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Personalized choice of maintenance therapies in non-small-cell lung cancer

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ABSTRACT

Lung cancer has become a leading cause of cancer-related death in the world. Patient survival has improved with the introduction of new chemotherapy regimens and targeted drugs, but still, because of tumour progression or deterioration in performance status, a high percentage of patients do not receive more than one line of treatment. Given this situation, studies of maintenance therapies have begun, with results that have led to the clinical use of various drugs in a maintenance scenario. Additionally, results obtained in various clinical trials have raised the question of personalized approaches based on the clinical, pathologic, and molecular features of the cancer—not only in the initial approach, but also in the context of maintenance. Overall, the survival benefit seen with maintenance treatment has introduced a new therapy option that should be considered and discussed with patients, and (given the controversies that currently remain) chosen based on the preferences of patients and physicians.

KEY WORDS

Adenocarcinoma, chemotherapy, early second line, maintenance, NSCLC, targeted therapy

1. INTRODUCTION

The understanding of lung cancer has evolved since the 1990s, with changes seen in epidemiology, diagnosis, and treatment. Lung cancer is by far the leading cause of cancer-related death in the world, with a 5-year mortality in the United States and Canada of more than 80% [1,2]. Without treatment, the median survival of patients diagnosed with advanced non-small-cell lung cancer (NSCLC) is 4–6 months [3]. With the introduction of first-generation chemotherapy regimens, a 10%–15% response rate was demonstrated, with a modest gain of 5 weeks in median overall survival (OS) compared with the survival achieved with best supportive care (BSC) [4]. Platinum-based combinations currently remain the preferred approach in the first-line setting [5,6]. Further studies have also established a role for second-line and, in some instances, third-line therapy with agents such as docetaxel, pemetrexed, and erlotinib. These advances have resulted in median survivals of 10–12 months in contemporary studies.

Although second-line therapies have improved overall survival, up to 50% of patients completing first-line treatment become ineligible for further treatment, mostly because of significant tumour progression or rapid decline in performance status (or both). This reality has pushed many investigators to study earlier use of second-line therapy in the form of maintenance therapy. First-line maintenance therapy is defined in the setting of patients not experiencing progression after a first-line platinum-containing regimen. Some investigators have studied the prolonged use of the platinum partner from the first-line regimen in what has been called "continuation maintenance"; others have studied the use of a non-cross-resistant agent after induction, which has been termed "switch maintenance" [7]. Clinically significant results generated from many studies have raised the question of personalized approaches based on clinical, pathologic, and molecular features of the cancer.

Recognizing the importance of the pathologic and molecular features of lung cancer, the Canadian consensus biomarker group recently recommended that histologic subtyping of NSCLC be performed in every case [8]. For example, non-squamous histology was shown to be predictive of superiority for the pemetrexed arm over the standard arm in three large randomized studies [6,9]. Prediction of serious bleeding toxicity with bevacizumab in squamous cell lung cancer patients was also suggested in an early phase II trial, leading to the eventual exclusion of patients with squamous histology from most trials testing that drug [10,11]. Thus, the distinction between squamous and non-squamous histology has become fundamental in the management of NSCLC.

Similarly, the identification of specific "druggable" targets such as mutated *EGFR* and overexpressed

ALK has paved the way to individualized therapeutic approaches based on molecular features of the tumour. Analysis of trials using gefitinib or erlotinib in NSCLC found that patients carrying *EGFR* exon 19 or 21 mutations benefited most from those agents. Although such mutations are frequently associated with Asian ethnicity, female sex, non-squamous histology, and nonsmoking status, more than 40% of patients with an *EGFR* activating mutation lack all of those risk factors [12]. Given those findings, current guidelines recommend analysis of *EGFR* mutations in all patients diagnosed with advanced non-squamous NSCLC so that they can be offered an adapted treatment [8,13]. The dramatic phase II results showing crizotinib activity in *ALK*-rearranged lung cancer convinced the U.S. Food and Drug Administration to approve crizotinib for tumours of that molecular subtype in 2011. A recent report showed a similar dramatic response to crizotinib in a *ROS1*-rearranged lung cancer patient [14]. These rapidly evolving findings underscore the impact of molecular subtyping of lung cancers for optimal decision-making in clinical management.

Here, we focus on maintenance therapy and highlight some considerations that may facilitate clinical decisions in specific lung cancer subtypes.

2. NSCLC MAINTENANCE THERAPY

Early phase III studies testing the use of maintenance paclitaxel [15] and vinorelbine [16] did not provide compelling data, and thus maintenance was not proposed as an option for treatment until new-generation studies were conducted after 2000 (Tables I and II).

2.1 Gemcitabine

Three studies have addressed the issue of continuation maintenance with gemcitabine.

Brodowicz *et al.* [19] compared gemcitabine maintenance and BSC with BSC alone in advanced NSCLC patients who had initially been treated with cisplatin and gemcitabine and who had experienced a complete response, a partial response, or stable disease. The authors reported a significant longer median time to progression (6.6 months vs. 5 months, $p < 0.001$) favouring patients taking maintenance gemcitabine.

In a similar trial, Belani *et al.* [20] enrolled 519 patients and randomized 255 nonprogressors to receive gemcitabine plus BSC or BSC alone. The median progression-free survival (PFS) was 3.9 months for gemcitabine plus BSC and 3.8 months for BSC alone. Median survival was 8.0 months for gemcitabine plus BSC and 9.3 months for BSC alone ($p = 0.84$). Of the study patients, 60% had a performance status of 2. Grades 3 and 4 toxicity were also higher in the gemcitabine arm (anemia: 9.4% vs. 2.4%; neutropenia: 13.3% vs. 1.6%; thrombocytopenia: 9.4% vs. 1.4%; fatigue: 3.9% vs. 1.6%).

More recently, Perol *et al.* treated 834 patients in trial IFCT-GFPC 0502 with induction chemotherapy; the 464 nonprogressors were randomized to observation, gemcitabine, or erlotinib [21]. Median PFS was 1.9 months for observation and 3.8 months for gemcitabine [$p < 0.001$ (erlotinib results are detailed later in this article)]. Notably, second-line pemetrexed was mandated by the protocol and was given to 72% and 55% respectively of the patients in the two arms. Grades 3 and 4 treatment-related adverse events were more common with gemcitabine (27%) than with observation (2%).

Although these individual trials lack the statistical power to support conclusions about the overall effect of continuation maintenance with gemcitabine, a meta-analysis of the studies shows a significant benefit in terms of PFS [hazard ratio (HR): 0.53; $p < 0.001$] and a nonsignificant increase in OS (HR: 0.88; $p = 0.124$) [30].

2.2 Docetaxel

Fidias *et al.* [17] studied 566 advanced NSCLC patients given 4 cycles of carboplatin and gemcitabine. The 309 patients who had not progressed were then randomized to docetaxel given either immediately after the induction regimen or delayed until disease progression. Median PFS was improved in the immediate-docetaxel group (5.7 months) compared with the delayed group (2.7 months, $p < 0.0001$). A trend for increased OS was noted with immediate (12.3 months) compared with delayed docetaxel administration (9.7 months, $p = 0.09$), but that trend did not translate into improved quality of life.

Although the results are encouraging, this maintenance approach has not been widely accepted in practice because of the toxicity profile of docetaxel. The study authors did not present data to support a subgroup experiencing a broader benefit with this switch maintenance strategy.

2.3 Pemetrexed

Pemetrexed was investigated in both switch and continuance maintenance strategies. Ciuleanu *et al.* [18] randomized 663 nonprogressing stage IIIB or IV patients to receive pemetrexed or placebo every 3 weeks immediately after 4 cycles of non-pemetrexed-containing platinum-based chemotherapy and until disease progression. Patients who were included in the pemetrexed arm experienced a statistically significant improvement in PFS (4.3 months vs. 2.6 months; HR: 0.50; $p < 0.0001$) and OS (13.4 months vs. 10.6 months; HR: 0.79; $p = 0.012$). At the time the study concluded, emerging science [31] and clinical data [32] supporting poor efficacy of pemetrexed in squamous cell tumours led to an analysis of maintenance therapy based on tumour histology subsets. The 481 patients with non-squamous histology

TABLE I Maintenance trials with chemotherapy in non-small-cell lung cancer

Agent	*Reference (study name)*	*Regimen*	*Screened (n)*	*Randomized (n)*	*PFS (months)*	*OS (months)*
Switch maintenance						
Vinorelbine						
	Westeel *et al.,* 2005 [16]	MIC × 4 → vinorelbine	573	181	5	12.3
	(GCOT)	MIC × 4 → observation			3	12.3
		(219 IIIB treated with MIC × 2 and external-beam RT)			(p=0.32)	(p=0.65)
Docetaxel						
	Fidias *et al.,* 2009 [17]	Cis–gem × 4 → immediate docetaxel	566	309	5.7	12.3
		Cis–gem × 4 → delayed docetaxel			2.7	9.7
					(p=0.0001)	(p=0.09)
Pemetrexed						
	Ciuleanu *et al.,* 2009 [18]	Platinum doublet × 4 → pemetrexed	NR	663 (2:1)	4.3	13.4
	(JMEN)	Platinum doublet × 4 → placebo			2.6	10.6
					(p<0.0001)	(p=0.01)
Continuation maintenance						
Paclitaxel						
	Belani *et al.,* 2003 [15]	Cb–paclitaxel × 4 → paclitaxel	401	130	8.8	17.3
		Cb–paclitaxel × 4 → observation			6.7	13.8
					(p=NR)	(p=NR)
Gemcitabine						
	Brodowicz *et al.,* 2006 [19]	Cis–gem → gem	354	206 (2:1)	6.6	10.2
		Cis–gem → observation			5.0	8.1
					(p<0.001)	(p=0.17)
	Belani *et al.,* 2010 [20]	Cb–gem → gem	519	255	3.9	8.0
		Cb–gem → observation			3.8	9.3
					(p=0.58)	(p=0.84)
	Perol *et al.,* 2010 [21]	Cis–gem → gem	NR	309	3.8	NR
	(IFCT-GFPC 0502)	Cis–gem → observation			1.9	NR
Pemetrexed					(p<0.0001)	
	Paz–Ares *et al.,* 2011 [22]	Cis–pemetrexed → pemetrexed	939	539 (2:1)	3.9	NR
	(PARAMOUNT)	Cis–pemetrexed → placebo			2.6	NR
					(p=0.0002)	
	Barlesi *et al.,* 2011 [23]	CPB → pemetrexed–bevacizumab	376	253	7.4	NR
	(AVAPERL)	CPB → bevacizumab			3.7	15.7[a]
					(p<0.001)	(p=0.23)

[a] From the start of first-line therapy in patients randomized to maintenance.
PFS = progression-free survival; OS = overall survival; MIC = mitomycin–ifosfamide–cisplatin; RT = radiation therapy; Cis = cisplatin; Gem = gemcitabine; NR = not reported; Cb = carboplatin; CPB = cisplatin–pemetrexed–bevacizumab.

(72.5% of the population) experienced a median PFS of 4.4 months in the pemetrexed group compared with 1.8 months in the placebo group (HR: 0.47; $p < 0.0001$) with a median OS of 16.8 months in the chemotherapy group and 11.5 months in the placebo group (HR: 0.70; $p = 0.002$). Conversely, patients with squamous cancers did not benefit from pemetrexed maintenance. Investigators reported a significant

TABLE II Phase III maintenance trials with epidermal growth factor receptor tyrosine kinase inhibitors

Agent	*Reference (study name)*	*Regimen*	*Screened (n)*	*Randomized (n)*	*PFS (months)*	*OS (months)*
Switch maintenance						
Erlotinib						
	Miller *et al.,* 2009 [24]	Platinum doublet–bev → bev–erlotinib	1160	768	4.8	15.9
	(ATLAS)	Platinum doublet–bev → bev–placebo			3.7	13.9
					(p=0.0012)	(p=0.27)
	Cappuzzo *et al.,* 2010 [25]	Platinum doublet × 4 → erlotinib	1949	889	3.1	12
	(SATURN)	Platinum doublet × 4 → placebo			2.8	11
					(p<0.0001)	(p=0.01)
	Perol *et al.,* 2010 [26]	Cisplatin–gemcitabine → erlotinib	NR	310	2.8	NR
	(IFCT-GFPC 0502)	Cisplatin–gemcitabine → observation			2.1	NR
					(p=0.002)	
Gefitinib						
	Gaafar *et al.,* 2010 [27]	Platinum doublet × 4 → gefitinib	173	173	4.1	10.9
	(EORTC 08021–ILCP 01/03)	Platinum doublet × 4 → placebo			2.9	9.4
					(p=0.0015)	(p=0.2)
	Takeda *et al.,* 2010 [28]	Platinum doublet × 3 → gefitinib	598	598	4.6	13.7
	(WJTOG 0203)	Platinum doublet × 6			4.3	12.9
					(p<0.001)	(p=0.11)
	Zhang *et al.,* 2011 [29]	Platinum doublet × 4 → gefitinib	298	296	4.8	18.7
	(INFORM)	Platinum doublet × 4 → placebo			2.6	16.9
					(p<0.0001)	(p=0.26)
Continuation maintenance						
	None designed					

PFS = progression-free survival; OS = overall survival; bev = bevacizumab; NR = not reported.

treatment-by-histology interaction for both PFS (p = 0.036) and OS (p = 0.033). Interestingly, the OS benefit appears to be larger in patients whose best response to induction is stable disease (HR: 0.61) than in those who respond to induction (HR: 0.81) [33]. Unfortunately, pemetrexed was not mandated by the protocol for patients progressing on placebo, and it was ultimately received by only 19% of patients in that group.

At the 2011 meeting of the American Society of Clinical Oncology, the preliminary results of the PARAMOUNT trial of continuation maintenance with pemetrexed were presented [22]. Induction consisted of 4 cycles of pemetrexed and cisplatin in 939 patients with non-squamous NSCLC. It is important to note that, for the reasons stated earlier, squamous cell cancer patients were not included in this trial. The 539 patients who had not progressed after initial treatment were then randomized to receive maintenance pemetrexed or placebo. Progression-free survival was 3.9 months in the pemetrexed arm and 2.6 months in the placebo arm (HR: 0.64; 95% confidence interval: 0.51 to 0.81; p = 0.00025). Grade III/IV toxicity was higher in the pemetrexed arm (9.2% vs. 0.6%). Quality of life and OS data have not yet been presented. The subgroup analyses suggest that the PFS benefit may be larger in patients responding to induction (HR: 0.48) than in those with stable disease (HR: 0.74). Pemetrexed was received after progression in fewer than 1% of the patients in both arms (see NCT01020786, NCT00948675, and NCT00606021 at http://clinicaltrials.gov/ct2/search) [34].

At the 2011 meeting of the European Society for Medical Oncology, the AVAPERL trial, another study of continuation maintenance with combined pemetrexed and bevacizumab, was presented [23]. After 4 cycles of cisplatin–pemetrexed–bevacizumab, 253 nonprogressing patients were randomized to bevacizumab and pemetrexed or to bevacizumab alone. In contrast with reporting from other studies, PFS in this trial was reported from the beginning of first-line chemotherapy instead of from the start of maintenance. Progression-free survival was 10.2 months in the pemetrexed–bevacizumab arm and 6.6 months in the

bevacizumab-only arm (HR: 0.50; $p < 0.001$). From the start of maintenance, PFS was 7.4 months in the combination arm and 3.7 months in the bevacizumab arm. Preliminary data showed a nonsignificant difference in OS (HR: 0.74; $p = 0.23$). Overall grades 3–5 toxicity during the maintenance phase occurred in 37.6% of patients in the combination arm and in 21.7% of patients in the bevacizumab arm. Quality of life did not appear different in either treatment arm.

2.4 Erlotinib

The SATURN trial was a randomized phase III switch maintenance trial. From among the 1949 advanced NSCLC patients who received a first-line platinum doublet that did not include pemetrexed, 889 nonprogressing patients were randomized to receive erlotinib or placebo. Progression-free survival was statistically improved with the use of erlotinib (12.3 weeks vs. 11.1 weeks; HR: 0.71; $p < 0.0001$). Overall survival was also improved in the erlotinib group (12 months vs. 11 months; HR: 0.81; $p = 0.009$). Grades 3 and 4 toxicity in the erlotinib group included rash in 9% and diarrhea in 2% [25]. Because of variable access to off-protocol erlotinib, only 21% of the patients in the placebo arm were able to receive it. Subgroup analyses of the OS results suggest a larger treatment benefit in patients with stable disease after induction (HR: 0.72) than in responding patients (HR: 0.94). An *EFGR* mutation analysis was possible in 49% of the randomized patients. Progression-free survival was statistically higher in patients with *EGFR* activating mutations (HR: 0.23) than in patients lacking such mutations (HR: 0.78). Curiously, this impressive difference between the groups did not translate into a survival difference (HR: 0.83 and 0.77 respectively), possibly a reflection of post-study treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor in a large proportion of the patients with a mutation.

The ATLAS trial evaluated switch maintenance therapy using bevacizumab and erlotinib with therapy using bevacizumab and placebo after 4 cycles of platinum-based chemotherapy with bevacizumab. Of the 1160 patients screened, 768 nonprogressing patients with advanced non-squamous NSCLC or with non-centralized or extrathoracic squamous cell cancer were randomized. Progression-free survival was improved in the erlotinib and bevacizumab maintenance arm (4.8 months vs. 3.7 months, $p = 0.0012$) [24]. No significant difference in OS was found (15.9 months vs. 13.9 months, $p = 0.2686$), which may be a reflection of the broader availability of erlotinib upon progression (received in 40% of the placebo group) [35]. A benefit in PFS similar to that seen in the SATURN trial was observed in the *EGFR* activating mutation–positive and –negative subgroups (HR: 0.44 and 0.85 respectively). Grades 3 and 4 adverse events were recorded in 44.1% of the combination arm and 30.4% of the bevacizumab-only arm.

In the IFCT-GFPC 0502 trial discussed earlier, PFS was 2.8 months for the erlotinib arm and 2.1 months for the observation arm (HR: 0.83; 95% confidence interval: 0.73 to 0.94). Preliminary OS data do not show clear differences emerging between the three treatment arms [26]. The investigators did not compare gemcitabine with erlotinib, because the trial was powered to compare the two treatment arms individually with placebo. Patients with *EGFR* activating mutations were too few to draw conclusions for that subgroup. A subset analysis of survival based on response to induction has not been presented so far.

2.5 Gefitinib

Three small randomized trials have addressed switch maintenance with gefitinib.

The European Organisation for Research and Treatment of Cancer 08021-ILCP included patients with advanced NSCLC not progressing after 4 cycles of platinum-based chemotherapy and randomized to receive gefitinib or placebo. Given slow accrual, the trial was prematurely closed with only 173 patients enrolled. Overall survival was higher in patients who received gefitinib, but the difference was not statistically significant (10.9 months vs. 9.4 months; HR: 0.83; $p = 0.2$). Progression-free survival was higher in the gefitinib group (4.1 months vs. 2.9 months; HR: 0.61; $p = 0.0015$) [27].

The INFORM trial, an Asian phase III trial, was conducted to evaluate gefitinib versus placebo as maintenance therapy in patients not experiencing progression after 4 cycles of platinum-based chemotherapy. Of the 296 included patients, 79 were positive for *EGFR* mutations. Progression-free survival was significantly higher in the gefitinib arm (4.8 months vs. 2.6 months; HR: 0.42; $p < 0.0001$). Subgroup analysis once again revealed a larger PFS benefit in the *EGFR* mutation-positive patients (HR: 0.17) than in those lacking such a mutation (HR: 0.87). Overall survival was not shown to be superior in the overall population (18.7 months vs. 16.9 months; HR: 0.84; $p = 0.2608$) [29]. The predictive effect of *EGFR* mutations on survival with therapy has not been reported.

Finally, the West Japan Thoracic Oncology Group 0203 phase III trial compared prolonged chemotherapy consisting of 6 cycles of a platinum doublet with a short course of 3 cycles of chemotherapy followed by gefitinib maintenance in 604 patients. The results for PFS were statistically different, favoring gefitinib maintenance (4.6 months vs. 4.3 months; HR: 0.68; $p < 0.001$). Overall survival was not statistically different at 13.7 months in the gefitinib arm compared with 12.9 months in the prolonged chemotherapy arm (HR: 0.86; $p = 0.11$) [28].

2.6 Other Agents

Discussions of maintenance therapy frequently

address the use of the monoclonal antibodies bevacizumab and cetuximab as maintenance agents. Studies such as Eastern Cooperative Oncology Group 4599, AVAIL, and FLEX randomized use of those drugs at the onset of first-line chemotherapy; the antibody component of the regimen was then continued until disease progression [36–38]. That design does not allow for a determination of whether the observed benefit is derived from the induction phase, the maintenance phase, or both. An ongoing study performed by the Eastern Cooperative Oncology Group (study 5508) will directly compare pemetrexed alone, bevacizumab alone, and the pemetrexed–bevacizumab combination in a maintenance approach and may better define the role of bevacizumab in that specific setting (search for NCT01107626 at http://clinicaltrials.gov/ct2/search).

3. DISCUSSION

Maintenance therapy has proved effective in patients with advanced NSCLC who have received up to 4 cycles of a platinum-containing regimen. Strategies include switch maintenance (in which a drug is given after an initial treatment that does not include the maintenance drug) and continuation maintenance (in which a drug used in the initial treatment is continued without its platinum partner after a limited number of cycles). The overall strength of the available data, the ease of treatment administration, and a clinically acceptable toxicity profile have together led to the approval of pemetrexed and erlotinib for maintenance in many countries. Nonetheless, the varying indications in different countries, the lack of a built-in crossover at progression in some studies, and a modest effect on survival without added quality of life have generated some controversy with respect to the most appropriate use of maintenance strategies. As a result, maintenance therapy has not been accepted as a standard, but as a reasonable option for patients after consideration of the arguments for and against.

3.1 Arguments Against Maintenance

Having received 4–6 cycles of a platinum-containing regimen, patients commonly request a treatment holiday to recuperate from accumulated toxicity. Immediately switching to a new regimen adds some anxiety about adapting to new toxicity and its management. Furthermore, a period free of treatment-related toxicity is gladly accepted by patients, especially when cancer symptoms have disappeared after first-line treatment. Unfortunately, trials of maintenance therapy have demonstrated that recurrence is very rapid after induction therapy: a median of 2–3 months in most trials. The risks of delaying therapy in favour of a second-line approach include either or both of rapid unpredicted progression and a decline in performance status, rendering those patients ineligible for further therapy. It is tempting to think that the OS benefits in SATURN and JMEN may have been negated if systematic availability of the study drug at progression had been included in the study design. Such an interpretation may explain the negative survival results of ATLAS, the trial by Fidias *et al.,* and other studies. Nonetheless, the significant OS benefit observed in many maintenance, second-line, and third-line studies [39,40] highlights the importance of pemetrexed, erlotinib, and docetaxel after first-line treatment. On that basis, it would seem prudent to follow a patient very closely if that patient prefers delayed treatment. Frequent imaging (at 6-week intervals)—at least in the first 3–6 months—may lead to clinical benefit parallelling the results obtained in the observation arm of most maintenance studies. A follow-up to SATURN in which second-line erlotinib will be mandated at progression in the placebo arm may help to determine if such a strategy is safe (search for NCT01328951 at http://clinicaltrials.gov/ct2/search).

3.2 Arguments for Maintenance

As discussed earlier, progressive disease after first-line treatment is associated with new symptoms, deterioration in performance status, and decreased tolerability of further treatment toxicities. Furthermore, a delay in effective therapy may generate anxiety related to new symptoms or new findings on follow-up imaging studies. Early second-line treatment or a choice to favour maintenance has the theoretical advantage of delaying tumour-related symptoms and optimizing treatment tolerance as well as delaying recurrence.

3.3 Personalizing Therapy

Because many patients are still symptomatic after first-line therapy is over, patients with a large tumour burden or significant symptoms despite first-line chemotherapy may be the most important patients to consider for a switch to a non-cross-resistant drug as early as possible. That approach may be one explanation for the apparent larger effect seen in many studies for switch maintenance in the stable-disease subgroups. By contrast, patients that have experienced a significant resolution of symptoms and an important decline in tumour burden with a first-line regimen may in fact benefit from continuation of effective therapy in maintenance without the cumulative toxicity associated with an increasing number of platinum cycles. Although data supporting this adapted approach are still preliminary, it is interesting to note that the PARAMOUNT and IFCT trials both observed improved outcomes with continuation maintenance in the responsive subgroups. Those findings suggest a possible role for pemetrexed or gemcitabine in this patient setting. Considering that, in some countries, pemetrexed and erlotinib maintenance have already

been approved only for patients with stable disease, response to first-line therapy has already become a major factor of an individualized approach to maintenance.

Histologic and molecular diagnosis of lung cancer have revolutionized the approach to patient care. Exclusion of bevacizumab and pemetrexed in the setting of squamous cell carcinoma and superiority of first-line cisplatin–pemetrexed for non-squamous histologies will lead to a multiplication in the variety of first-line regimens used in the clinic and will obviously affect maintenance considerations. First-line use of EGFR tyrosine kinase inhibitors for patients with an *EGFR* activating mutation will also lower the number of patients considered for those drugs in a maintenance setting. Furthermore, identification of *ALK* and *ROS1* rearrangements will lead to a preference for crizotinib. Based on the available subgroup analyses from maintenance trials, erlotinib appears to have the most clinical appeal for patients with squamous cell cancer and with activating *EGFR*-mutated tumours considered for maintenance. Patients with non-squamous, non-*EGFR*-mutated tumours constitute the larger patient subgroup. For those patients, results for pemetrexed and erlotinib appear similar. Treatment choice is therefore individualized based on toxicity considerations, preference for mode of administration (intravenous or oral), and drug coverage plans.

In an era in which most studies of lung cancer are devoted to biomarker-based strategies, it is important to realize that the most important studies of maintenance therapy are completed. Although additional information might be obtained by an analysis of mature data from some studies and from meta-analyses of all studies, it is likely that the controversies and attitudes toward maintenance will remain and that treatment choices will be based on physician and patient preference. In this regard, further improvements in the field may come from the development, for physicians and patients, of clinical decision tools that can help to guide therapy for the individual patient (Table III).

TABLE III Significant subset analyses from selected trials, which may guide patient-adapted treatment

Reference (study name)	*Agent*	*Analysis subset*	*Pts (n)*	*Hazard ratio*	
				PFS	*OS*
Switch maintenance					
Ciuleanu *et al.,* 2009 [18]	Pemetrexed	Squamous	182	1.03	1.07
(JMEN)		Non-squamous	481	0.47	0.70
		Non-squamous, CR/PR	322	NR	0.81
		Non-squamous, SD	337	NR	0.61
Fidias *et al.,* 2009 [17]	Docetaxel	CR/PR		NR	NR
		SD		NR	NR
Cappuzzo *et al.,* 2010 [25]	Erlotinib	Squamous		0.76	0.86
(SATURN)		Non-squamous		0.60	0.77
		EGFR mutation–positive	49	0.23	0.83
		EGFR mutation–negative	388	0.78	0.77
		CR/PR	394	0.74	0.94
		SD	487	0.68	0.72
Kabbinavar *et al.,* 2010 [35]	Erlotinib–bevacizumab	*EGFR* mutation–positive	52	0.44	NR
(ATLAS)		*EGFR* mutation–negative	295	0.85	NR
Perol *et al.,* 2010 [26]	Erlotinib	CR/PR	160	0.80	NR
(IFCT-GFPC 0502)		SD	145	0.85	NR
Zhang *et al.,* 2011 [29]	Gefitinib	*EGFR* mutation–positive	30	0.17	NR
(INFORM)		*EGFR* mutation–negative	49	0.87	NR
Continuation maintenance					
Perol *et al.,* 2010 [26]	Gemcitabine	CR/PR	155	0.44	NR
(IFCT-GFPC 0502)		SD	146	0.68	NR
Paz–Ares *et al.,* 2011 [22]	Pemetrexed	All non-squamous:			
(PARAMOUNT)		CR/PR	242	0.48	NR
		SD	280	0.74	NR

Pts = patients; PFS = progression-free survival; OS = overall survival; CR/PR = complete/partial response; NR = not reported; SD = stable disease.

4. SUMMARY

Various approaches to maintenance therapy in NSCLC have been studied. Methodologic issues and poor accrual to some studies have hampered the widespread adoption of maintenance for all patients with NSCLC. Nonetheless, OS benefits seen in some larger studies have opened a new option of treatment that should be considered and discussed with most patients before the conclusion of first-line chemotherapy.

5. CONFLICT OF INTEREST DISCLOSURES

NB has served as a consultant to Hoffmann–La Roche. LCR has no financial conflicts to disclose.

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