Second-line treatment in advanced non-small-cell lung cancer in the epidermal growth factor receptor wild-type population: review of patient profile

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After progression during first-line treatment in advanced non-small-cell lung cancer (NSCLC), a large percentage of patients are candidates for second-line treatment. The majority do not have epidermal growth factor receptor-activating mutations (*EGFRwt*). This article reviews the treatment options available for this subpopulation of patients, which includes essentially docetaxel, pemetrexed and erlotinib. These drugs all have similar efficacy, both in terms of objective response rates and overall survival, although with different toxicity profiles. In view of the similar efficacy of the three agents (docetaxel, pemetrexed and erlotinib) in the second-line treatment of NSCLC in the *EGFRwt* population, and although there are no prospective studies on predictive variables or new molecular markers available, selection of the treatment will depend on the histological type (pemetrexed); patient preference (oral as opposed to intravenous formulation); the presence of comorbid conditions; quality of life; previous or residual toxicities; the risk of neutropenia; response to and the duration of the first-line chemotherapy; and history of smoking.

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Introduction

Lung cancer continues to be the leading cause of cancer-related death in Europe [1], with 85% of all cases classified as non-small-cell lung cancer (NSCLC) and the majority of cases in advanced stages of the disease when diagnosed [2]. The first-line treatment for stage IV NSCLC has changed over the last 10 years, primarily as a result of better patient selection, on the basis of histology or molecular markers and new treatment approaches. In the case of patients without the epidermal growth factor receptor gene mutation (*EGFRwt*), the treatment consists of a platinum combination. A greater benefit in terms of survival has been achieved in nonsquamous histology through the use of pemetrexed in doublets with cisplatin [3] and through the incorporation of biological agents, such as bevacizumab [4] and tyrosine kinase inhibitors (TKIs), in patients with *EGFR* gene mutations [5]. Maintenance treatments with pemetrexed [6] or erlotinib [7] have also proven to be beneficial in these situations.

All this has provided a different perspective on second-line treatment, but there is still considerable debate on the best treatment option to choose [8]. Three agents have been shown to provide benefits in terms of survival, two of them, docetaxel [9] and erlotinib [10] in nonselected populations and the third, pemetrexed, for nonsquamous histologies [11,12]. None has been shown to have efficacy superior to the others. This article aims to provide a detailed review of the role of these three principal agents and others used in second-line treatment in patients with *EGFRwt* NSCLC and to find a suitable clinical profile in patients to provide optimum benefit from each treatment.

Second-line treatment agents

Docetaxel

Docetaxel was the first agent to be approved for second-line treatment in patients with NSCLC on the basis of the results of two phase III trials. In the TAX 317 trial [9], 204 patients with Stage IIIB/IV NSCLC, whose disease had progressed during or after at least one line of platinum-based chemotherapy without taxane, were randomized to compare docetaxel with best supportive care (BSC). The initial dose of docetaxel was 100 mg/m^2 every 3 weeks (D100). However, as a result of excessive toxicity, the dose was changed in the second part of the

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trial to 75 mg/m^2 every 3 weeks (D75). The objective response rate (ORR) was 6% in the patients treated with docetaxel, with a median overall survival (OS) of 7.5 months compared with 4.6 months for the BSC group ($P = 0.047$) (Table 1). The survival rate at 1 year was 29% in the docetaxel group and 19% in the BSC group. In the next study, TAX 320 [13], 373 patients were randomized to two dosage levels of docetaxel, 100 and 75 mg/m^2, every 3 weeks (D100 and D75), with a control arm, which received vinorelbine or ifosfamide (V/I) at the investigator's discretion (Table 1). The response rates for both docetaxel groups were higher than those for the control group (D100 = 10.8%, $P = 0.001$; D75 = 6.7%, $P = 0.036$; V/I = 0.8%). The response rate among patients who had received paclitaxel previously was similar to the response rate for all patients. OS was similar in all three treatment groups (between 5.5 and 5.7 months). The primary dose-limiting toxicity of docetaxel was haematological. Grade 3–4 neutropenia occurred in 54–67% of the patients and febrile neutropenia in 1.8–8.0% (Table 4). Quality of life was also evaluated in both studies, with a significant improvement being found in the patients treated with docetaxel; these patients had less pain, fatigue and weight loss than the control groups and had better overall quality of life [18,19]. After docetaxel had been approved as the standard second-line treatment, subsequent clinical trials used it as a control treatment versus different drugs, among them TKIs. The INTEREST trial established the noninferiority of gefitinib with respect to docetaxel in terms of survival [20]. In the analysis of subgroups according to biomarkers [21], the *EGFR* mutation state was only determined in 297 patients (20%); 75% had *EGFRwt*. The response rate, at 9.8%, was similar to that of the group treated with gefitinib and OS for the docetaxel group was 6 months.

Pemetrexed

In the JMEI trial, 571 patients were randomized to pemetrexed versus docetaxel after first-line chemotherapy failure in advanced NSCLC (Table 1) [11]. No differences were found between pemetrexed and docetaxel in terms of response rates (9.1 and 8.8%, respectively) or OS, 8.3 months for pemetrexed versus 7.9 months for docetaxel [hazard ratio (HR) 1.0; 95% confidence interval (CI) 0.8–1.2; $P = 0.226$]. Significant differences were found, however, in toxicity, with patients who received docetaxel having higher incidences of neutropenia (grade 3–4; 5.3 vs. 40%), febrile neutropenia (1.9 vs. 12.7%) and hospitalization, in addition to greater use of granulocyte colony-stimulating factor (Tables 4 and 5).

A secondary analysis of this study [12] found pemetrexed to be more active than docetaxel in patients with nonsquamous histology (OS 9.3 vs. 8.0 months; HR 0.8; 95% CI 0.6–1.0; $P = 0.047$). This histology effect was confirmed in other studies of first-line or maintenance treatment [3,6]. Pemetrexed was more active in nonsquamous histology tumours, which are enriched for *EGFR*-activating mutations. These mutations are present in 17% of nonsquamous lung carcinomas in Whites [22], being more common in Asians (50–60%) [23]. The efficacy of pemetrexed correlated with the mutation status was analysed retrospectively in 156 Asian patients with adenocarcinoma histology [24] and 59.6% of the patients had *EGFR*-activating mutations. The difference between the response rates of the patients with mutated *EGFR* and *EGFRwt* was statistically significant (12.9 vs. 1.6%, respectively; $P = 0.016$), as it was with progression-free survival (PFS) (3.9 vs. 2.3 months; $P = 0.030$). In the multivariate analysis, only the Eastern Cooperative

Table 1 Clinical results obtained by different phase III clinical trials with docetaxel, pemetrexed or erlotinib as second-line treatment in non-small-cell lung cancer in the overall patient population

Trials	Treatment	Patients (*n*)	OR (%)	Overall survival (months)	1-year survival (%)
TAX 317 [9]	D75	55	5.5	7.5*	37.0*
	D100	49	6.3	5.9	19.0
	BSC	100	NA	4.6	19.0
TAX 320 [13]	D100	125	10.8*	5.5	21.0
	D75	125	6.7*	5.7	32.0*
	V/I	123	0.8	5.6	19.0
JMEI [11]	Pem	265	9.1	8.3	29.7
	D75	276	8.8	7.9	29.7
BR.21 [10]	E150	488	8.9**	6.7**	31.2
	BSC	243	<1.0	4.7	21.5
TITAN [14]	E150	203	7.9	5.3	26.0
	P/D	221	6.3	5.5	24.0
HORG [15]	E150	166	9	8.2	39.5
	Pem	166	11.4	10.1	43.6
PROSE [16]	E150	134	–	7.7	–
	D75/Pem	129	–	9.0	–
DELTA [17]	E150	150	17.0	14.8	–
	D60	151	17.7	12.2	–

BSC, best supportive care; D100, docetaxel 100 mg/m^2 every 3 weeks; D60, docetaxel 60 mg/m^2 every 3 weeks; D75, docetaxel 75 mg/m^2 every 3 weeks; E150, erlotinib 150 mg daily; NA, not available; OR, objective response; P/D, standard pemetrexed or docetaxel treatments (at the treatment investigator's discretion); Pem, pemetrexed 500 mg/m^2 every 3 weeks; V/I, vinorelbine or ifosfamide.
*$P < 0.05$.
**$P < 0.001$.

Table 2 Clinical results obtained by different clinical trials with erlotinib as second-line treatment in non-small-cell lung cancer in the *EGFRwt* patient population

Trial	Patients (*n*)	Phase	Treatment	OR (%)	PFS (months)	OS (months)
BR.21 [27]	174	3	Erlotinib	7.0	NA	7.9
			BSC	<1.0	NA	3.3
TITAN [14]	149	3	Erlotinib	6.3	NA	6.6
			Doc/Pem	7.9	NA	4.4
TAILOR [28]	219	3	Erlotinib	3	2.4	5.4
			Docetaxel	15.5†	2.9[#]	8.2
HORG [15]	112	3	Erlotinib	7.3	2.9[a]	9.7
			Pemetrexed	[b]	[b]	[b]
DELTA [17]	199	3	Erlotinib	5.6	1.3	9.0
			Docetaxel	20.0†	2.9[‡]	10.1
TRUST [29]	86	4	Erlotinib	2.9	2.3	6.1
[30]	30	2	Erlotinib	3.3	2.1	9.2
[31]	31	2	Erlotinib	17.2	2.1	7.7

BSC, best supportive care; Doc/Pem, docetaxel or pemetrexed (at the investigator's discretion); NA, not available; OR, objective response; OS, overall survival; PFS, progression-free survival.
[a]TTP.
[b]No differences were observed between erlotinib and pemetrexed groups, data not shown.
†$P=0.003$.
[#]$P=0.02$.
[‡]$P=0.01$.

Table 3 Baseline characteristics of the patients included in the phase III trials of second-line treatment in non-small-cell lung cancer

		Number of previous lines (%)		Best previous response (%)		
Trials	PS>1 (%)	1	≥ 2	PR/CR	SD	PD
TAX 317 [9]	24	74	26	34	48	18
TAX 320 [13]	17	70	30	71		29
JMEI [11]	12	100	0	36	35	29
BR.21 [10]	34	50	50	40	39	21
TITAN [14]	19	100	0	0	0	100
TAILOR [28]	7	100	0	40	30	30
HORG [15]	15	57	43	19	81	
PROSE [16]	6	100	–	–	–	–
DELTA [17]	4	–	–	–	–	–

–, data not published; PD, progressive disease; PR/CP, partial response/complete response; PS, performance status (Eastern Cooperative Oncology Group); SD, stable disease.

Table 4 Grade 3/4 haematological toxicities registered in the JMEI and BR.21 trials

	Docetaxel 75 (% patients)	Pemetrexed (% patients)	Erlotinib (% patients)
Neutropenia	40.2	5.3	0.0
Anaemia	4.3	4.2	0.0
Thrombocytopenia	0.4	1.9	0.0
Febrile neutropenia	12.7	1.9	0.0

Table 5 Grade 3/4 nonhaematological toxicities registered in the JMEI and BR.21 trials

	Docetaxel 75 (% patients)	Pemetrexed (% patients)	Erlotinib (% patients)
Asthenia	5.4	5.3	0.0
Nausea	1.8	2.6	3.0
Vomiting	1.1	1.5	3.0
Diarrhoea	2.5	0.4	6.0
Stomatitis	1.1	1.1	<1.0
Neurosensory	1.1	0.0	0.0
Rash	0.7	0.8	9.0
Pneumonitis	1.4	0.0	<1.0
Alopecia[a]	37.7	6.4	0.0

[a]Any grade.

Oncology Group performance status 0–1 and the presence of mutations were associated positively with PFS. Significant differences were not found in OS (30.8 vs. 25.8 months; $P=0.439$). The relationship between pemetrexed and ALK translocation in *EGFRwt* patients was analysed retrospectively in 121 ALK-positive patients and 266 ALK-negative patients [25], with PFS being similar in the two groups. In another retrospective study in which 381 patients were included, pemetrexed was found to have activity in ALK-positive patients [26]. It was therefore not possible to define the influence of ALK translocation on the efficacy of pemetrexed in second-line treatment.

Erlotinib

Erlotinib has been the most studied drug as a second-line treatment in NSCLC in the *EGFRwt* population. In the BR.21 trial, 731 patients with stage IIIB/IV NSCLC were

randomized after progression following first-line or second-line chemotherapy [10]. This phase III trial compared erlotinib therapy with BSC. The response rates were 8.9% for erlotinib and less than 1% for BSC ($P < 0.001$) (Table 1). OS was 6.7 months in the erlotinib group, as opposed to 4.7 months with BSC (HR 0.7; 95% CI 0.6–0.8; $P < 0.001$), and PFS was 2.2 months with erlotinib and 1.8 months with BSC (HR 0.6; 95% CI 0.5–0.7; $P < 0.001$). Erlotinib was also found to delay the time to worsening of the lung cancer-related symptoms. A later subanalysis [27] confirmed that smoking was the most significant predictor associated with survival in the patients treated with erlotinib ($P = 0.009$). Of 204 samples analysed, 174 (83%) were classified as *EGFRwt*. The OS with erlotinib in this subgroup of *EGFRwt* patients was 7.9 months, compared with 3.3 months with placebo (HR 0.7; $P = 0.090$) (Table 2), this benefit being very similar to that gained by the study population as a whole. The TITAN study was a phase III trial of erlotinib versus chemotherapy (docetaxel or pemetrexed, at the discretion of the investigator) as second-line treatment in advanced NSCLC after progression during first-line platinum doublet chemotherapy (Table 1) [14]. The trial closed prematurely with 424 patients because of slow recruitment, with no differences being found between the two arms with respect to OS (5.3 months with erlotinib vs. 5.5 months with chemotherapy; HR 1.0; 95% CI 0.8–1.2; $P = 0.730$), PFS (6.3 vs. 8.6 weeks; HR 1.2; 95% CI 1.0–1.5; $P = 0.089$) or response rate (7.9 vs. 6.3%; $P = 0.530$). *EGFR* mutation status was analysed in 160 patients and 93.2% were *EGFRwt*. OS in this subpopulation was greater for erlotinib, but not statistically significant (6.6 vs. 4.4 months; HR 0.8; 95% CI 0.6–1.2; $P = 0.370$) (Table 2). The TAILOR study was a phase III clinical trial of erlotinib versus docetaxel as second-line treatment in an exclusively *EGFRwt* population [28]. Although the trial was initially designed to correlate the activity of docetaxel and erlotinib in *EGFRwt* patients with overexpression of *EGFR* or KRAS, it was later changed to show the superiority of docetaxel over erlotinib in terms of OS. Among the 222 randomized patients, some methodological inconsistencies were performed and some factors were unbalanced at baseline; thus, a multivariate analysis adjusted for possible confounding factors was carried out. Although there was a difference of 2.8 months in OS, statistical significance was not reached (8.2 months in the docetaxel group and 5.4 months in the erlotinib group; adjusted HR 0.73; 95% CI 0.53–1.00; $P = 0.05$; unadjusted HR 0.78; 95% CI 0.51–1.05; $P = 0.10$) but there was a significant benefit in PFS with docetaxel (2.9 months) compared with erlotinib (2.4 months) (adjusted HR 0.71; 95% CI 0.53–0.95; $P = 0.02$; unadjusted HR 0.72; 95% CI 0.55–0.94; $P = 0.01$) (Table 2). The response rate was significantly higher with docetaxel (15.5%, with complete response in 5.2%) than with erlotinib (3.0%; $P = 0.003$). KRAS status was not a prognostic factor for longer PFS or OS in this study. Toxicity profiles of both drugs were different, with a higher incidence of neutropenia, febrile neutropenia, alopecia and neurological toxicity in the docetaxel group versus increased dermatological toxicity in the erlotinib group. The HORG trial [15] was a phase III study in which 357 patients were randomized to receive erlotinib or pemetrexed as a second-line or a third-line treatment after platinum-based therapy. There were no differences in terms of TTP (3.9 months with erlotinib vs. 3.0 months with pemetrexed; $P = 0.195$), PFS (3.6 months with erlotinib vs. 2.9 months with pemetrexed; $P = 0.136$), partial response (9% with erlotinib vs. 11.4% with pemetrexed; $P = 0.469$) and OS (8.2 months with erlotinib vs. 10.1 months with pemetrexed; $P = 0.986$). *EGFR* mutation status was analysed in 123 patients and 112 of them were *EGFRwt*. In this subgroup of patients, no differences were also observed in ORR, TTP or OS between the two treatment groups (Table 2). The PROSE study [16] was a phase III of chemotherapy (docetaxel or pemetrexed) versus erlotinib as a second-line treatment in advanced NSCLC after progression during first-line platinum doublet chemotherapy to evaluate the predictive utility of serum proteomic Veristrat classification utility on survival. Data from 263 patients were analysed and no statistical differences were found in OS (9.0 months with chemotherapy vs. 7.7 months with erlotinib; HR 1.14; 95%IC 0.88–1.49); no data were published from this study on PFS. The DELTA trial [17] was a phase III study in which 301 Japanese patients were randomized to receive erlotinib or docetaxel (at a dose of 60 mg/m^2 every 3 weeks) as second-line or third-line therapy in patients with advanced NSCLC. No differences were found in PFS (2.0 months in erlotinib group vs. 3.2 months in the docetaxel group; HR 1.22; 95% CI 0.97–1.55; $P = 0.092$), OS (14.8 months in erlotinib vs. 12.2 months in docetaxel; HR 0.91; 95% CI 0.68–1.22; $P = 0.527$) or ORR (17% in the erlotinib group vs. 17.9% in the docetaxel group; $P = 0.878$). In the subgroup of patients with *EGFRwt*, a difference was found between both therapies in PFS (1.3 months in erlotinib vs. 2.9 months in docetaxel; HR 1.45; 95% CI 1.09–1.94; $P = 0.010$), but not in OS (9.0 months in erlotinib vs. 10.1 months in docetaxel; HR 0.98; 95% CI 0.69–1.39; $P = 0.907$). Significant differences were found, however, in grade 3–4 toxicity, with patients who received docetaxel having higher incidences of neutropenia (0.7 vs. 79.5%), febrile neutropenia (0 vs. 15.2%) or leukopenia (0.7 vs. 63.6%) and patients who received erlotinib having higher incidences of rash (13.3 vs. 0.7%).The results of the pivotal BR.21 trial were later confirmed in the TRUST study, a phase IV trial of erlotinib with 6580 patients in a real-life clinical setting [32]. The response rate was 13%, with PFS of 3.2 months (95% CI 3.1–3.4) and OS of 7.9 months (95% CI 7.6–8.3). *EGFR* mutation status was analysed in 92 of the subgroup of 311 patients recruited in centres in Germany and 93% were found to be *EGFRwt*; the response rate was 2.9%, with PFS of 2.3

months (95% CI 2.0–3.0) and OS of 6.1 months (95% CI 5.1–7.3) (Table 2) [29]. Another two phase II trials analysed the role of erlotinib in second-line treatment in an exclusively *EGFRwt* population (Table 2). The first of these [30] included 30 patients, finding a response rate of 3.3%, PFS of 2.1 months (95% CI 1.4–3.0) and OS of 9.2 months (95% CI 7.5–11.2). The second trial [31] analysed 31 patients and found an OR of 17.2% (95% CI 7.6–35.4), PFS of 2.1 months (95% CI 0.9–2.8) and OS of 7.7 months (95% CI 3.8–20.4).

Other therapeutic agents

In addition to the drugs mentioned above that are approved for second-line treatment, the role of other agents, such as gemcitabine, vinorelbine, paclitaxel and irinotecan, has been investigated, primarily in phase I and II trials [33–36], which were designed before the therapeutic implications of the presence of *EGFR* mutations became known. Gemcitabine is the drug studied most in second-line treatment [37–39]. The TORCH study was a phase III clinical trial that randomized 760 patients to the combination of gemcitabine and cisplatin after progression with erlotinib versus the sequence in reverse. OS (11.6 vs. 8.7 months) and PFS (8.9 vs. 6.4 months) were significantly greater in the arm considered as standard treatment (chemotherapy followed by erlotinib). In the *EGFRwt* patient subgroup, OS reached 9.6 versus 6.5 months and PFS 7.7 versus 5.0 months [40].

Baseline patient profile and treatment selection factors

Docetaxel, pemetrexed and erlotinib are currently the three standard second-line treatments in advanced NSCLC in the *EGFRwt* population. As mentioned above, the ORR obtained irrespective of which of these three agents is used is ~7–11%, with OS between 6 and 8 months and a survival rate at 1 year of 30%. The absolute figures for OS seem lower with erlotinib, but this is probably related to the different baseline characteristics of the patients included. Analysis of the baseline characteristics in the four pivotal trials (TAX 317, TAX 320, JMEI, BR.21) [9–11,13] shows that the BR.21 trial had a higher percentage of patients with performance status 2 or more and with two or more previous lines of treatment (Table 3). Moreover, the progression rate as best response to first-line treatment was slightly higher in the TAX 320 and JMEI trials. However, in the TITAN phase III trial [14], no significant differences were found between the erlotinib arm and the chemotherapy arm (pemetrexed or docetaxel) with respect to PFS or OS in patients who had progressed during the first-line treatment.

Considering the palliative role of each of these therapies, certain criteria come into play when selecting which to use in each individual patient in terms of preference, patient clinical characteristics and treatment-related toxicities, both in first-line and in second-line treatment. The fact that erlotinib is taken orally is important for some patients as it can mean fewer visits to the medical centre, making it preferable for patients whose general condition is poorer or who live some distance away. Treatment with docetaxel can cause sensory neuropathy, which could be an important factor in some patients depending on their profession or interests. The fact that docetaxel causes alopecia may make some patients more inclined to choose one of the other two options. In addition, docetaxel and pemetrexed require premedication with corticosteroids, which can cause a number of side effects such as hyperglycaemia and insomnia, and this has to be taken into account when making such a choice. Docetaxel has a higher haematological toxicity rate than pemetrexed or erlotinib (Table 4). The nonhaematological toxicity rate is similar for docetaxel and pemetrexed (Table 5). Of the three, erlotinib is the best tolerated, although its toxicities (such as skin rash and diarrhoea) can be an important factor for some patients. In patients at high risk of developing febrile neutropenia or who have previously had severe myelosuppression, pemetrexed and erlotinib may be the best choice in view of the lower associated rates of febrile neutropenia.

Similarly, the patient's comorbid conditions can be useful when selecting a second line. Pemetrexed is contraindicated in patients with creatinine clearance less than 40 ml/min. Docetaxel and erlotinib are mainly metabolized by the liver (only 5 and 9%, respectively, is excreted in the urine). The sensory neuropathy caused by docetaxel may constitute a contraindication in patients with diabetic neuropathy or significant residual neuropathy after first-line therapy.

Smoking as a predictive factor was studied in a subanalysis in the BR.21 trial, where a greater benefit was found with respect to OS for nonsmokers than for smokers, although the smokers also benefited [41]. Similarly, a systematic review considered smoking to be a predictor for response, PFS and OS with TKI therapy, but not chemotherapy, especially in pretreated patients [42]. Unlike with chemotherapy, the pharmacokinetics of erlotinib seem to differ between smokers and nonsmokers. However, as there have been no specific studies on *EGFRwt* patients, it cannot be confirmed whether the poorer results in patients who smoke are because of greater metabolism of the drug by the liver [43,44] or a lower incidence of *EGFR* mutations in these patients [45]. No molecular markers have been found in the *EGFRwt* population that might help identify patients who should be administered erlotinib as second-line treatment. In the meta-analysis of the BR.21 and SATURN trials, no sufficiently robust biomarkers were identified to select erlotinib in the second-line or maintenance treatment scenarios [46]. The ORR, progression-free interval and toxicities related to first-line treatment can also play a role in the selection of the second-line treatment.

Conclusion

Given the similar efficacy of the three agents (docetaxel, erlotinib and pemetrexed) in the second-line treatment of NSCLC in the *EGFRwt* population, although there are no prospective studies of predictive variables or new molecular markers available, selection of the treatment will have to be according to histological type (pemetrexed), patient preference (oral vs. intravenous), presence of comorbid conditions and quality of life, previous or residual toxicities, the risk of neutropenia, response to and duration of first-line chemotherapy and history of smoking.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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