Maintenance Therapy in Non-small-cell Lung Cancer – Review of Rationale, Clinical Need and Available Data

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Abstract

Non-small-cell lung cancer management is classically based on several lines of therapy separated by treatment-free intervals, in which each new line is started when tumour progression is detected. The maintenance strategy consists of pursuing an appropriate, well-tolerated treatment after the end of first-line chemotherapy in order to maintain the initial therapeutic benefit and to avoid rapid clinical deterioration that would rule out further treatment. Clinical trials show that maintenance therapy with pemetrexed or erlotinib provides a significant clinical benefit in terms of disease control and survival. This survival benefit appears to be due mainly to the increase in the proportion of patients who can receive several lines of active treatment. Maintenance therapy is an important option for patients receiving initial treatment, particularly for those with rapid disease progression, but more reliable criteria are needed to identify the patients most likely to benefit from this approach.

Keywords

Erlotinib, bevacizumab, non-small-cell lung cancer, maintenance, pemetrexed

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First-line treatment for patients with metastatic non-small-cell lung cancer (NSCLC) is classically based on combination chemotherapy comprising a platinum salt and a third-generation cytotoxic agent. Because of the toxicity of this regimen, few patients are able to receive more than six cycles.[1] As the clinical benefit is often only moderate and transient, several strategies have recently been developed with the aim of maintaining this benefit without undermining quality of life. These new approaches have been made possible by the arrival of more active and better tolerated cytotoxic drugs and targeted biotherapies compatible with long-term administration.

Duration of First-line Treatment for Metastatic Non-small-cell Lung Cancer – The Concept of Maintenance Therapy

Duration of First-line Chemotherapy

The latest guidelines published by the American Society of Clinical Oncology on first-line chemotherapy for patients with advanced-stage NSCLC recommend no more than four cycles for patients with stabilised disease and no more than six cycles for responders.[1] Phase III trials show that previously untreated patients actually receive a median of about four cycles of platinum-based chemotherapy.[1] This is due to the high proportion of patients with refractory tumours (about 30%), as well as cumulative drug toxicity and an early maximal reduction in tumour volume.[2,3] Several randomised trials have examined the optimal number of cycles of platinum-based doublets for previously untreated patients.[3–6] Treatment prolongation has been shown to offer no advantages in terms of response, symptom control, quality of life or survival, while it tends to aggravate cumulative toxicities such as anaemia and neuropathies.[5] A meta-analysis of such trials,[7] including two studies of maintenance therapy based on the drug initially combined with the platinum salt, confirmed that prolonging first-line chemotherapy yielded no survival benefit (hazard ratio [HR] 0.97, 95% confidence interval [CI] 0.84–1.11), even though it improved progression-free survival (PFS) (HR 0.75, 95% CI 0.65–0.85).

The 'Stop and Go' Strategy

Thus, current data support the use of brief first-line treatment limited to four cycles, as it appears to augment the number of patients eligible for a second line of treatment.[6,8] The arrival of several second-line treatment options (docetaxel, pemetrexed and erlotinib, and gefitinib in Asia) has led to the adoption of a strategy in which patients receive multiple lines of treatment based on several regimens that are initiated at the onset of disease progression and are separated by treatment-free intervals.[8] However, rather than being a true therapeutic concept, this so-called 'stop and go' or 'wait and watch' strategy is imposed by drug toxicity. It has the advantage of offering patients treatment-free rest periods, which might also help to preserve tumour cell sensitivity to later therapeutic options. However, these treatment-free intervals are generally short and carry a risk of rapid clinical deterioration, ruling out second-line treatment. Indeed, only 50–65% of patients initially treated with a platinum-based dual-agent combination actually go on to receive a second line of therapy.[1,9]

Table 1: Results of Main Trials of Maintenance Therapy After First-line Treatment of Advanced Non-small-cell Lung Cancer

Trial	Maintenance Drug	Median PFS (months) – Control Arm	Median PFS (months) – Maintenance Arm	HR (95% CI) for PFS	Median OS (months) Control Arm	Median OS (months) Maintenance Arm	HR (95% CI) for OS
Continuation of Existing Therapy in Maintenance with Chemotherapy							
Belani[12]	Paclitaxel	6.7*	8.7*	NR	13.8*	17.2*	1.02 (0.66–1.57)
Brodowicz[13]	Gemcitabine	2	3.6	0.69 (0.56–0.86)	8.1	10.2	0.84 (0.52–1.38)
Maintenance with Introduction of Another Cytotoxic Agent							
Westeel[14]	Vinorelbine	3	5	0.77 (0.55–1.08)	12.3	12.3	1.08 (0.79–1.48)
Fidias[16]	Docetaxel	2.7	5.7	0.71 (0.55–0.92)	9.7	12.3	0.84 (0.65–1.08)
Ciuleanu[20]	Pemetrexed	2.0†	4.0†	0.60 (0.49–0.73)†	10.6	13.4	0.79 (0.65–0.95)
Maintenance with EGFR TKI							
WJTOG[33]	Gefitinib	4.3*	4.6*	0.68 (0.57–0.80)	12.9*	13.7*	0.86 (0.72–1.03)
FASTACT[31]	Erlotinib	5.4*	6.8*	0.47 (0.33–0.68)	17.1	17.5	1.09 (0.70–1.69)
SATURN[34]	Erlotinib	2.55	2.83	0.71 (0.62–0.82)	11.0	12.0	0.81 (0.70–0.95)
ATLAS[36]	Erlotinib	3.7	4.6	0.72 (0.59–0.88)	NR	NR	NR

**Measured from the beginning of treatment; †By independent review.*
CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reported; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

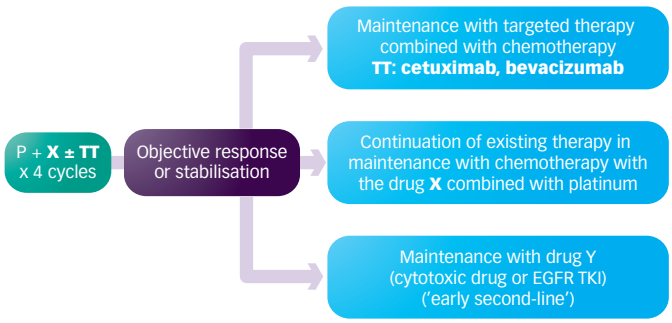
The Concept of Maintenance Therapy

First-line maintenance therapy can be defined as the continuation of treatment after the maximal response to 'induction' chemotherapy has been obtained, up to the onset of disease progression.[10,11] Thus, by definition, only patients who respond to induction therapy or whose disease is stabilised will qualify for maintenance therapy. In theory, this approach avoids the drawbacks of the stop and go strategy, as it can maintain the clinical benefit of first-line treatment and thereby avoid the risk that the patient will become too poorly to receive further active treatment. This strategy is therefore particularly suited to patients with rapidly progressive NSCLC. The maintenance strategy offers the advantage of maintaining constant therapeutic pressure on a small residual tumour burden until progression occurs. The first option is to use one of the drugs contained in the induction regimen, based on initial tumour sensitivity. This corresponds to continuation of existing therapy in maintenance. The alternative is to introduce a new treatment based on the concept of immediate initiation of a different treatment without cross-resistance; this allows all patients experiencing disease control to receive a further active treatment. This strategy has also been termed 'consolidation therapy' or, inappropriately, 'immediate second-line therapy' (the term 'second-line' implies disease progression, which, by definition, rules out the concept of maintenance therapy). The maintenance strategy can only be envisaged with relatively well tolerated treatments that can be administered for long periods without negatively affecting quality of life.

Methodology and End-points of Clinical Trials of Maintenance Therapy

For trials of maintenance therapy, patients who have responded to induction therapy or whose disease has stabilised are randomly assigned to receive continued treatment (experimental maintenance arm) or else a placebo or simple follow-up. They then receive a second line of treatment at the onset of disease progression (stop and go strategy, currently the standard therapy). The end-point for efficacy is the increase in the duration of disease control (PFS) or the overall survival (OS) benefit. PFS has the advantage of not being influenced by subsequent treatments, and is therefore a useful end-point for judging the clinical benefit of first-line treatment. However, it is relatively imprecise and does not take into account toxicity or symptoms. It also depends on how often tumour status is assessed during follow-up, and therefore requires a double-blind design or independent review. Ideally, symptoms and quality of life should also be taken into account. OS is the gold standard end-point for trials of cancer treatments. However, in first-line treatment settings it has the disadvantage of being influenced by the effect of subsequent treatments, which are increasingly frequent in NSCLC and are difficult to control for in clinical trials. Nonetheless, it seems crucial to assess the survival benefit of maintenance strategies, as their added toxicity and financial cost cannot be justified solely by an increase in PFS relative to the stop and go approach.

Figure 1: Maintenance Strategies in First-line Treatment of Advanced Non-small-cell Lung Cancer



EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; P = platinum; TT = targeted therapy (bevacizumab or cetuximab) used in combination with first-line platinum-based chemotherapy; X = third-generation cytotoxic combined with platinum.

Results of Trials Evaluating the First-line Maintenance Concept (see *Table 1*)

First-line Maintenance Options for Advanced-stage Non-small-cell Lung Cancer

Several maintenance strategies can be envisaged after first-line platinum-based dual-agent therapy (see *Figure 1*):

- continuation of existing therapy in maintenance, in which the patient continues to receive a targeted therapy initially combined with first-line chemotherapy (i.e. bevacizumab or cetuximab), or otherwise single-agent therapy with the drug that was initially combined with the platinum salt (i.e. gemcitabine or paclitaxel); or

- initiation, at the end of the induction phase, of a new drug, usually consisting of an agent validated for second-line use: either a cytotoxic agent (docetaxel, pemetrexed, etc.) or an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.

Maintenance with a Cytotoxic Drug

Paclitaxel

A randomised clinical trial evaluated maintenance therapy based on weekly paclitaxel administration (70mg/m^2) in responders to a carboplatin–paclitaxel combination.[12] Despite the very limited statistical power of this study, weekly paclitaxel maintenance prolonged the time to progression (TTP) and the survival time, but at the cost of major toxicity (grade 3–4 in 45% of patients).

Gemcitabine

The only cumulative toxicity of gemcitabine is haematological. Gemcitabine has been studied in a phase III trial of continuation of existing therapy in maintenance.[13] Initially, 352 patients received four cycles of the cisplatin–gemcitabine combination, then the 206 patients who responded to this treatment or whose disease had stabilised were randomly allocated either to continue on gemcitabine single-agent therapy (1,250mg/m^2 on days one and eight of three-week cycles) or to receive simple monitoring. The main end-point was the TTP. Gemcitabine maintenance significantly prolonged the TTP and provided a large survival benefit, although the latter was not statistically significant, owing to a lack of power (median survival time 13 months in the maintenance arm and 11 months in the monitoring arm; p=0.195). Toxicity was moderate, with no episodes of febrile neutropenia and grade 3–4 neutropenia in only 15% of the cycles.

Vinorelbine

Vinorelbine was used in the first trial designed to evaluate the introduction for six months of a different cytotoxic drug after induction therapy. Patients with stage IV NSCLC initially received the cisplatin–mitomycin–ifosfamide (MIP) regimen, while those with stage IIIB disease received MIP followed by radiotherapy.[14] Toxicity was significant during vinorelbine maintenance, with 12% of patients experiencing grade 3–4 infections. No benefit was found in terms of PFS or OS. Retrospectively, the choice of vinorelbine seems inappropriate, owing to its unfavourable toxicity profile and its lack of documented second-line activity.

Docetaxel

In theory, docetaxel is a better candidate for immediate administration after platinum-based chemotherapy given its proven second-line activity.[15] In a North American trial involving patients whose NSCLC had been controlled by four cycles of the carboplatin–gemcitabine combination, immediate administration of six cycles of docetaxel was compared with the standard strategy in which docetaxel is administered at the onset of tumour progression.[16] The main end-point was OS. Of the 566 patients, 309 (54%) treated with carboplatin–gemcitabine were randomised. Immediate docetaxel administration provided a large gain in PFS and a very clear OS benefit (median 12.3 months versus 9.7 months), although the difference was not statistically significant, again owing to a lack of power. The survival benefit appeared to be due mainly to the fact that only 63% of the patients in the control arm effectively received docetaxel (at disease progression) compared with 95% of those in the immediate docetaxel arm. Failure to receive second-line treatment in the control arm was mainly due to clinical deterioration associated with tumour progression. However, it is possible that the relatively long tumour-monitoring interval – every three months – in the control arm meant that tumour progression was detected late. Indeed, survival among patients who actually received docetaxel was the same in the two arms, whether docetaxel was administered immediately or only when disease progression was diagnosed.

Pemetrexed

Pemetrexed is used for both first-line and second-line treatment of advanced-stage NSCLC, with good tolerability.[17,18] Retrospective analysis of phase III trials according to the histological type of NSCLC[17,18] showed that efficacy was restricted to patients with non-epidermoid carcinoma. A phase II trial evaluated continuation of existing therapy in maintenance therapy based on pemetrexed plus bevacizumab after six cycles of a carboplatin, pemetrexed and bevacizumab combination in 50 patients with non-epidermoid NSCLC.[19] Tolerability was good, with nine patients receiving more than 18 cycles of maintenance therapy and seven receiving more than 24 cycles. The good median PFS and OS (7.8 and 14.1 months, respectively) were partly due to the selection of patients with a relatively favourable prognosis.

The most interesting data on pemetrexed maintenance therapy come from a phase III trial using a sequential approach: patients who responded or whose disease stabilised after four cycles of a dual-agent platinum combination not including pemetrexed were randomised to receive either pemetrexed or placebo every three weeks until disease progression.[20] The main end-point was PFS.

Six hundred and sixty-three patients were randomised, of whom 27% were women, 23% Asian and 27% non-smokers; 49% of patients had adenocarcinoma. Pemetrexed maintenance therapy was well tolerated, with only 14.6% of patients experiencing grade 3–4 adverse effects. Pemetrexed maintenance therapy significantly improved both PFS (HR 0.50, 95% CI 0.42–0.61) and OS (HR 0.79, 95% CI 0.65–0.95). Sixty-seven per cent of patients in the placebo arm received a second line of treatment at tumour progression (pemetrexed in only 19% of cases) compared with 52% of those in the pemetrexed arm. Thus, the survival comparison included 52% of patients in the pemetrexed arm who received at least three lines of treatment and 33% of patients in the placebo arm who received only one line of treatment. Analysis based on histology showed that the therapeutic benefit was due to the efficacy of pemetrexed on non-squamous carcinoma, with no effect being noted in patients with squamous carcinoma. The median survival gain was about five months in patients with non-squamous carcinoma (see *Table 2*), and pemetrexed was subsequently authorised for maintenance treatment in this subpopulation.

First-line Maintenance with Targeted Therapies

Bevacizumab and Cetuximab

Two trials evaluating the combination of first-line chemotherapy with bevacizumab, a monoclonal anti-vascular endothelial growth factor (VEGF) antibody that inhibits tumour neoangiogenesis, showed a gain in PFS[21,22] and OS with the carboplatin–paclitaxel combination[21] in patients with advanced-stage non-squamous NSCLC. Cetuximab is a chimeric antibody targeting the EGFR extracellular domain. The First-Line Erbitux in Lung Cancer (FLEX) trial[23] showed a survival benefit when cetuximab was combined with first-line chemotherapy in advanced-stage NSCLC. These trials all included post-induction 'maintenance' treatment based on the respective monoclonal antibodies,[21–23] but their design rules out firm conclusions regarding the part played by this maintenance therapy in the observed benefit.

Table 2: Results of the JMEN Trial of Pemetrexed Maintenance Therapy, According to Histology[20]

Histology	Median OS (months)		HR for OS	Median PFS (months)		HR for PFS
	Pemetrexed	Placebo		Pemetrexed	Placebo	
Adenocarcinoma n=328	16.8	11.5	0.70 p=0.002	4.6	2.7	0.51 p<0.00001
Large cell n=20	8.4	7.9	0.98 p=0.964	4.5	1.5	0.40 p=0.104
Squamous cell carcinoma n=182	9.9	10.8	1.07 p=0.678	2.4	2.5	1.03 p=0.896
Other n=133	11.3	7.7	0.61 p=0.025	4.1	1.6	0.44 p=0.0002

PFS data from independent review. HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Table 3: Results of the SATURN Trial According to Clinical Subgroup[34]

	Number of Patients (PFS)	PFS – HR (95% CI) Erlotinib versus Placebo	Number of Patients (OS)	OS – HR (95% CI) Erlotinib versus Placebo
Male	654	0.78 (0.66–0.92)	659	0.88 (0.74–1.05)
Female	230	0.56 (0.42–0.76)	230	0.64 (0.46–0.91)
Caucasian	744	0.75 (0.64–0.88)	746	0.86 (0.73–1.01)
Asian	128	0.58 (0.38–0.87)	131	0.66 (0.42–1.05)
Adenocarcinoma	401	0.60 (0.48–0.75)	403	0.77 (0.61–0.97)
Squamous cell	359	0.76 (0.60–0.95)	360	0.86 (0.68–1.10)
Never smoker	152	0.56 (0.38–0.81)	152	0.69 (0.45–1.05)
Former smoker	242	0.66 (0.50–0.88)	244	0.75 (0.56–1.00)
Current smoker	490	0.80 (0.67–0.97)	493	0.88 (0.72–1.08)

CI = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Oral EGFR tyrosine kinase inhibitors (TKIs) are interesting candidates for first-line maintenance therapy. Their tolerability is generally good, apart from frequent acneiform skin rash and rare cases of severe diarrhoea. In the BR.21 trial, erlotinib yielded a significant survival benefit in second- and third-line settings compared with placebo therapy,[24] whereas this was not the case in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial of gefitinib,[25] possibly because the higher relative dose of erlotinib was more likely to inhibit the wild-type EGFR. The discovery of mutations that activate the *EGFR* gene later provided a biomarker for predicting the efficacy of EGFR TKIs.[26]

Joint administration of EGFR TKIs and cytotoxic drugs in previously untreated patients proved to be no better than chemotherapy alone.[27–30] The landmark survival analysis of the Tarceva responses in conjunction with paclitaxel and carboplatin (TRIBUTE) trial after the end of chemotherapy nevertheless showed a survival benefit among patients who continued to receive erlotinib single-agent therapy, supporting erlotinib maintenance after chemotherapy.[30] A phase II randomised trial conducted in Korea evaluated erlotinib maintenance therapy after first-line treatment in which erlotinib or placebo was alternated (days 15–28) with chemotherapy (cisplatin or carboplatin–gemcitabine).[31] Erlotinib had a major impact on PFS (HR 0.47, 95% CI 0.33–0.68) but not on overall survival. It is difficult to determine the respective roles played by erlotinib maintenance and by erlotinib alternation with chemotherapy.

Several trials have assessed early 'maintenance' with an EGFR inhibitor (gefitinib or erlotinib) starting at the end of induction therapy. Gefitinib was tested as a consolidation treatment in locally advanced NSCLC after concomitant chemo-radiotherapy followed by a first consolidation course of docetaxel.[32] Unexpectedly, this trial showed a deleterious effect of gefitinib on survival due to an excess of deaths linked to cancer progression, possibly involving a negative interaction between thoracic radiotherapy and gefitinib. The second trial of gefitinib was performed in Japan, and compared a standard treatment consisting of six cycles of dual-agent platinum-based therapy with an experimental treatment including sequential gefitinib after the first three cycles of chemotherapy.[33] The PFS was significantly improved by early gefitinib introduction (HR 0.68, 95% CI 0.57–0.80), but this did not translate into an OS benefit (HR 0.86, 95% CI 0.72–1.03), except in the subgroup of patients with adenocarcinoma. Erlotinib maintenance therapy has been tested in two large studies, one with erlotinib alone[34,35] and the other with erlotinib plus bevacizumab.[36] The SATURN trial[34,35] involved 889 patients whose disease had been controlled by four cycles of first-line platinum-based chemotherapy. The patients were randomised between immediate erlotinib therapy (150mg/day) and placebo. The main end-point was PFS. The study population included 25% women, 14% patients of Asian origin, 40% patients with squamous cell carcinoma, 17% non-smokers and 45% responders to chemotherapy. PFS was significantly improved by erlotinib (HR 0.71, 95% CI 0.62–0.82). Subgroup analyses based on clinical characteristics failed to identify a particular category of patients who did not benefit from erlotinib maintenance therapy (see *Table 3*).

An analysis of EGFR pathway biomarkers[35] showed that only the presence of a mutation activating the *EGFR* gene was predictive of a significant PFS benefit (HR 0.10 in patients with the mutation). The gain in PFS associated with erlotinib remained significant in patients with the wild-type EGFR (HR 0.78, 95% CI 0.63–0.96), showing that the benefit is not solely dependent on *EGFR* mutations (see *Table 4*). Finally, the onset of symptom aggravation, in terms of pain and analgesic consumption, was significantly delayed by erlotinib, with no accompanying loss of quality of life. This gain in PFS translated into an OS benefit (HR 0.81, 95% CI 0.70–0.95), including in patients with tumours lacking *EGFR* mutations

Table 4: Progression-free Survival with Erlotinib Maintenance Therapy in the SATURN Trial, According to Epidermal Growth Factor Receptor Biomarkers[35]

	Number of Patients		% Patients	PFS – HR (95% CI) Erlotinib versus Placebo	Interaction Test
IHC	742	IHC+	84	0.69 (0.58–0.82)	Negative
		IHC-	16	0.77 (0.51–1.14)	
FISH	488	FISH+	48	0.68 (0.51–0.90)	Negative
		FISH-	52	0.81 (0.62–1.07)	
EGFR mutation	449	Mutated EGFR	11	0.10 (0.04–0.25)	p=0.0185
		Wild-type EGFR	89	0.78 (0.63–0.96)	
K-ras mutation	494	Mutated K-ras	18	0.77 (0.50–1.19)	Negative
		Wild-type K-ras	82	0.70 (0.57–0.87)	

CI = confidence interval; EGFR = epidermal growth factor receptor; FISH = fluorescence in situ *hybridisation; HR = hazard ratio; IHC = immunohistochemistry; PFS = progression-free survival.*

(HR 0.77, 95% CI 0.61–0.97). Post-study analyses showed that 72% of patients in the control arm received further treatment when they progressed (EGFR TKIs in only 21% of patients) compared with 71% of those in the erlotinib arm.

The double-blind, placebo-controlled ATLAS trial[36] examined the value of adding erlotinib to continued bevacizumab therapy after induction chemotherapy in patients with non-squamous NSCLC initially treated with a combination of chemotherapy and bevacizumab. The main objective was to show a gain in PFS. The trial was interrupted when, after the inclusion of 743 patients (48% women, 17% non-smokers, 82% with adenocarcinoma), an interim analysis showed a significant PFS advantage in the erlotinib arm (HR 0.72, 95% CI 0.59–0.88). The benefit was similar in men and women but larger in non-smokers (HR 0.34, 95% CI 0.19–0.61) than in smokers and ex-smokers (HR 0.76, 95% CI 0.62–0.93).

Interpreting the Results of Maintenance Trials, and Unresolved Questions

Prolonging first-line treatment for advanced-stage NSCLC increases the duration of disease control and may improve overall survival.[37] Maintenance therapy is reserved for selected patients based on the efficacy and tolerability of platinum-based dual-agent therapy; these represent only 45–60% of patients who receive a first line of treatment. Eligible patients have a better prognosis than the general population of patients receiving first-line treatment, and this must be taken into account when interpreting survival data. Recent trials of maintenance therapy (see *Table 1*) have all shown that about 50% of patients whose disease is controlled by platinum-based dual-agent therapy progress within two or three months after treatment cessation, and this clearly calls for new strategies capable of maintaining the initial benefit.

Regardless of the precise modalities, the effect of maintenance therapy on PFS is remarkably homogeneous, with a relative reduction in the risk of progression of about 30–40% and no apparent deterioration in quality of life (although this is based on very biased data); symptom aggravation is also delayed.[20,34] The impact of maintenance strategies on OS is more variable, but a fairly uniform reduction in the risk of death of about 20% is observed in trials testing a particular cytotoxic agent (gemcitabine, docetaxel or pemetrexed) or erlotinib (SATURN trial).[13,16,20,34]

This survival benefit does not seem to be linked to the 'timing' effect inherent in maintenance therapy, i.e. early treatment of residual disease. Indeed, survival among patients who actually receive a second-line treatment when they progress is similar to that of patients who receive maintenance therapy with the same drugs.[16] In other words, the efficacy of the treatments tested so far (docetaxel, pemetrexed, erlotinib) seems to be the same regardless of whether they are used as maintenance therapy or only at disease progression.[38–40] The survival benefit observed in clinical trials of maintenance therapy seems to be due more to the increase in the proportion of patients who can receive several lines of treatment.[16,38–40] Indeed, despite close monitoring (every six weeks) after the end of induction chemotherapy, about one-third of patients never receive a second line of treatment, mainly because of their rapid clinical decline. Maintenance therapy therefore allows more patients to receive several active treatments, particularly when it involves a different drug from that used for induction therapy.

Thus, not all patients benefit from maintenance therapy. A treatment-free period after induction chemotherapy is more beneficial in some cases, provided a second line of treatment remains feasible. Clinical trials have not been designed to identify any particular clinical characteristics indicating which patients should be treated before their disease progresses.[16] Factors predictive of the probability of receiving second-line chemotherapy tend to be related to the prognosis, probably because they are more dependent on intrinsic tumour aggressiveness than on the efficacy of first-line treatment.[9] Other important factors in this decision are the presence of stable or symptomatic disease after induction therapy, a large tumour volume with visceral metastases, major adverse effects during first-line treatment and, of course, the patient's own wishes. The difficulty of predicting the individual chance of receiving second-line treatment, together with the median PFS of only three months, means that patients should at least be closely monitored after their initial treatment.

If the maintenance strategy is chosen, the choice between continuation of existing therapy in maintenance therapy (continued administration of one of the drugs used for induction therapy) and the use of a different agent remains an open question. The benefit of continuation of existing therapy in maintenance with gemcitabine is similar to that obtained with docetaxel or erlotinib. It may be better to reserve continuation of existing therapy in maintenance for patients who respond to induction therapy, and to give an immediate new treatment to patients whose disease is simply stabilised. The choice between a cytotoxic drug and an EGFR inhibitor can be based on histology (pemetrexed use is restricted to non-squamous-cell carcinoma), biological findings such as *EGFR* mutations (if their presence did not lead to the choice of an EGFR TKI for first-line treatment),[41] knowing that erlotinib is also active for EGFR wild-type tumours and on the very different tolerability profiles and modes of administration. In particular, EGFR TKIs have the advantage of oral administration and can usually be continued up to disease progression without the risk of cumulative toxicity.

Conclusion

First-line maintenance therapy represents an important strategic advance in advanced-stage NSCLC, being capable of providing a very significant increase in the duration of disease control and a noteworthy impact on survival, with acceptable additional toxicity, notably in the case of gemcitabine, pemetrexed and erlotinib. Maintenance therapy is now an option after first-line chemotherapy. The next step is to identify those patients who are most likely to benefit from this strategy, and the optimal modalities for the individual patient. ■

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