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Expert Opinion

Pemetrexed in advanced non-small-cell lung cancer

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Importance of the field: Current therapeutic options for advanced non-small-cell lung cancer (NSCLC) yield relatively modest improvements in survival leading to an ongoing search for new active treatment agents. In the past decade, pemetrexed has had an increasingly established role in the treatment of advanced NSCLC in both first- and second-line settings.

Areas covered in this review: Currently available published data on mechanism of action, pharmacokinetics, safety and efficacy of pemetrexed in the treatment of advanced NSCLC are described. Peer-reviewed publications on the development of pemetrexed and its clinical use in NSCLC were reviewed (1995 – 2009).

What the reader will gain: Pemetrexed is a multitargeted antifolate cytotoxic agent. Key Phase II and Phase III trials are described that have shown pemetrexed's efficacy in both the first- and second-line treatment of advanced NSCLC. The efficacy of pemetrexed seems to vary between squamous and nonsquamous histologies. Possible reasons for this are explored. Additionally, the potential role of pemetrexed in maintenance therapy is discussed.

Take home message: Pemetrexed is an effective treatment for advanced NSCLC, with an overall favorable toxicity profile. There is growing evidence that, in patients treated with pemetrexed, nonsquamous tumors have improved outcomes compared to squamous cell tumors. Pemetrexed may also have a role in maintenance therapy for NSCLC.

Keywords: antimetabolite, first-line therapy, non-small-cell lung cancer, pemetrexed, second-line therapy

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1. Introduction

Lung cancer is the leading cause of cancer death globally and in the USA [1]. In the USA, there will be an estimated 219,000 new cases of lung cancer and 159,000 lung cancer deaths in 2009 [2]. The overall 5-year survival rate for lung cancer is 15% [3]. Non-small-cell lung cancer (NSCLC) comprises more than 80% of lung cancer [4]. For the ~ 50% of patients who present with metastatic disease, or stage III disease that is not amenable to curative therapy, palliative chemotherapy is the mainstay of treatment. A meta-analysis of 16 randomized trials demonstrated survival improvements of 6 – 10 weeks in those who receive chemotherapy compared with supportive care [5]. Current guidelines recommend first-line therapy with two-agent, platinum-based cytotoxic therapy in patients with good performance status [6], based on studies that have shown similar efficacy amongst varying regimens with general overall response rates of 17 – 32%, median time to progression of 3 – 5 months and median survival of 8 – 11 months [7-9]. While chemotherapy has also been shown to effect a survival and quality of life advantage in the second line, the gains are similarly modest [10].

An increased understanding of the molecular basis of lung cancer holds great promise for the advent of 'personalized' management for individual patients based

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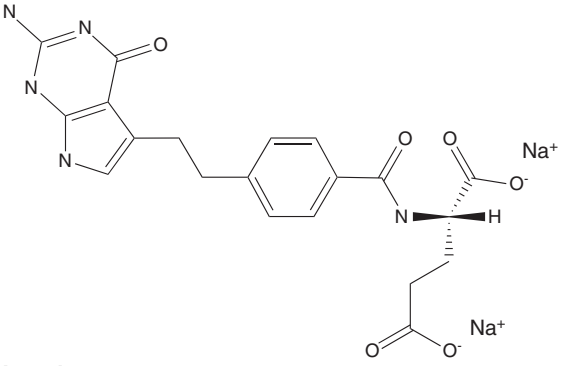
Box 1. Drug summary.

Drug name	Pemetrexed disodium
Phase	Launched
Indications	Non-small-cell lung cancer
Pharmacology description	Thymidylate synthase inhibitor Dihydrofolate reductase inhibitor Phosphoribosylglycinamide formyltransferase inhibitor
Route of administration	Parenteral, i.v.
Chemical structure	
Pivotal trial(s)	[40,59]

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on their specific tumor characteristics. For example, tumor expression of genes such as RRM1, the gene that encodes the regulatory subunit of ribonucleotide reductase, and the excision repair cross-complementation group 1 gene (ERCC1), have predictive importance, and molecular markers such as epidermal growth factor receptor (EGFR) are now treatment targets [11,12]. Given these discoveries and the lack of highly effective treatments so far, multiple new agents are being tested in the treatment of NSCLC in both first- and second-line settings. Pemetrexed (**Box 1**), a relatively new treatment with a particular role in the treatment of nonsquamous tumors, is the subject of this review.

2. Introduction to pemetrexed

2.1 Mechanism of action

Folate is an essential element for cell division by serving as a coenzyme in multiple metabolic pathways that lead to synthesis of DNA. These paths accept or donate one-carbon units in what is collectively referred to as 'one-carbon metabolism' [13]. Reactions that require folate are essential for purine and pyrimidine base synthesis, upon which cancer cells are dependent for rapid proliferation [14]. The use of antifolates in cancer treatment traces back decades to the development and use of the folate analogs aminopterin and, subsequently, methotrexate [15,16].

More recently in the 1990s, newer antifolates were developed [17]. Pemetrexed is a folate analog that competes with reduced folate for binding sites, thereby significantly disrupting the activity of multiple folate-requiring enzymes: dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltansferase (GARFT) and thymidylate synthase (TS) [18-20]. DHFR, which is the primary target of methotrexate, is required for the synthesis of both purines and pyrimidines. Thymidylate synthase, which is also the target of the antimetabolite chemotherapeutic agent 5-fluorouracil, catalyses the transformation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), which then allows for thymidine synthesis. Thymidylate synthase seems to be the primary target of pemetrexed. Glycinamide ribonucleotide formyltansferase is required for synthesis of purines and was the original target of the investigators developing the newer antifolates (see **Figure 1**). Additionally, recent cell culture experiments have indicated that another folate-dependent enzyme in purine synthesis, aminoimidazolecarboxamide ribonucleotide formyltransferase (AICART), is a secondary target for pemetrexed. In tumor cells where AICART is inhibited, there is accumulation of substrates that cause subsequent inhibition of the mammalian target of rapamycin (mTOR), thereby impeding protein synthesis and cell growth [21]. The varying enzymatic profiles of different tumor lines may have implications for clinical efficacy differences that have been seen based on histology, as will be discussed later.

Pemetrexed is taken into the cell by the reduced folate carrier and then undergoes polyglutamation by folypolyglutamate synthase (FPGS). In *in vitro* studies, compared with the parent drug, the polyglutamated form of pemetrexed had a 100-fold and 140-fold increase in its ability to inhibit

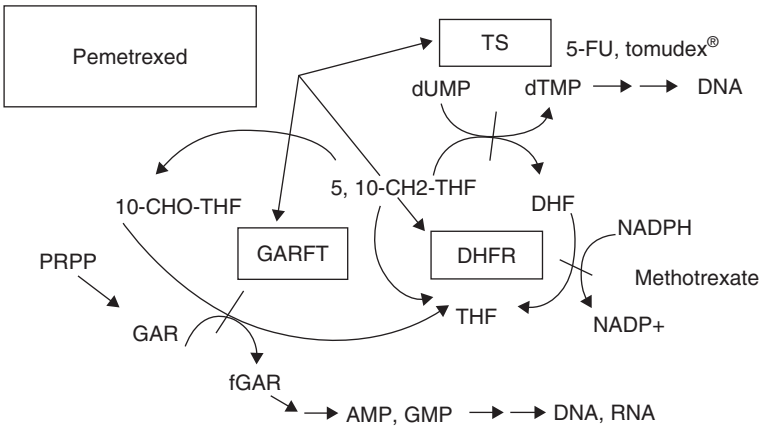

Figure 1. Pemetrexed mechanism of action.
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thymidylate synthase and GARFT, respectively [19]. The polyglutamation contributes to increased retention of the drug in cells allowing for prolonged suppression of the target enzymes [22].

2.2 Pharmacokinetics

Initial, single-agent, Phase I dose-escalation studies of pemetrexed determined that a dose of 600 mg/m^2 administered over 10 min every 21 days was optimal for Phase II studies. Neutropenia, thrombocytopenia and cumulative fatigue were the dose-limiting toxicities in the study by Rinaldi *et al.* [23-25]. Neutropenia was a dose-limiting toxicity in the two earlier trials as well. Patients who had a creatinine clearance of < 45 ml/min using the modified Cockcroft and Gault formula were excluded [22]. At the 600-mg/m^2 dose, the population pharmacokinetics had a harmonic mean half-life of 3.08 h, an area under the curve (AUC) of 266 μg/h/ml, a mean clearance of 40 ml/min/m^2 and a volume of distribution of 7.0 l/m^2. The primary route of elimination of the drug was renal excretion with 78% of the drug excreted unchanged in the urine at 24 h.

Importantly, the earliest trials were done without supplementation of folate or vitamin B12. As will be discussed in more detail below, subsequent Phase II trials demonstrated that vitamin supplementation reduced the myelosuppression of pemetrexed and therefore supplementation became standard. Subsequently, additional Phase I trials were done with vitamin supplementation. These studies did not show a significant change in the pharmacokinetic parameters from the Rinaldi study but did establish higher maximum tolerated doses [26,27]. However, as will be discussed further in the next section, subsequent studies at higher doses did not yield improved outcomes.

2.3 Safety and tolerability

The importance of vitamin B12 and folate supplementation emerged after early studies of pemetrexed were marked by significant grade 3 or 4 myelosuppression [28-32]. To evaluate the etiology of this toxicity profile, a multivariate analysis was conducted on 246 patients treated with pemetrexed between 1995 and 1999 [33]. Based on a hypothesis generated by studies in lometrexol that had shown a connection between folate intake and toxicity, the authors demonstrated that pretreatment plasma homocysteine and methylmalonic acid concentrations significantly predicted severe hematological toxicity as well as infection, mucositis, diarrhea and death in patients taking pemetrexed. Thus, as noted above, since December 1999, folic acid and vitamin B12 supplementation have been included in all pemetrexed trials. Two trials evaluating pemetrexed in malignant pleural mesothelioma that incorporated supplementation midway confirmed the significant reduction in toxicity in the patients who received vitamins compared with those who did not receive vitamins, without diminished efficacy [34,35].

Given that nonsteroidal anti-inflammatory drugs (NSAIDs) compete with the antifolate methotrexate, trials of pemetrexed often excluded patients requiring chronic use of aspirin or NSAIDs. Therefore Sweeney *et al.* did a drug-interaction study, demonstrating that pemetrexed at 500 mg/m^2 when given with vitamin supplementation did not require dosage adjustment when used with moderate doses of aspirin (1.3 g/day) in patients with creatinine clearance of ≥ 60 ml/min or with moderate doses of ibuprofen (400 mg every 6 h) in patients with creatinine clearance ≥ 80 ml/min [36]. The authors cautioned against using NSAIDs and pemetrexed concurrently in patients with renal impairment.

A more recent Phase I trial was performed with vitamin supplementation to determine the safety and pharmacokinetics in patients with normal or impaired renal function [37]. The study showed substantial reduction in drug clearance for patients with diminished renal function; however, the increase in systemic exposure was not associated with an increase in drug-related dose-limiting toxicities for vitamin-supplemented patients with glomerular filtration rates (GFR) of ≥ 40 ml/min receiving the 500-mg/m^2 dose, though

the authors note that calculated creatinine clearance may not exactly correlate with GFR [37].

Rash was also frequently reported in early trials, but improved significantly with routine administration of prophylactic corticosteroid. There has been a case report of pemetrexed associated typhlitis [38].

3. Clinical efficacy and trial data

3.1 Pemetrexed as second-line therapy

Based on the promising activity of pemetrexed, albeit without vitamin supplementation, initial Phase II trials were conducted at a dose of 600 mg/m^2. However, owing to excess toxicity in early Phase II trials in both NSCLC and colorectal cancer, the starting dose was reduced to 500 mg/m^2 [28,39]. Smit *et al.* conducted a Phase II trial of pemetrexed 500 mg/m^2 in 81 pretreated patients without vitamin supplementation broken into cohorts based on whether or not previous treatment had contained platinum [32]. The overall response rate was 8.9% with a median time to progression (TTP) of 2 months. The response rate was 4.5% in patients who had received previous platinum versus 14.1% in patients who had received non-platinum regimens, but this was not statistically significant. These results led to a Phase III trial by Hanna *et al.* in previously treated patients [40]. Patients were randomized to receive pemetrexed 500 mg/m^2 (n = 283) or docetaxel 75 mg/m^2 (n = 288) every 3 weeks [40]. The response rates were similar between the pemetrexed and docetaxel groups at 9.1 and 8.8% respectively. The median progression-free survival (PFS) and 1-year survival were identical for both groups at 2.9 months and 29.7%. Overall survival, the primary end point, was similar for the two arms: 8.3 and 7.9 months. Noninferiority of pemetrexed could not be established based on the prespecified upper bound of the 95% confidence interval to be less than 1.11 for the hazard ratio (HR = 0.99; 95% CI 0.82 – 1.2; noninferiority: p = 0.226). However, pemetrexed met another prespecified efficacy requirement. Using the percentage retention method, it retained the survival benefit of docetaxel when the latter was compared with best supportive care in a different trial [41]. While there was no significant difference between the two arms in reported changes in quality of life, the toxicity analysis demonstrated significantly fewer adverse effects with pemetrexed compared with docetaxel, including grade 3 or 4 neutropenia (5.3 vs 40.2%), febrile neutropenia (1.9 vs 12.7%), hospitalizations for neutropenic fever (1.5 vs 13.4%) and use of granulocyte colony-stimulating factor support (2.6 vs 19.2%). This trial led to the approval of pemetrexed as monotherapy in the second-line setting.

Weiss *et al.* retrospectively examined whether the elderly patients (age ≥ 70 years) who comprised 15% of the above study population differed in outcomes compared with younger patients [42]. There were no significant differences in efficacy (response rate, TTP, overall survival) or toxicity between elderly and younger patients. Both elderly and younger patients experienced a more tolerable toxicity profile with pemetrexed compared with docetaxel. Postregistration studies have shown similar degrees of efficacy and tolerability. Bearz *et al.* reported a response rate of 11.2%, a median PFS of 3.0 months, and a median overall survival of 12 months in 160 advanced NSCLC patients treated in Italy [43]. Toxicity was mild with less than 2% of patients experiencing any grade 3 or 4 toxicity. Lee *et al.* performed a study in a Korean population (n = 81) and reported an overall response rate of 5.1%, median time to progression of 3.1 months and an overall survival of 7.8 months [44].

After the advent of standard vitamin supplementation, Phase I trials indicated that doses greater than 500 mg/m^2 could be tolerated [26]. Ohe *et al.* carried out a randomized Phase II comparing doses of 500 and 1000 mg/m^2 in 225 previously treated Japanese patients [45]. Comparing the 500-mg/m^2 arm with 1000-mg/m^2, the response rate was 18.5 versus 14.8% and the median survival time was 16.0 versus 12.6 months respectively. The safety profile of the 500-mg/m^2 arm showed generally milder side effects. That 500 mg/m^2 should remain the standard dose of pemetrexed was supported by a subsequent Phase III trial published in 2008 comparing 500 mg/m^2 with 900 mg/m^2 involving 588 patients [46]. Accrual was terminated early after an interim analysis indicated a low probability of improved survival and a numerically increased toxicity in the higher dose arm.

Recently, a Phase II trial exploring the role of combination chemotherapy with pemetrexed in the second-line setting following first-line platinum therapy was published [47]. Two hundred and forty patients were randomized to receive either pemetrexed 500 mg/m^2 or pemetrexed plus carboplatin with an AUC of 5. The primary end point was PFS. Median PFS was significantly longer in the combination arm: 4.2 months compared with 2.8 months for pemetrexed alone. There was slightly more grade 3 and 4 hematological toxicity for the combination arm compared with pemetrexed alone with differences in neutropenia (21 vs 7%) and thrombocytopenia (15 vs 2%) being statistically significant. Given an increasing interest in the role of histology in predicting response to pemetrexed (which will be discussed further below), this study also sought to explore genetic polymorphisms that might correlate with outcome in patients treated with pemetrexed.

Notable trials of pemetrexed in the second line are summarized in **Table 1**.

3.2 Pemetrexed as first-line therapy

Two studies, done without vitamin supplementation, established the role of pemetrexed as an active single agent in the first-line treatment of NSCLC. Rusthoven *et al.* enrolled 33 total patients and used the 500-mg/m^2 dose following treatment of the first three patients at 600 mg/m^2 [28]. There was a 23.3% overall response rate with a median TTP of 3.8 months and median survival of 9.2 months. Thirty-nine per cent of patients had grade 3 or 4 neutropenia, 12% had febrile neutropenia, 39% had grade 3 rash, and 27%

Table 1. Notable trials of pemetrexed in second-line treatment of advanced NSCLC.

Author	Treatment	No. of patients	RR (%)	PFS (months)	OS (months)	Notable toxicities
Phase III						
Hanna [40]	P500	283	9.1	2.9	8.3	G3/4 Ntp = 5.3%
	vs					
	D75	288	8.8	2.9	7.9	G3/4 Ntp = 40.2%
Cullen [46]	P500	295	7.1	2.6	6.7	G3/4 Ntp = 2.1%
	vs					
	P900	293	4.3	2.8	6.9	G3/4 Ntp = 4.2%
Phase II						
Smit [32]	P500	81	8.9	TTP: 2	5.7	G3/4 Ntp = 39%; G3/4 Thrmbcyt = 15%
Ohe [45]	Randomized					
	P500	114	18.5	3.0	16.0	G3/4 Ntp = 21%
	vs					
	P1000	111	14.8	2.5	12.6	G3/4 Ntp = 24%
Smit [47]	Randomized					
	P500	121	6	2.8	7.6	G3/4 Ntp = 7%; G3/4 Thrmbcyt = 2%
	vs					
	Cb5 + P500	119	17	4.2	8.0	G3/4 Ntp = 21%; G3/4 Thrmbcyt = 15%

All schedules were given every 3 weeks. Treatment dosages are in mg/m^2 except as indicated.
Cb5: Carboplatin area under the curve of 5; Doc: Docetaxel; G3/G4: Common Terminology Criteria for Adverse Events Grade 3 and Grade 4 toxicities; Ntp: Neutropenia; OS: Median overall survival; P: Pemetrexed; PFS: Median progression-free survival; RR: response rate; TTP: Median time to progression; Thrmbcyt: Thrombocytopenia.

had grade 3 lethargy. A retrospective analysis demonstrated that prophylactic steroids reduced the frequency of rash (47.5% in patients without prophylaxis vs 12% of patients who received steroids). Another single-agent study used 600 mg/m^2 in 59 patients and showed a 15.8% response rate, median TTP of 4.4 months, median overall survival of 7.2 months and a 1-year survival rate of 32% [31]. Significant toxicities included grade 3 or 4 neutropenia (42% of patients), and reversible grade 3 or 4 liver enzymes elevations (24% of patients). Grade 3 or 4 cutaneous toxicity was seen in 31% of patients but was again noted to improve with administration of steroids in subsequent cycles.

Based on these promising efficacy results, additional studies sought to use pemetrexed in combination with other cytotoxic therapies in the first line. Two Phase II studies, again without vitamin supplementation, combined pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 every 3 weeks. Manegold enrolled 36 patients and showed a response rate of 39% with a median TTP of 6.3 months and median survival time of 10.9 months [29]. Fifty-nine per cent of patients developed grade 3 or 4 neutropenia and 17% developed grade 3 or 4 thrombocytopenia. Shepherd *et al.* enrolled 31 patients showing a 45% response rate and a median survival of 8.9 months [30]. Grade 3 or 4 neutropenia developed in 37% of patients. (Of note, all subsequent trials discussed in this review incorporated vitamin supplementation.)

Other platinum-based combinations have also been explored to see if the apparent efficacy of combination cisplatin therapy could be achieved with other, potentially less toxic, platinum agents. Zinner *et al.* administered pemetrexed 500 mg/m^2 in combination with carboplatin AUC 6 every 3 weeks to 50 patients. Overall response rate was 24% with a median TTP of 5.4 months and median survival of 13.5 months [48]. Grade 3 or 4 neutropenia developed in 26% of patients. A randomized Phase II trial compared pemetrexed 500 mg/m^2 plus oxaliplatin 120 mg/m^2 (PemOx) to pemetrexed 500 mg/m^2 plus carboplatin AUC of 6 (PemCb), each given every 3 weeks [49]. Forty-one and thirty-nine patients were randomized to each arm respectively. Results were similar between the PemOx and PemCb arms in objective response rate (26.8 vs 31.6%, respectively), median TTP (5.5 vs 5.7 months, respectively) and median overall survival (10.5 months for each arm). Of note, patient compliance with quality-of-life assessment questionnaires was quite high in this study. Approximately 60% of patients in each arm documented either stable or improved symptom metrics. Neutropenia was the most prevalent toxicity with grade 3 or 4 toxicity occurring in 7.3% of PemOx patients and 25.7% of PemCb patients. Neurotoxicity was generally mild with only one patient experiencing more than grade 2 neuropathy in the PemOx group.

Other trials combined pemetrexed with nonplatinum cytotoxic therapy. Stathopoulos did a Phase I/II trial combining pemetrexed with paclitaxel [50]. Based on the Phase I portion of the study, pemetrexed 500 mg/m^2 plus paclitaxel 175 mg/m^2 was administered to 48 patients every 3 weeks.

The overall response rate was 39.6% with a median TTP of 7 months and a median survival of 14 months. Toxicity was notably mild, with 8% of patients experiencing grade 3 or 4 neutropenia and no other significant grade 3 or 4 toxicities. Vinorelbine was combined with pemetrexed in a Phase I/II study by Clarke *et al.* [51]. Based on the Phase I results, 37 patients were enrolled in the Phase II study and given 500 mg/m^2 of pemetrexed on day 1 and 30 mg/m^2 of vinorelbine on day 1 and 8 every 3 weeks. The response rate was 38%, median PFS 4.2 months and the overall median survival 7.9 months. Toxicity data were notable for the development of grade 3 or 4 neutropenia in 65% of patients, grade 3 or 4 febrile neutropenia in 11% of patients and grade 3 or 4 fatigue in 27% of patients. The authors noted that, because of the modest overall survival figure, additional Phase III studies would not be pursued with this combination.

Given gemcitabine's activity in NSCLC, a series of trials sought to combine it with pemetrexed and to compare it with platinum-based regimens. Monnerat *et al.* published a Phase II trial using day 1 gemcitabine 1250 mg/m^2 and then day 8 gemcitabine followed 90 min later by pemetrexed 500 mg/m^2 in 60 patients on a 3-week cycle [52]. (Vitamin supplementation was started midway through this trial.) The overall response rate was 15.5% with a median PFS of 5.0 months. The majority of patients also reported improvement or stability in their Lung Cancer Symptom Scale assessments in anorexia, fatigue, cough, dyspnea, hemoptysis and pain. Grade 3 or 4 neutropenia developed in 62% of patients, with 15% having grade 3 or 4 febrile neutropenia. Grade 3 or 4 fatigue occurred in 23% of patients. Ma *et al.* conducted a Phase II trial that examined three different schedules of gemcitabine combined with pemetrexed [53]. One hundred and fifty-two patients were randomized to receive day 1 pemetrexed 500 mg/m^2 followed by gemcitabine 1250 mg/m^2 and then day 8 gemcitabine; or day 1 gemcitabine followed by pemetrexed and day 8 gemcitabine; or day 1 gemcitabine and day 8 pemetrexed followed by gemcitabine. The second arm was closed after an interim analysis showed inferior efficacy. There was a rate of 64% grade 3 or 4 neutropenia with 5% of patients having grade 3 or 4 febrile neutropenia and 8.5% grade 3 or 4 thrombocytopenia in the first arm compared with 69%, 5 and 19%, respectively, in the third arm. The authors concluded that the first schedule demonstrated equivalent efficacy, with a median TTP of 11.4 months, but with a lower toxicity profile compared with the third arm.

Based on pharmacokinetic data that indicated that the 90-min delay between pemetrexed and gemcitabine was not required, two trials sought to determine whether the gemcitabine and pemetrexed could be administered in a more rapid sequence. Treat and colleagues administered gemcitabine 1250 mg/m^2 on days 1 and 8, with immediately sequenced pemetrexed 500 mg/m^2 on day 1 every 3 weeks to 53 patients [54]. The overall response rate was 30.2%, median TTP 3.3 months and median survival 10.3 months. Grade 3 or 4 neutropenia was seen in 43% of patients; grade 3 or 4 febrile neutropenia occurred in 7.5% of patients; and grade 3 or 4 fatigue occurred in 11% of patients. West and colleagues did a similar study looking at rapid succession dosing [55]. Fifty-four patients were enrolled in a Phase II trial that administered gemcitabine 1250 mg/m^2 on days 1 and 8 with pemetrexed immediately following the day 8 gemcitabine dose. The response rate was 13%, median PFS 4.6 months and median overall survival 12.4 months. Grade 3 or 4 neutropenia occurred in 40% of patients; grade 3 or 4 febrile neutropenia occurred in 11% of patients; and grade 3 or 4 thrombocytopenia occurred in 11% of patients. Twenty-one per cent of patients experienced grade 3 or 4 fatigue. The results indicated that the more convenient dosing schedule did not significantly alter efficacy or toxicity. Additional studies looked at different schedule combinations of pemetrexed and gemcitabine, though no specific schedule or frequency of doses emerged as clearly superior [56-58].

Two large Phase III trials studying pemetrexed in the first-line setting have been published. Scagliotti *et al.* conducted a noninferiority study randomizing 1725 patients to compare day 1 cisplatin 75 mg/m^2 plus gemcitabine 1250 mg/m^2 on days 1 and 8 with a regimen of day 1 cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2, all given every 3 weeks for up to six cycles [59]. The primary end point was overall survival. Overall survival for patients in the cisplatin/pemetrexed group was noninferior compared with cisplatin/gemcitabine, with a median overall survival of 10.3 months for each arm (HR = 0.94; 95% CI 0.84 – 1.05). Survival rates for the cisplatin/pemetrexed arm at 12 and 24 months were 43.5 and 18.9% respectively, compared with 41.9 and 14.0% for the cisplatin/gemcitabine arm. Progression-free survival in the cisplatin/pemetrexed arm was also noninferior compared with the cisplatin/gemcitabine arm, with a time of 4.8 months and 5.1 months respectively. Grade 3 or 4 drug-related toxicities were significantly lower for cisplatin/pemetrexed compared with cisplatin/gemcitabine (neutropenia: 15 vs 27%; thrombocytopenia: 4 vs 13%; $p \leq 0.001$). Grade 3 or 4 nausea was significantly more common in the cisplatin/pemetrexed arm compared with cisplatin/gemcitabine (7.2 vs 3.9%; $p = 0.004$). Of note, this trial included a prespecified analysis of survival by histological subtype, the first such prospective analysis. The effect on survival of cisplatin/pemetrexed relative to cisplatin/gemcitabine was significantly different according to nonsquamous versus squamous histology, as will be discussed further in the next section. Factors that had a statistically significant prognostic impact on survival independent of treatment included: sex, race, performance status, disease stage and histology. The authors noted in their conclusions that the modest improvement in overall survival seen in this study compared with previous studies with platinum may reflect improvements in NSCLC staging, a relatively higher proportion of stage IIIB patients and the exclusion of patients with an ECOG performance status of 2.

Recently, Gronberg and colleagues in Norway published a Phase III trial that compared pemetrexed 500 mg/m^2 plus

carboplatin AUC 5 on day 1 with a regimen of days 1 and 8 gemcitabine 1000 mg/m^2 plus carboplatin AUC 5 on day 1, both given every 3 weeks for up to four cycles [60]. The primary end point was health-related quality of life (with a focus on global quality of life, nausea/vomiting, fatigue and dyspnea), with secondary end points of overall survival, safety and tolerability. Four hundred and forty-six patients were randomized. Of note, 22% of patients in the pemetrexed/carboplatin arm and 23% of patients in the gemcitabine/carboplatin arm had an ECOG performance status of 2. There was a high rate (87%) of completion of the quality-of-life questionnaires for this study. There was no significant difference found between the two arms in quality-of-life end points. There was no difference in median overall survival between the pemetrexed/carboplatin group versus the gemcitabine/carboplatin (7.0 vs 7.3 months, respectively) or in 1-year survival rate (34 vs 31%, respectively). Patients in the gemcitabine/carboplatin arm, compared with the pemetrexed/carboplatin arm, had significantly more grade 3 or 4 neutropenia (51 vs 40%; $p = 0.024$), grade 3 or 4 thrombocytopenia (56 vs 24%; $p < 0.001$), need for transfusions of red blood cells (43 vs 29%; $p = 0.003$) and platelets (9 vs 3%; $p = 0.007$). There was no significant difference in the frequency of any single grade 3 or 4 nonhematologic toxicity, but more patients on the gemcitabine/carboplatin arm had one or more grade 3 or 4 toxicities (28 vs 19% for pemetrexed/carboplatin; $p = 0.037$).

Notable trials of pemetrexed in the first line are summarized in **Table 2** and **3**.

4. Impact of histology

An intriguing aspect in the development of pemetrexed has been the role of histology in predicting efficacy. Historically, different histologies (adenocarcinoma, large cell carcinoma, squamous carcinoma) in NSCLC have not been considered predictive of response to treatment, though studies were seldom designed in a manner to allow subset analyses of this nature [61,62]. However, retrospective and subgroup analyses of pemetrexed trials suggested a differing response amongst patients with squamous versus nonsquamous histology. In their Phase II trial examining different doses of pemetrexed in the second line, Ohe *et al.* reported that the median survival time of patients with nonsquamous carcinoma was significantly longer compared with squamous cell carcinoma (16.0 vs 9.3 months; $p = 0.0026$) [45]. The trial was not designed for subgroup analyses but the results were provocative. Peterson and colleagues performed a retrospective analysis on the large Phase III trial conducted by Hanna *et al.,* to determine the impact of histology [63]. A treatment-by-histology interaction was statistically significant, demonstrating that patients with nonsquamous histology had higher survival compared with all others on trial. Docetaxel's efficacy, however, did not significantly differ between squamous and nonsquamous groups.

In the recent Phase II study combining gemcitabine and pemetrexed, West *et al.* noted modestly superior efficacy results for pemetrexed in nonsquamous patients compared with the squamous group with a median PFS of 5.4 versus 4.0 months respectively.

Given the interest in the role of histology, Scagliotti and colleagues designed their large Phase III trial to include a prespecified analysis of overall survival by histology, though the patients were not randomized by histology [59]. In the 847 patients with adenocarcinoma, there was significantly improved survival in the cisplatin/pemetrexed arm compared with the cisplatin/gemcitabine arm (12.6 vs 10.9 months, respectively; HR = 0.84; 95% CI 0.71 – 0.99; $p = 0.03$). However, in the 473 patients with squamous cell carcinoma the opposite trend was seen, with improved survival in the cisplatin/gemcitabine arm compared with the cisplatin/pemetrexed arm (10.8 vs 9.4 months, respectively; HR = 1.23; 95% CI 1.00 – 1.51; $p = 0.05$). To assess further the role of histology, Scagliotti *et al.* conducted a retrospective review of the interaction of histology and efficacy using data from this trial as well as from the earlier Phase III trial by Hanna *et al.* that looked at pemetrexed in the second line [40,64]. Cox proportional hazard models were used to test for covariate-adjusted treatment-by-histology interactions. Analysis showed that the treatment arms in both studies were well balanced for histology, though the Hanna study had some numerical imbalances in other prognostic factors across histologic subgroups, including gender, stage and performance status. The statistically adjusted results indicated that overall there was significant treatment-by-histology interaction for both overall survival and PFS. In the recent Phase III trial by Gronberg *et al.,* comparing gemcitabine/carboplatin with pemetrexed/carboplatin, a subgroup analysis did not find any association between survival and histology, though this was not a prespecified subgroup analysis [60]. Overall, the results led to a modification in the approval for pemetrexed, whereby its indications stipulate that it should be used in NSCLC of a histological subtype other than squamous cell. Results of selected studies that have analyzed the impact of histology are summarized in **Table 4**.

One of the proposed mechanisms to explain the varying efficacy by histological subtype is differences in the expression of thymidylate synthase (TS), which is the primary enzymatic target of pemetrexed, in different tumor histologies. While results have been at times inconsistent, higher levels of TS have been shown to predict poor clinical outcome in patients treated with 5-fluorouracil chemotherapy regimens in earlier studies [65]. In NSCLC, tumor cells with higher TS expression have higher proliferative activity [66], which may predict worse clinical outcome [67,68]. A study by Ceppi and colleagues demonstrated significantly higher levels of TS expression in squamous cell carcinoma than in adenocarcinoma [69]. Preclinical data have indicated a reduced activity of pemetrexed in cells with high expression of TS [70]. Given that functional gene polymorphisms of TS have been correlated with outcome in patients receiving methotrexate, Smit *et al.* assessed pemetrexed drug pathway-associated gene polymorphisms as

Table 2. Phase III trials of pemetrexed in the first-line treatment of NSCLC.

Author	Treatment	No. of patients	RR (%)	TTP (months)	OS (months)	Notable G3/G4 toxicities
Phase III						
Scagliotti [59]	D1Cis75 + G1250/D8G1250	863	28.2	PFS: 5.1	10.3	Ntp = 26.7%; Thrmbcyt = 12.7%
	vs					
	Cis75/P500	862	30.6	4.8	10.3	Ntp = 15.1%; Thrmbcyt = 4.1%
Grønberg [60]	P500/Cb5	219	NR	NR	7.3	Ntp = 40%; Thrmbcyt = 24%; Ntp Ifxn = 8%
	vs					
	D1G1000D1 + Cb5/D8G1000	217			7.0	Ntp = 51%; Thrmbcyt = 56%; Ntp Ifxn = 9%
Reference trial						
Schiller [7]	Phase III					
	D1Pac175/D2Cis75	303	21	3.4	7.8	Ntp = 75%; Febrile Ntp = 16%; Thrmbcyt = 6%; Vomiting = 24%
	vs					
	D1Cis100 + G1000/ D8&D15G1000	301	22	4.2	8.1	Ntp = 63%; Febrile Ntp = 4%; Thrmbcyt = 50%; Vomiting = 35%
	vs					
	Cis75/Doc75	304	17	3.7	7.4	Ntp = 69%; Febrile Ntp = 11%; Thrmbcyt = 3%; Vomiting = 21%
	vs					
	Cb6/Pac225	299	17	3.1	8.1	Ntp = 63%; Febrile Ntp = 4%; Thrmbcyt = 10%; Vomiting = 8%

All cycles were administered every 3 weeks except as where indicated. Treatment dosages are in mg/m^2 except as indicated.
Cb5:Carboplatin AUC5; Cb6:Carboplatin AUC6; Cis: Cisplatin; D1: Day 1; D8: Day 8; Doc: Docetaxel; Gem: Gemcitabine; G3/G4: Common Terminology Criteria for Adverse Events Grade 3 and Grade 4 toxicities; Ifxn: Infection; NR: Not reported; Ntp: Neutropenia; OS: Median overall survival; Oxali: Oxaliplatin; Pac: Paclitaxel; P: Pemetrexed; PFS: Median progression-free survival; RR: Response rate; TTP: Median time to progression; Thrmbcyt: Thrombocytopenia.

part of their Phase II study comparing pemetrexed with pemetrexed plus carboplatin in the second line [47]. Blood samples from 127 patients with baseline characteristics similar to the study population were collected. They did not find a correlation between high and low TS expression genotype and tumor histology leading to the authors' recommendation that real-time PCR be used to evaluate for levels of TS in tumor cells. They did find that patients with homozygous mutations for methylenetetrahydrofolate reductase C677T allele had a significant correlation with improved clinical outcome.

5. Role in maintenance therapy

There is no accepted consensus definition as of yet of maintenance therapy in NSCLC. Some authorities suggest that early second-line therapy implies interval progression, whereas maintenance implies continuation of the original regimen [71]. Regardless, maintenance therapy in its most basic form can be thought of as a continuation of therapy beyond a set number of cycles (typically 4 – 6 cycles in the first-line setting for NSCLC) after the initial regimen has achieved a response. The role of maintenance therapy in the treatment of advanced NSCLC has not been clearly defined and there have been few trials to guide the decision of whether or not to continue chemotherapy beyond a specified number of initial cycles [71,72]. A meta-analysis showed that continuing treatment beyond a set number of cycles provided significant improvement in PFS but a modest improvement in overall survival and possible impairments in health-related quality of life [73]. In a recent, double-blind, Phase III trial of pemetrexed in the maintenance setting for advanced lung cancer, 441 patients were randomized 2:1 to either pemetrexed 500 mg/m^2 or

Table 3. Notable Phase II trials of pemetrexed in the first line.

Author	Treatment	No. of patients	RR (%)	TTP (months)	OS (months)	Notable G3/G4 toxicities
Rusthoven [28]*	P500	30	23.3	3.8	9.6	Ntp = 39%
Manegold [29]*	P500/Cis75	36	39	6.3	10.9	Ntp = 59%; Thrmbcyt = 17%
Shepherd [30]*	P500/Cis75	31	45	NR	8.9	Ntp = 37%
Clarke [31]*	P600	59	15.8	4.4	7.2	Ntp = 42%
Zinner [48]	P500/Cb6	50	24	5.4	13.5	Ntp = 26%
Scagliotti [49]	Randomized					
	P500/Ox120	41	26.8	5.5	10.5	Ntp = 7.3%; Thrmbcyt = 2.4%
	vs					
	P500/C6	39	31.6	5.7	10.5	Ntp = 25.7%; Thrmbcyt = 18.0%
Stathopoulous [50]	P500/Pac135 – 175	48	39.6	7	14	Ntp = 8.4%;
Clarke [51]	D1P500 + V30/ D8V30	37	38	4.4 PFS: 4.2	7.9	Ntp = 65%; Febrile Ntp = 11%; Fatigue = 27%
Monnerat [52]	D1G1250/ D8G1250 + P500	60	15.5	PFS: 5.0	10.1	Ntp = 61.6%; Febrile Ntp = 15%; Fatigue = 23.3%
Ma [53]	Randomized					
	D1P500 + G1250/ D8 G1250	59	31.0	4.7	11.4	Ntp = 64.4%; Thrmbcyt = 8.5%
	vs					
	D1G1250 + P500/ D8G1250	31	6.5	4.1	10.3	Ntp = 64.5%; Thrmbcyt = 12.9%
	vs					
	D1G1250/ D8P500 + G1250	62	16.1	4.4	11.8	Ntp = 69.4%; Thrmbcyt = 19.4%
Treat [54]	D1G1250 + P500/ D8G1250	53	30.2	3.3	10.3	Ntp = 43.4%; Fatigue = 11.3%
West [55]	D1 G1250/ D8G1250 + P500	54	13	PFS: 4.6	12.4	Ntp = 26%; Thrmbcyt = 9%
Gridelli [56]	P500	44	4.5	4.5 PFS: 3.3	4.7	Ntp = 4.6%; Thrmbcyt = 4.6%
	vs					
	P500x2→G1200D1 & D8x2	43	11.6	4.1 PFS: 3.3	5.4	Ntp = 2.3%; Thrmbcyt = 7.0%
Dudek [57]	P500 + G1500 biweekly	53	20.8	4.6	10.1	Ntp = 28.3%; Fatigue/weakness = 22.6%
Blakely[58]	P500 + G1500 biweekly	45	17.8	PFS: 3.5	NR	Ntp = 22%; Fatigue/weakness = 15%

All cycles were administered every 3 weeks except as indicated. Treatment dosages are in mg/m^2 except as indicated.

*Indicates trial that was done without vitamin supplementation.

Cb5: Carboplatin AUC5; Cb6: Carboplatin AUC6; Cis: Cisplatin; D1: Day 1; D8: Day 8; Doc: Docetaxel; Gem: Gemcitabine; G3/G4: Common Terminology Criteria for Adverse Events Grade 3 and Grade 4 toxicities; Ifxn: Infection; NR: Not reported; Ntp: Neutropenia; OS: Median overall survival; Ox: Oxaliplatin; Pac: Paclitaxel; P: Pemetrexed; PFS: Median progression-free survival; RR: Response rate; TTP: Median time to progression; Thrmbcyt: Thrombocytopenia; V: Vinorelbine.

best supportive care following four cycles of platinum every 3 weeks until disease progression [74]. Patients in the pemetrexed arm had significantly better overall survival (13.4 vs 10.6 months; HR = 0.79, 95% CI 0.65 – 0.95, p = 0.012) and PFS (4.3 vs 2.6 months; HR = 0.50, p < 0.0001). The improvements in efficacy were seen primarily in patients with nonsquamous histology. In terms of drug-related adverse effects, grade 3 or 4 toxicities in general were higher in the pemetrexed compared with the supportive care arm (16 vs 4%, respectively p < 0.0001) and there was significantly more grade 3 or 4 neutropenia (2.9 vs 0%, respectively) and fatigue (5 vs 0.5%, respectively). Based on this recent study, pemetrexed was approved for use in the maintenance setting for patients with NSCLC who have not had disease progression following four cycles of initial platinum-based therapy that did not include pemetrexed.

Table 4. Results from analyses of histology in selected trials of pemetrexed.

Study	Histology	Setting	Arm size (Pem/Comparator)	Pemetrexed arm	Comparator arm	HR (95% CI)
Scagliotti [59]		1st line		Pem/Cis	Gem/Cis	
	Squamous		244/299	OS: 9.4 mth	10.8 mth	1.23 (1.00 – 1.51)
				PFS: 4.4 mth	5.5 mth	1.36 (1.12 – 1.65)
	Nonsquamous		618/634	OS: 11.8 mth	10.4 mth	0.81 (0.70 – 0.94)
				PFS: 5.26 mth	4.96 mth	0.95 (0.84 – 1.06)
Ciuleanu [89]		Maint.		Pem + BSC	Placebo + BSC	
	Squamous		116/66	OS: 9.9 mth	10.8 mth	1.07 (0.77 – 1.50)
				PFS: 2.8 mth	2.6 mth	0.69 (0.49 – 0.98)
	Nonsquamous		325/156	OS: 15.5 mth	10.3 mth	0.70 (0.56 – 0.88)
				PFS: 4.5 mth	2.6 mth	0.44 (0.36 – 0.55)
Scagliotti analysis of Hanna [40,64]		2nd line		Pemetrexed	Docetaxel	
	Squamous		78/94	OS: 6.2 mth	7.4 mth	1.56 (1.08 – 2.26)
				PFS: 2.3 mth	2.7 mth	1.40 (1.01 – 1.96)
	Nonsquamous		205/194	OS: 9.3 mth	8.0 mth	0.78 (0.61 – 1.00)
				PFS: 3.1 mth	3.0 mth	0.82 (0.66 – 1.02)
Gronberg [60]		1st line		Pem/Carbo	Gem/Carbo	
	Squamous		57/50	No significant association between histology and survival		
	Nonsquamous		162/167			
Kubota [90]		2nd line		Pem 500 mg/m^2	Pem 1000 mg/m^2	
	Squamous			OS: 7.9 mth	8.6 mth	N/A
				PFS: 1.4 mth	1.7 mth	
	Nonsquamous			OS: 19.4 mth	13.5 mth	N/A
				PFS: 3.1 mth	3.1 mth	

All doses of pemetrexed 500 mg/m^2 except as indicated.
BSC: Best supportive Care; Carbo: Carboplatin; CI: 95% confidence interval; Cis: Cisplatin; Gem: Gemcitabine; HR: hazard ratio; Maint.: Maintenance; OS: Median overall survival; Pem: Pemetrexed; PFS: Progression-free survival.

6. Regulatory affairs

At present, pemetrexed is approved in the USA and Europe for the following indications in NSCLC [75,76]:

- In combination with cisplatin in the first-line treatment of locally advanced or metastatic NSCLC other than predominantly squamous histology
- As monotherapy for second-line treatment in patients with locally advanced or metastatic NSCLC other than predominantly squamous histology.

Additionally, in the USA pemetrexed is approved for the indication [75]:

- As maintenance treatment in patients with NSCLC who have not had disease progression after four cycles of platinum-based first-line chemotherapy.

7. Conclusions

Pemetrexed is an efficacious agent in the treatment of advanced NSCLC. Trials have shown its activity in both first- and second-line settings with an overall favorable toxicity profile. Additionally, there is evidence that patients with nonsquamous tumors have improved outcomes with pemetrexed compared with their counterparts with squamous cell cancer.

8. Expert opinion

The treatment options for patients with metastatic lung cancer have increased over the last decade. Various combination regimens have resulted in improved outcomes, with median survival of 1 year and a substantial minority of patients living 2 years and longer. Given the efficacy and tolerability of pemetrexed in the treatment of advanced NSCLC, current and upcoming studies seek to combine it with newer targeted and biological agents. A Phase II trial using pemetrexed plus bevacizumab every 3 weeks in the second line had PFS of 4.0 months and overall survival of 8.6 months [77]. Another Phase II trial in the first-line treatment was recently published that combined pemetrexed, carboplatin and bevacizumab for six cycles followed by pemetrexed and bevacizumab until disease progression [78]. There was a 55% response rate with a PFS of 7.8 months and a median survival of 14.1 months with tolerable toxicity. Other Phase II and III trials using pemetrexed and bevacizumab are now underway [79,80], including the Phase III

Table 5. Selected ongoing trials involving pemetrexed in advanced NSCLC.

Study title	Design/intervention	Phase	Line	Primary end point	Estimated completion date
A Phase II trial of carboplatin, bevacizumab and pemetrexed in advanced non-small cell lung cancer [79]	Cb/Pem/Bev for 6 cycles with continuation of Bev for up to 1 year	II	1st	PFS	December 2011
Pemetrexed plus bevacizumab in pretreated, advanced or metastatic NSCLC [80]	Pem/Bev for 6 cycles with subsequent Bev until disease progression	II	2nd	PFS	April 2010
Pemetrexed/carboplatin/ bevacizumab followed by maintenance pemetrexed/ bevacizumab versus paclitaxel/ carboplatin/ bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer [81]	A: Pem/Cb/Bev for 4 cycles followed by Pem/Bev maintenance until PD vs B: Pac/Cb/Bev for 4 cycles followed by Bev maintenance until PD	III	1st	OS	January 2012
An open-label, randomized study to evaluate the effect of tarceva, compared with alimta (pemetrexed) or taxotere (docetaxel),on survival in patients with advanced, recurrent or metastatic non-small cell lung cancer who have experienced disease progression during platinum-based chemotherapy [82]	A: Erlotinib daily until PD vs B: Pem or Docetaxel q3wks until PD	III	2nd	OS	August 2014
A multicenter randomized Phase III study of pemetrexed versus erlotinib in patients with pretreated advanced NSCLC [83]	A: Pemetrexed vs B: Erlotinib	III	2nd	TTP	April 2010
A Phase II study of pemetrexed versus pemetrexed plus erlotinib in second-line treatment in patients with nonsquamous NSCLC [84]	A: Pemetrexed vs B: Pemetrexed plus erlotinib	II	2nd	PFS	August 2011
A Phase III, double-blind, placebo-controlled study of maintenance pemetrexed plus best supportive care versus best supportive care immediately following induction treatment with pemetrexed + cisplatin for advanced nonsquamous NSCLC [87]	A: Pem/Cis for 4 cycles followed by Pem maintenance & BSC until PD vs B: Pem/Cis for 4 cycles followed by placebo & BSC until PD	III	1st	PFS	May 2012
A study of pemetrexed plus carboplatin followed by maintenance pemetrexed vs paclitaxel plus carboplatin and	A: Pem/Cb for 4 cycles followed by Pem maintenance until PD vs B: Pac/Cb/Bev for 4 cycles	III	1st	PFS w/o G4 toxicity	August 2012

Bev: Bevacizumab; BSC: Best supportive care; Cb: Carboplatin; Cis: Cisplatin; OS: Overall survival; Pem: Pemetrexed; PD: Progression of disease; PFS: Progression-free survival; PS: Performance status; TTP: Time to progression.

Table 5. Selected ongoing trials involving pemetrexed in advanced NSCLC (continued).

Study title	Design/intervention	Phase	Line	Primary end point	Estimated completion date
bevacizumab followed by maintenance bevacizumab in patients with advanced NCSLC of nonsquamous histology [88]	followed by Bev maintenance until PD				
Randomized Phase II trial of pemetrexed vs pemetrexed/ bevacizumab vs pemetrexed/ carboplatin/bevacizumab in patients with stage iiib/iv non-small-cell lung cancer and ECOG performance status 2 [91]	A: Pemetrexed vs B: Pem/Bev vs C: Pem/Cb/Bev	II	1st	PFS	September 2011
A Phase II first-line study of a combination of pemetrexed, carboplatin and bevacizumab in advanced nonsquamous NSCLC [92]	Pem/Cb/Bev for up to 6 cycles with option to continue Pem/ Bev in those with stable disease or response	II	1st	6-mth PFS	March 2010

Bev: Bevacizumab; BSC: Best supportive care; Cb: Carboplatin; Cis: Cisplatin; OS: Overall survival; Pem: Pemetrexed; PD: Progression of disease; PFS: Progression-free survival; PS: Performance status; TTP: Time to progression.

PointBreak study, which will compare pemetrexed/carboplatin/ bevacizumab followed by pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by bevacizumab, with overall survival as the primary outcome [81]. The first-line use of carboplatin/pemetrexed/bevacizumab seems to be increasing, but we should exercise caution and await the results of these comparative studies.

Erlotinib, docetaxel and pemetrexed are approved agents by the FDA for use in previously treated patients with advanced NSCLC. At present, multiple Phase III trials are underway comparing erlotinib and pemetrexed in pretreated advanced NSCLC patients [82,83]. Another Phase II trial is comparing erlotinib versus pemetrexed plus erlotinib in the second line [84].

Studies discussed in this review suggest that histology plays a key role in predicting the response to pemetrexed and that it is particularly effective in nonsquamous tumors. The strongest comparison is with gemcitabine. The histology data for docetaxel presented above are based on retrospective subset analyses and no such information is available for paclitaxel, vinorelbine or erlotinib. Therefore, in practical terms, we know that pemetrexed should not be used in patients with squamous cell lung cancer, but we still do not have adequate means to select from among the other treatment options. While there are hypotheses trying to explain the histology findings, it seems likely that a better understanding of the unique molecular underpinnings of a given tumor will be ultimately more important than the relatively crude histopathologic assessment. The promise of individually 'tailored' therapy is great, though it is not fully realized as yet.

The use of pemetrexed in a maintenance setting is also intriguing, though more studies are needed to establish more clearly this new treatment paradigm. One concern regarding the results of the study by Ciuleanu *et al.* is whether the finding of increased overall survival with maintenance therapy represents a true impact of the ongoing therapy as opposed to reflecting that patients with immediate access to effective therapy tend to do better than patients who have a delay and are therefore less likely ever to receive any additional therapy [71,85]. In the arm randomized to pemetrexed maintenance, 98% received second-line therapy with pemetrexed and 51% received poststudy treatment; whereas in the placebo arm only 67% of patients received poststudy treatment and only 18% received pemetrexed. In a trial of immediate versus delayed docetaxel following first-line chemotherapy, there was improved PFS, but not overall survival. Only two-thirds of the patients on the delayed arm received docetaxel. When the study results were analyzed based on the subsets of patients who actually received docetaxel, the overall survival was identical [86]. Thus, it may be more important to monitor patients closely so that second-line treatment is initiated before clinical deterioration rather than rigidly apply the maintenance approach. Accordingly, multiple studies are now recruiting patients to explore the role of maintenance in greater depth, including the aforementioned PointBreak trial [81]. A randomized, double-blind, placebo-controlled, Phase III trial is looking at PFS in patients with advanced nonsquamous NSCLC treated with pemetrexed plus cisplatin followed by either pemetrexed maintenance or best supportive care [87]. Another Phase III trial seeks to compare pemetrexed plus carboplatin followed by maintenance pemetrexed versus paclitaxel plus carboplatin plus bevacizumab followed by maintenance bevacizumab in advanced nonsquamous tumors [88]. Selected ongoing trials of pemetrexed are described in **Table 5**.

Despite the grim prognosis for advanced NSCLC, incremental improvements in outcomes are being realized with new cytotoxic and biologic/targeted therapies. Given its good efficacy, and relatively mild toxicity profile, pemetrexed seems to be an important therapeutic option in the first- and second-line setting of advanced NSCLC and potentially in the maintenance setting as well. Many studies are now underway to define better its role in the treatment of NSCLC. Additional assessments of its efficacy, particularly in poorer performance-status patients, but also of its impact on quality of life and its cost effectiveness, will be helpful in allowing a clinician to choose most appropriately from the growing number of treatment options available.

Declaration of interest

KH Dragnev has received speaking and consulting fees from Eli Lilly. JR Rigas and AD Fuld declare no conflicts of interest.

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