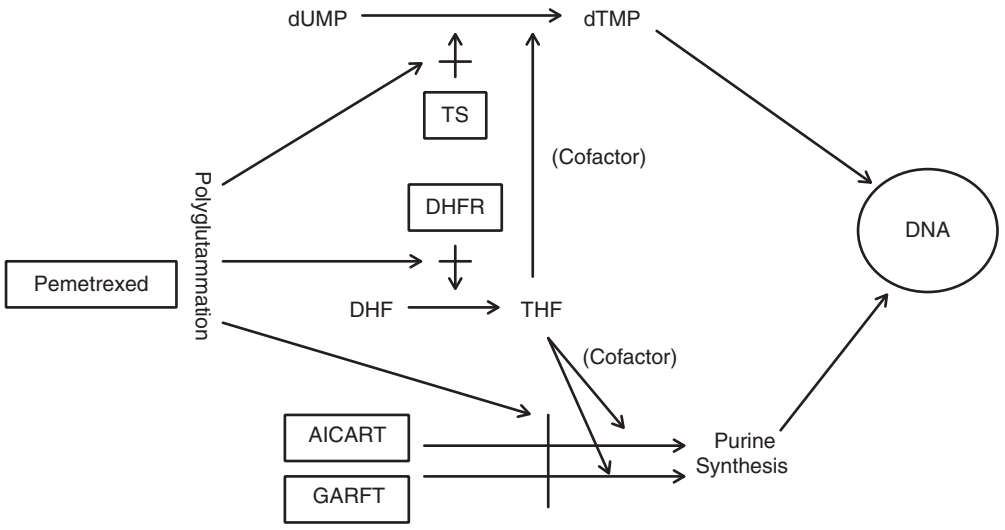

Figure 1. Mechanism of action of pemetrexed. After polyglutamation, pemetrexed inhibits several enzymes playing a key-role in the synthesis of DNA. See text for details.

AICART: Aminoimidazolecarboxamide ribonucleotide formyl transferase; DHF: Dihydrofolate; DHFR: Dihydrofolate reductase; dTMP: Deoxythymidylate; dUMP: Deoxyuridylate; GARFT: Glycinamide ribonucleotide formyl transferase; THF: Tetrahydrofolate; TS: Thymidylate synthase.

arm, but the frequencies of infections due to neutropenia and bleedings due to thrombocytopenia were similar. In another randomized, Phase III trial, the carboplatin–pemetrexed combination was compared with another standard doublet, carboplatin–docetaxel, in patients affected by advanced, non-squamous NSCLC [27]. The primary end-point was survival without toxicity, defined as the interval from randomization to the first treatment-induced grade 3 – 4 adverse event. Patients in the carboplatin–pemetrexed arm achieved a longer median survival without toxicity than those enrolled in the other arm (3.2 vs 0.7 months; HR = 0.45; 95% CI 0.34 – 0.61). The median OS was similar between the two arms (14.9 months for carboplatin–pemetrexed vs 14.7 months for carboplatin–docetaxel; HR = 0.93; 95% CI 0.66 – 1.32). Taken together, these data suggest that carboplatin–pemetrexed can represent an adequate first-line regimen for non-squamous NSCLC. Cisplatin and pemetrexed were compared with afatinib (an irreversible EGFR inhibitor) in a large, prospective trial including 345 patients with EGFR mutations. The primary end-point, median PFS, was higher in the arm treated with afatinib (11.1 vs 6.9 months; HR = 0.58; $p < 0.0001$), as was RR (56% vs 23%; $p < 0.0001$). Afatinib was well tolerated [28].

3.2 Maintenance

Maintenance is a promising approach for the treatment of advanced NSCLC and consists of the administration of an anti-neoplastic agent following a first-line treatment until disease progression, unacceptable toxicity or death. Patients achieving disease stabilization or objective responses after first-line treatment are candidates to receive maintenance treatment. Two modalities are currently employed: switch maintenance and continuation maintenance. In the switch modality, after first-line treatment, patients receive a different, non-cross-resistant agent; in the continuation modality, one of the agents employed in the first-line treatment is continued as maintenance. Because agents employed in switch modality are usually agents available in second-line, some authors define this modality as a form of early second-line treatment [29].

Taking into account the activity and safety of pemetrexed in NSCLC, this drug represents an appealing candidate for maintenance trials. In a randomized, Phase III trial of switch maintenance, 663 patients affected by stage IIIB/IV non-squamous NSCLC received pemetrexed or placebo after four cycles of chemotherapy [30]. Allowed first-line regimens included doublets of cisplatin with one of the following agents: gemcitabine, docetaxel, or paclitaxel. Patients receiving pemetrexed achieved statistically significantly longer PFS (4.3 vs 2.6 months; HR = 0.50; $p < 0.0001$) and OS (13.4 vs 10.6 months; HR = 0.79; $p = 0.012$). A final analysis demonstrated that survival benefit was higher in patients achieving stable disease than objective response after first-line chemotherapy. Survival benefits were different depending on the histology: median OS of patients with non-squamous histology receiving pemetrexed was significantly improved (15.5 vs 10.3 months; $p = 0.012$), while the difference in squamous histology was not significant (9.9 vs 10.8 months) [31]. A favorable tolerability was reported. A limitation of this trial has been observed, as most patients receiving placebo did not receive pemetrexed after disease progression, and as a consequence, immediate and delayed administrations of the agent were not compared [32]. The role of pemetrexed as continuation maintenance after first-line treatment was

investigated in a randomized, double-blind, Phase III trial (PARAMOUNT). Globally, 939 patients received induction with four cycles of cisplatin–pemetrexed. After induction, 539 stable or responding patients received pemetrexed or placebo as maintenance [33]. Median PFS from randomization (the primary end-point) was 4.1 months in the pemetrexed arm and 2.8 months in the placebo arm (HR = 0.62). Discontinuation due to unacceptable toxicity occurred in 5% of the patients receiving pemetrexed. The final OS analysis resulted in a statistically significant benefit using pemetrexed compared with placebo (13.9 vs 11.1 months; HR = 0.78) [34].

In the open-label, randomized Phase III AVAPERL trial, 376 patients treated with a cisplatin–pemetrexed–bevacizumab combination in first-line received maintenance with pemetrexed–bevacizumab or with bevacizumab alone [35]. The primary end-point, PFS, was superior in the combination arm (10.2 vs 6.6 months; HR = 0.50; $p < 0.001$) compared to bevacizumab alone. Currently, although median OS for the bevacizumab arm has been established (15.7 months), median OS for the combination arm has not yet been reached; therefore, final OS data are not currently available.

Despite these results, some concern has been raised as the trial did not include an arm receiving pemetrexed alone as maintenance and thus the role of each single agent (pemetrexed and bevacizumab) and the potential advantage of the combination over pemetrexed alone could not be assessed [32]. In a non-randomized, Phase II trial, 50 patients received carboplatin–pemetrexed–bevacizumab for first-line treatment, followed by maintenance with pemetrexed–bevacizumab. Favorable tolerability and a relatively long survival were observed [36]. Following these encouraging results, a randomized, Phase III clinical trial (POINTBREAK) was conducted; in this trial, a schedule including carboplatin–pemetrexed–bevacizumab followed by maintenance with pemetrexed–bevacizumab was compared with a schedule including carboplatin–paclitaxel–bevacizumab followed by maintenance with bevacizumab [37]. Data from this trial were presented at the 2012 ASCO Multidisciplinary Symposium in Thoracic Oncology [38]: the combination including pemetrexed showed improved PFS (6 vs 5.6 months; HR = 0.83; $p = 0.012$), but the primary end-point of superior OS was not met (12.6 vs 13.4 months; HR = 1.0; $p = 0.949$). Because oral vinorelbine combined with cisplatin is one of the standard first-line treatments for NSCLC and because vinorelbine has a higher efficacy in non-squamous NSCLC than in squamous NSCLC, a cisplatin–pemetrexed combination was compared with cisplatin–oral vinorelbine in a Phase II, randomized trial including 153 patients with NSCLC. Continuation maintenance with a single agent was proposed to patients achieving disease control after four cycles in each arm. Cisplatin–pemetrexed proved to be similar to cisplatin–oral vinorelbine in terms of RR (26 vs 24%) and disease control rate (DCR; 75 vs 78%) after four cycles. Final survival data showed similar efficacy for cisplatin–pemetrexed and cisplatin–oral vinorelbine in terms of PFS (4.2 vs 4.2 months) and OS (10.8 vs 10.6 months) [39].

Currently, pemetrexed is indicated as maintenance for non-squamous NSCLC patients, whose disease has not progressed after first-line treatment with platinum-based chemotherapy [2,40].

3.3 Second line

Advanced NSCLC inevitably progresses despite first-line treatment. Although objective response is difficult to achieve after first-line treatment, the employment of anti-neoplastic agents is rational because they improve survival and quality of life compared with best supportive care alone [15].

Pemetrexed has been evaluated in several second-line trials, as a single agent or in combination. After positive results in single-arm trials [41,42], pemetrexed was compared with docetaxel in a randomized, Phase III trial; the primary end-point was non-inferiority in terms of OS [43]. Docetaxel was chosen as a comparator because, in 2004, it was the only chemotherapeutic agent approved for second-line treatment for NSCLC. Globally, 571 patients were randomized. Median OS was similar between the two arms (8.3 months for pemetrexed vs 7.9 months for docetaxel; p = not significant); thus, the primary end-point (non-inferiority of pemetrexed) was met. Similarly, median PFS was equal in both arms (2.9 months). Overall, RRs were 9.1% for pemetrexed and 8.8% for docetaxel ($p = 0.105$). Hematologic toxicity was more prominent with docetaxel; in particular, patients receiving docetaxel had a higher incidence of grade 3 – 4 neutropenia (40.2 vs 5.3%; $p < 0.001$), including febrile neutropenia (12.7 vs 1.9%; $p < 0.001$); similarly, administration of granulocyte colony-stimulating factor (G-CSF) and hospitalization due to neutropenic fever were more frequent in the docetaxel arm. The incidences of anemia and thrombocytopenia were similar between the two arms (p = not significant). Non-hematologic toxicities were similar, with the exception of alopecia, which was less frequent with pemetrexed (6.4 vs 37.7%; $p < 0.001$). A subsequent risk–benefit analysis confirmed the more favorable safety profile of pemetrexed compared with docetaxel [44]. Data from this trial were later reviewed in a retrospective analysis designed to determine the impact of histology on treatment efficacy [45]. In the squamous cell subgroup, patients in the pemetrexed arm achieved a lower median OS than those in the docetaxel arm (6.2 vs 7.4 months; adjusted HR = 1.563; $p = 0.018$); by contrast, in the non-squamous cell subgroup, pemetrexed was superior to docetaxel in terms of OS (9.3 vs 8.0 months; adjusted HR = 0.778; $p = 0.048$). Following the results described above, pemetrexed was approved for previously treated non-squamous NSCLC [2].

The activity and toxicity of pemetrexed in second and subsequent lines of treatment were evaluated in a post-registration analysis including 160 patients receiving pemetrexed in standard clinical practice; RR (11.2%) and the toxicity profile were consistent with previous data, while median

OS (12 months) was better than previous reports in the literature [46].

Different dosing schedules have been compared to determine whether higher doses could be more effective. In a Phase III trial, 588 patients were randomized to receive pemetrexed at the doses of 500 mg/m^2 (Pem500) or 900 mg/m^2 (Pem900) every 3 weeks [47]. Pem500 was non-inferior to Pem900, both in terms of median PFS (2.6 vs 2.8 months; HR = 0.9681) and median OS (6.7 vs 6.9 months; HR = 1.0132). Both schedules were tolerated, but treatment with Pem900 led to more frequent adverse events. In a Phase II, randomized trial, previously treated NSCLC patients received pemetrexed at the dose of 500 mg/m^2 (P500) or 1000 mg/m^2 (P1000) [48]. P1000 and P500 showed no statistically significant differences in terms of RR (18.5% for P1000 vs 14.8% for P500; p = 0.5839); P500 was non-inferior to P1000 in terms of median PFS (3.0 vs 2.5 months; p = 0.7139) and median OS (16 vs 12.6 months; p = 0.1463). Both schedules were well tolerated, although P500 showed generally milder toxicity. Currently, available data support the use of pemetrexed at the dose of 500 mg/m^2 every 3 weeks.

Because pemetrexed has become one of the standard second-line treatments for NSCLC, several trials have been designed with the purpose of investigating the possible advantage of combining pemetrexed with other agents. Combinations of pemetrexed and cisplatin or carboplatin in previously treated NSCLC demonstrated favorable activity and tolerability in non-randomized, Phase II trials [49,50], while a non-randomized trial of pemetrexed plus oxaliplatin was interrupted early due to lack of activity [51]. Pemetrexed was administered alone or in combination with carboplatin in a randomized, Phase II trial (NVALT7) [52]. Median PFS was longer in the combination arm (4.2 vs 2.8 months; HR = 0.67; p = 0.005), while median OS was similar (8.0 vs 7.6 months; HR = 0.85; p = not significant). The same schedules were compared in another Phase II trial, which also included a pre-planned pooled analysis with NVALT7. The combination did not improve PFS (3.5 vs 3.6 months) or OS (8.8 vs 9.2 months). Pre-planned pooled analysis showed that carboplatin did not improve OS globally (HR = 0.90; p = 0.316); however, an OS advantage with the addition of carboplatin was observed in patients with squamous histology (adjusted HR = 0.58; p interaction test = 0.039) [53].

4. Pemetrexed in early stage NSCLC

Combinations including pemetrexed have also been evaluated as adjuvant treatment for early stage, resected NSCLC. In a non-randomized, Phase II trial, 45 resected stage IB-IIIA patients received adjuvant treatment with carboplatin AUC 5 and pemetrexed 500 mg/m^2 on days 1 and 14 for three cycles of 28 days; prophylactic G-CSF was administered. The majority of patients had stage IIIA disease (40.0%) and underwent lobectomy (71.1%); the most frequent histologic sub-type was adenocarcinoma (57.8%). Chemotherapy was well tolerated, and no patient discontinued treatment; median time to recurrence was 26 months, which is comparable with previously published data [54].

In a multicentre, open-label, Phase II trial, 118 patients with resected, stage IB/II NSCLC were randomized to receive cisplatin–pemetrexed or carboplatin–pemetrexed for four cycles [55]. The primary end-point was the feasibility of the regimens defined as compliance to four cycles with the planned doses without grade 3 – 4 toxicities; a regimen was considered feasible if the rate of feasible patients/total patients was > 60%. None of the regimens reached the primary end-point; however, the dose intensity and rate of patients completing the treatment were higher than what was reported in other adjuvant trials. Feasibility was higher in the cisplatin–pemetrexed arm.

In a multicentre, open-label, randomized, Phase II trial (TREAT), 132 resected NSCLC patients (stages IB, IIA, IIB, T3N1) were randomized to receive four cycles of standard cisplatin–vinorelbine or cisplatin–pemetrexed [56]. The primary objective of the trial was to compare the feasibility of the different regimens defined as the non-occurrence of grade 4 neutropenia, grade 4 thrombocytopenia, grade 3 – 4 febrile neutropenia, grade 3 – 4 non-hematologic toxicity or premature treatment withdrawal; secondary objectives were to determine mean dose delivery (defined as the planned dose actually administered), safety, time to relapse and OS. The feasibility rates were 95.5% for cisplatin–pemetrexed and 75.4% for cisplatin–vinorelbine (p = 0.001). Hematologic grade 3 – 4 adverse events were lower in the cisplatin–pemetrexed arm (10 vs 74%; p < 0.001), while non-hematologic toxicity was similar between the two arms (33% for cisplatin–pemetrexed vs 31% for cisplatin–vinorelbine; p = 0.798). Mean dose delivery was higher with cisplatin–pemetrexed (90%) than with cisplatin–vinorelbine (66% for cisplatin; 64% for vinorelbine).

5. Pemetrexed in locally advanced NSCLC

Locally advanced NSCLC is usually managed through combined modalities, including combinations of chemotherapy, radiotherapy, and surgery. Resectable, stage IIIA NSCLC can be treated with neoadjuvant chemotherapy, followed by surgical resection. Available data of pemetrexed in this setting are limited. In a non-randomized, Phase II clinical trial, a combination of cisplatin–pemetrexed was administered to suitable patients for three cycles before curative surgery; unfortunately, this trial was stopped early due to low enrolment [57]. Currently, pemetrexed is being studied in several ongoing clinical trials [58,59]. For example, in a trial of personalized neoadjuvant chemotherapy (CONTEST), pemetrexed is an agent of choice for non-squamous NSCLC with low expression of TS [60].

Patients affected by unresectable, locally advanced NSCLC can be treated with concurrent chemo-radiation or sequential chemotherapy and radiotherapy. Various regimens have been investigated, with the aim of identifying schedules that prove to be both effective and tolerated in association with radiotherapy. The combination of carboplatin (AUC = 5 – 6) and pemetrexed (500 mg/m^2) with concurrent radiation was tolerated and showed signs of activity in a Phase I trial [61]. In a non-randomized, Phase II trial, 21 unresectable, stage III patients received carboplatin AUC 5 plus pemetrexed 500 mg/m^2 with concurrent radiation for two cycles, followed by carboplatin plus pemetrexed for three consolidation cycles [62]. The treatment was well tolerated and active (median PFS = 12.0 months; overall RR = 85.7%); statistical analysis of PFS and RR showed a trend favoring adenocarcinoma histology. In an open-label, randomized, Phase II trial, 98 patients with inoperable stage III NSCLC received pemetrexed (500 mg/m^2) plus carboplatin (AUC 5) or pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) for three cycles; both schedules were administered with concurrent radiation (64 – 68 Gy; 2 Gy/day, 5 days/week for 45 days) and were followed by three consolidation cycles [63]. Although the small size of the trial may limit possible conclusions, this study suggests an OS and TTP advantage in the cisplatin–pemetrexed arm. Both schedules were well tolerated.

Currently, in a randomized, Phase III trial, 600 stage III inoperable, non-squamous NSCLC patients are being randomized to receive cisplatin–pemetrexed with concurrent radiation followed by consolidation pemetrexed or cisplatin–etoposide and concurrent radiation followed by a consolidation cytotoxic agent of choice. The primary outcome is represented by survival [64]. As cisplatin–etoposide is a current standard in this setting, should this trial achieve positive results, cisplatin–pemetrexed could represent a promising alternative.

6. Pemetrexed in elderly and in unfit patients

Elderly patients (≥ 70 years) represent a particular population, and many clinicians avoid first-line chemotherapy due to tolerability concerns. In a randomized, Phase II trial, elderly patients received pemetrexed alone (500 mg/m^2 for eight cycles) or a sequence of pemetrexed (500 mg/m^2 for two cycles) followed by gemcitabine (1200 mg/m^2 on days 1 and 8 for two cycles), for a total of eight cycles. Both schedules showed moderate activity and a favorable tolerability [65]. Recently, data from elderly patients with PS 0 – 1 receiving cisplatin–pemetrexed as a first-line treatment or pemetrexed as a maintenance treatment in two previously reported trials [22,33] were analyzed: in both studies, adjusted HR favored pemetrexed and was similar between older and younger patients; similarly, delivered dose and treatment-related toxicities were similar between age sub-groups [66]. Due to the renal safety of carboplatin compared with cisplatin, 62 elderly patients received carboplatin–pemetrexed in a non-randomized, Phase II trial. The combination was active (RR = 28.6%; stable disease rate = 42.9%) and the tolerability was acceptable [67]. In a dose-escalating study, 17 patients with a median age of 78 years (ranging from 75 to 83) received pemetrexed (500 mg/m^2) plus carboplatin (AUC 4, 5, or 6). After four cycles of induction chemotherapy, patients achieving disease control received maintenance with pemetrexed [68]. The combination resulted generally well tolerated and effective (overall RR: 47.1%). Maintenance with pemetrexed was administered to ten patients, and was well tolerated.

The first-line treatment for unfit patients, with PS = 2 of any age, ranges from best supportive care to platinum-based combination. In a randomized, Phase III trial, 217 PS = 2 patients with adequate organ function received single-agent pemetrexed or carboplatin–pemetrexed. The combination achieved a better RR (24% vs 10%; p = 0.019), a longer median PFS (5.9 vs 3.0 months; HR = 0.46) and a longer median OS (9.1 vs 5.6 months; HR = 0.57). Toxicity was acceptable in both arms, with an increased incidence of hematologic adverse events in the combination arm [69].

7. Economic evaluation

Pemetrexed is a costly drug that can be administered for relatively long periods; therefore, expense is a high priority issue. Cisplatin–pemetrexed was indirectly compared with cisplatin–gemcitabine–bevacizumab in several cost-effectiveness analyses. In an Italian analysis, bevacizumab-based therapy resulted more cost-effective than pemetrexed [70]. In a similar analysis conducted in Korea and Taiwan, the combination including bevacizumab was more costly than the cisplatin–pemetrexed doublet, although it was associated with increased survival [71]. In contrast, in a Russian analysis, cisplatin–pemetrexed resulted in cost-saving and showed equal survival and inferior toxicity compared with cisplatin–gemcitabine–bevacizumab [72].

8. Conclusion

Pemetrexed is an antimetabolite employed in non-squamous NSCLC. It exerts its activity by inhibiting DHFR, GARFT, AICART and TS, consequently, halting the synthesis of DNA and RNA. The pharmacologic activity of this drug is correlated with the expression of TS. For this reason, histologic sub-types expressing lower levels of TS, such as adenocarcinoma, are more sensitive to pemetrexed; squamous cell carcinoma of the lung expresses high levels of TS, and this finding is likely related to the reduced action of pemetrexed reported in this histologic sub-group.

Currently, pemetrexed is registered in combination with cisplatin or carboplatin as a first-line treatment for metastatic non-squamous NSCLC, as this combination was more effective than a standard schedule (cisplatin–gemcitabine) in terms of PFS and OS. The administration of pemetrexed alone as a maintenance therapy after induction chemotherapy is

associated with improvement in terms of PFS and OS and is a suitable option after first-line treatment for selected patients. Pemetrexed is also registered as a single agent as a second-line treatment, and it represents a valid alternative for patients who have not received the drug in first line [73]. Currently, pemetrexed is not registered as adjuvant treatment in resected lung cancer, nor is it employed in combination with thoracic radiation therapy in locally advanced disease, although further studies are being conducted.

9. Expert opinion

After its introduction into clinical practice, pemetrexed has become a standard for the treatment of non-squamous NSCLC. Since it is registered in different lines for advanced disease, specifically first-line, second-line, and maintenance, pemetrexed has a wide spectrum of employment. Its favorable safety profile, reported in different studies, has been widely confirmed in post-registration experiences; additionally, the good subjective tolerance observed (low emetic potential, low incidence of alopecia, etc.) makes it an appealing option for clinicians and patients alike.

Since the advantage in terms of efficacy of pemetrexed over its comparators was generally related to the presence of non-squamous histology, its employment in clinical practice and in further clinical trials should be limited, as a general rule, to patients affected by non-squamous NSCLC.

In a meta-analysis published in 2012, Li and colleagues evaluated a selection of clinical trials in which platinum-based combinations including pemetrexed were compared with platinum-based combinations including other third-generation agents for first-line treatment. A consistent survival advantage with pemetrexed, especially in non-squamous NSCLC (which represented the majority of the patients), was observed [74]. This meta-analysis also included a randomized, Phase II trial including three treatment arms: carboplatin–pemetrexed, carboplatin–pemetrexed–enzastaurin and carboplatin–docetaxel [75]; because enzastaurin did not produce a clinical benefit and the carboplatin–pemetrexed and carboplatin–docetaxel arms were available for comparison, this trial was considered suitable for the meta-analysis.

A meta-analysis of five trials (three first-line trials, one second-line trial, one maintenance trial) confirmed that pemetrexed, compared with alternative treatments or placebo, is consistently associated with a significant OS improvement in non-squamous histology (HR = 0.82; I^2 = 12%) but not in squamous histology (HR = 1.19%) [76].

Recently, five trials comparing pemetrexed alone and in combination with other agents for second-line treatment [52,77-80] were evaluated in a meta-analysis conducted by Qi *et al.*, including 1186 patients, globally [81]. The pooled hazard ratio for OS did not show significant differences between pemetrexed-based doublets and pemetrexed alone (pooled HR = 0.89; p = 0.129), while a significant benefit in terms of PFS was observed in the doublet arms (pooled HR = 0.82; p = 0.007); the pooled odds ratio (OR) for overall RR showed improvement with the doublet arms (OR 2.39; p = 0.000). Possible biases that can increase the heterogeneity of this meta-analysis include the employment of different combination agents and the lack of blinding in three of the five selected trials.

The histology-driven specificity of pemetrexed has undergone further evaluations, and the expression of TS, evaluated through a semi-quantitative histologic score, was higher in the squamous sub-type than in adenocarcinoma. Moreover, there is an association between differential TS expression and the efficacy of pemetrexed in non-squamous histology, as patients affected by lung adenocarcinoma with low TS expression achieved longer median PFS and OS than patients whose adenocarcinoma had high TS expression [82,83]. These data imply that the effectiveness of pemetrexed is related more to the expression of TS than to the histology; further, prospective studies of pemetrexed on the basis of the expression of TS, rather than histologic sub-type, could help define the actual specter of action of this drug. Should a suitable molecular predictor of efficacy be validated for pemetrexed, it could be employed to select the patients who are more likely to benefit from this drug, irrespective of histologic sub-type. In addition, because physicians have different options for first-line treatment for non-squamous NSCLC, such as doublets including cisplatin (or carboplatin) and pemetrexed or combinations including chemotherapy plus bevacizumab and because pemetrexed is available for both first and second line, identifying the most beneficial treatment strategy in each case is crucial [84]. Novel predictors of response could help achieve this task: through a tailored approach, some selected patients could receive pemetrexed immediately, while other patients may be treated with different regimens, eventually reserving pemetrexed for second-line treatment.

After first-line treatment with pemetrexed, physicians evaluate the option of using maintenance treatment. The administration of pemetrexed after induction chemotherapy prolongs survival at the expense of continuously exposing the patient to drug-related toxicity. Several parameters should be evaluated when considering maintenance, including objective response, global conditions, organ function, and adverse events reported during treatment; the patient's preference should be taken into consideration. Some patients may benefit from prolonged treatment, while, for other patients, a "treatment holiday" could be the best option. Unfortunately, at the moment, there is no validated specific clinical feature or bio-marker able to predict survival benefits with maintenance over interruption in a single patient; such predictors could help oncologists and patients while discussing the option of maintenance with pemetrexed. Although Phase III trials of pemetrexed in the adjuvant setting are lacking, NCCN guidelines include it as an option in combination with cisplatin [15]; available data suggest a more favorable safety profile compared with other combinations. Similarly, the favorable tolerability of pemetrexed could make it a promising option in the neoadjuvant setting, where patients are planned to undergo surgery after chemotherapy.

The use of pemetrexed in concurrent chemo-radiation regimens needs to be confirmed with further data; however, cisplatin–pemetrexed is the only combination, with cisplatin–etoposide, that can be administered with radiation without dose reductions.

Declaration of interest

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