

First-line maintenance (1LM) treatment: a new strategy to treat advanced NSCLC

Lung cancer is the most common cause of cancer death in men and women, both worldwide [1] and in the UK [2], with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases [3]. Most patients present at an advanced, inoperable stage of disease with no prospect of cure and a poor prognosis. Most patients die within five years of diagnosis.

The current standard front-line treatment for advanced NSCLC is with 4–6 cycles of a modern platinum-based chemotherapy regimen, which offers a modest survival benefit and improvements in patient quality of life (QoL) over best supportive care (BSC) [4,5]. This is despite the recent identification of patients with activating Epidermal Growth Factor Receptor (EGFR) mutations, who survive significantly longer and achieve dramatically high response rates when treated with EGFR tyrosine kinase inhibitors (TKIs) compared with chemotherapy, although EGFR-mutant-positive (EGFR-mut+) tumours are only seen in around 8% of the non-Asian population of lung cancer patients [6] and overall prognosis remains poor. For patients who have a measurable response or who have disease stabilisation following first-line (1L) treatment, adopting a ‘watch-and-wait’ policy has generally been the customary approach. However, response rates for 1L chemotherapy are low (20–40%), prognosis remains poor, with a median survival time of 7–12 months [7,8], and most patients will eventually experience disease progression. Extending 1L chemotherapy beyond 4–6 cycles is not recommended because cumulative toxicities and impaired QoL outweigh any potential advantage in progression-free survival (PFS) and overall survival (OS) that may be gained with the increased duration of therapy [9,10].

For patients with evidence of disease progression after initial chemotherapy, second-line (2L) treatment confers benefits and should be offered to those patients with a good performance status (PS) [4,5,11]. However, studies have shown that only 30–50% of patients that received 1L treatment went on to get 2L therapy [12–14] due to rapid disease progression, worsening of symptoms and declining PS, which reduce the opportunity to administer 2L treatment. Consequently, better processes to

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identify disease progression earlier, as well as better treatment options, are needed to improve outcomes for patients with NSCLC after 1L therapy.

In recent years, investigations have focused on 1L maintenance (1LM) treatment following 1L chemotherapy in an attempt to improve disease control rates and survival because of the availability of better tolerated 2L treatment drugs. In 2009 two large, phase III trials demonstrated the clinical benefits, including significant OS benefits, of 1LM therapy with pemetrexed and erlotinib, two agents that are well-established treatments for NSCLC. As a result of these landmark trials, both agents have had their licensed indications extended to include 1LM treatment of NSCLC. This article examines the current evidence for 1LM treatment for advanced NSCLC, reviews the role of this treatment strategy in current clinical practice and considers how the implementation of 1LM is likely to impact on the way patients are treated in future.

The concept of 1LM treatment

Maintenance therapy is defined by the National Cancer Institute as treatment given to help keep cancer from returning after it has responded to initial therapy. The goals of maintenance are to prolong survival, and improve or maintain QoL. There are two forms of maintenance therapy: continuation maintenance and switch maintenance.

Continuation maintenance therapy is defined as continuation of one of the agents given as 1L treatment after 4–6 cycles of initial therapy in the absence of disease progression. One of the earliest studies to suggest that continuation maintenance is effective is the Eastern Cooperative Oncology Group (ECOG) 4599 study, a phase III, randomised study of 878 patients who received 1L paclitaxel-carboplatin

therapy (6 cycles) with or without bevacizumab, which was continued until disease progression. A significant 2-month OS benefit was seen with bevacizumab ($p = 0.003$) [15]. Another maintenance trial with the biologic agent, cetuximab, significantly prolonged OS by 1.2 months ($p = 0.044$) in patients following cisplatin-vinorelbine-cetuximab 1L treatment [16]. However, there is no direct comparison of maintenance vs no maintenance with these biological agents after initial therapy and the contribution of each drug to the maintenance effect remains unclear. Unlike the survival benefits reported with biological agents as continuation maintenance, this approach with cytotoxic agents used in 1L chemotherapy remained unproven [17,18]. Furthermore, recent data from two maintenance trials reported at ASCO in 2010 with gemcitabine maintenance after initial platinum-gemcitabine chemotherapy did not show survival benefits, though one trial demonstrated an improvement in PFS but at the expense of increased toxicity [19,20].

In contrast to continuation maintenance, more encouraging results are reported with the switch maintenance approach. This is defined as the initiation of a different agent, not included as part of the 1L regimen, after 4–6 cycles of initial therapy in the absence of disease progression. In a study reported by Fidias and colleagues, comparing immediate with delayed docetaxel (essentially, maintenance vs conventional 2L treatment) after 1L gemcitabine-carboplatin, docetaxel maintenance was associated with statistically improved PFS and a trend to improved OS. The latter was due towards the fact that more patients in the immediate arm (94.8%) received docetaxel compared with those who received 2L treatment (62.8%). However if the analysis included only patients receiving 2L treatment, OS time was similar in both arms [21].

Currently there are two FDA- and EMEA-approved indications for pemetrexed and erlotinib as ‘switch’ maintenance after response and/or stable disease (SD) following 1L chemotherapy, based on the JMEN and SATURN trials, respectively. These trials will be examined in more detail and compared with conventional 2L treatment.

1LM vs early 2L: Assessing the evidence

JMEN

This randomised, double-blind trial compared pemetrexed 1LM with placebo in 663 patients with stage IIIB/IV disease (PS 0–1) that had not progressed after 4 cycles after platinum-based chemotherapy (the regimens used did not include pemetrexed). Maintenance pemetrexed significantly improved median PFS by 1.7 months ($p < 0.0001$) and median OS by 3.2 months ($p = 0.012$) with pemetrexed [22]. In a further report, the survival benefits of pemetrexed were demonstrated only in the subgroup of patients with non-squamous histology in the 1L (hazard ratio [HR], 0.84, $p = 0.011$) and 2L (HR 0.78, $p = 0.048$) settings [23] and this finding was confirmed in the maintenance setting (5.2 month improvement in median OS, HR 0.70, $p = 0.002$) [22]. Subgroup analysis of OS revealed a greater benefit for patients with SD following 1L treatment compared with those who had a complete or partial response (CR/PR; HR 0.68 vs 0.9) [24]. Unfortunately only 18% of patients in the placebo arm received 2L pemetrexed [22] and this perhaps had an impact on OS. Pemetrexed is licensed in Europe for the treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology [25].

SATURN

SATURN was a randomised, double-blind trial that compared erlotinib 1LM vs placebo in 889 patients with stage IIIB/IV disease that had not progressed after 4 cycles of platinum-based chemotherapy. Erlotinib demonstrated a significant 29% improvement in PFS vs placebo and benefit was also seen across the majority of patient subgroups, irrespective of histology, race, gender or smoking status. A modest improvement in OS was also seen with erlotinib vs placebo, with a 19% reduction in risk of death (median OS 12.0 vs 11.0 months, respectively). A survival benefit was also seen with erlotinib in the subgroup of patients with EGFR wild-type tumours (HR 0.77, $p = 0.02$). When analysed according to response to 1L chemotherapy, patients with SD had a significantly greater survival benefit with erlotinib vs placebo (median 11.9 vs 9.6 months; $p = 0.0019$) than patients with CR/PR [26]. In fact, erlotinib conferred the greatest OS benefit in the SD group (HR 0.72) and on the basis of these data was licensed as maintenance treatment in patients with SD after 4 cycles of standard platinum-based 1L chemotherapy [27]. As expected, erlotinib maintenance was highly effective in patients with activating EGFR mutations (PFS HR

Table 1: Progression-free survival (PFS) and overall survival (OS) in the intent-to treat (ITT) and licensed populations in trials of 1LM treatment

Maintenance treatment	PFS*	p value	OS*	p value
Erlotinib (vs placebo)				
ITT population [26]	0.71	< 0.0001	0.81	0.0088
Stable disease population [34]	0.68	< 0.0001	0.65	0.0041
Pemetrexed (vs placebo) [22]				
ITT population	0.50	< 0.0001	0.79	0.012
Non-squamous population	0.44	< 0.0001	0.70	0.002
Docetaxel (immediate vs delayed) [21]	5.7 vs 2.7 months	0.0001	12.3 vs 9.7 months	0.0853
Gemcitabine (vs BSC) [19]	3.9 vs 3.8 months	NS	0.97	0.84
Gemcitabine (vs observation) [20]	0.55	< 0.0001	0.86	NR

*Values are hazard ratios unless otherwise stated. BSC, best supportive care; NR, not reported; NS, not significant.

0.10, $p < 0.0001$) [26] but it can be argued that these patients should be treated with a TKI upfront, based on the IPASS [28] and Spanish Lung Cancer Group data [29]. In SATURN, only 21% of the patients in the placebo arm went on to receive subsequent treatment with a TKI and this may explain the OS benefit seen in the trial [26].

Both the JMEN and SATURN trials demonstrated a significant improvement in PFS and OS with 1LM treatment (compared with placebo) (Table 1). However, it must be emphasised that less than 50% of the patients who received 1L chemotherapy in both JMEN and SATURN went on to receive maintenance treatment, and these results are, therefore, not comparable to 1L treatment trials because of the selection of only those patients with SD or CR/PR for subsequent maintenance therapy.

Who is eligible for 1LM treatment?

Current evidence from JMEN and SATURN indicates that 1LM offers many patients the chance to receive further effective therapy that can improve survival, especially patients with SD after initial chemotherapy. For oncologists, the introduction of maintenance increases the number of available therapy options and several factors must be taken into consideration when deciding who to treat in this setting.

The JMEN and SATURN trials did not ask a clear question of switch maintenance vs early 2L treatment because patients in the placebo arms were not required to switch to the effective drug after progression. Evidence shows that switch maintenance improves PFS and OS with pemetrexed and erlotinib but these agents do have side effects, and there is no evidence to show that patients receiving active treatment have an improved QoL. It is possible that patients live just as long if they

are actively monitored and receive an active 2L treatment immediately on progression. An overview of PFS and OS in trials of four agents currently licensed for 2L treatment (Table 2) suggests that receiving effective treatment in the 2L treatment setting prolongs survival. Whether or not 1LM is as effective as early 2L treatment remains uncertain. What is clear, however, is that patients should be given the opportunity to receive additional therapy while they are fit enough to do so.

Receiving maintenance therapy allows many patients to be treated with further lines of effective therapy after progression. In SATURN, 71% of the patients who received active 1LM went on to receive further post-study treatment [26], indicating clear benefits of 1LM for eligible patients, in addition to 2L or subsequent treatment. If patients are symptomatic, improving PFS may be beneficial, and clinicians may want to consider maintenance treatment if it is well tolerated. However, if patients have significant treatment-related toxicities from 1L treatment or marginal PS, clinicians may want to consider a treatment break and to monitor patients closely for disease progression to ensure they receive an effective 2L treatment. Close surveillance with appropriate 2L therapy given on progression may be just as effective as, and more cost-effective than, maintenance therapy. This strategy will allow patient to have better QoL and fewer side effects from cancer treatments.

Selecting 1LM treatment

Once eligibility for 1LM has been established, clinicians must consider which drug to recommend for a particular patient. Working within the licensed indications of the available options, pemetrexed can only be used in patients with non-squamous disease, while erlotinib is licensed specifically for patients with SD following

Table 2: Progression-free survival (PFS) and overall survival (OS) in the intent-to treat (ITT) populations in trials of 2L treatment

2L treatment	PFS*	p value	OS*	p value
Erlotinib (vs placebo) [31]	0.61	< 0.001	0.70	< 0.001
Pemetrexed (vs docetaxel) [30]	0.97	0.759	0.99	0.226
Docetaxel (vs BSC) [35]	10.6 vs 6.7 weeks (time to progression)	0.001	7.0 vs 4.6 months (median survival time)	0.047
Gefitinib (vs docetaxel) [36]	1.04	0.47	1.020	NR
Network meta-analysis [37]	NR	NR	Erlotinib 0.71 [†] Pemetrexed 0.85 [†] Docetaxel 0.85 [†] Gefitinib 0.88 [†]	NR

*Values are hazard ratios unless otherwise stated. [†]Estimated hazard ratio relative to placebo. BSC, best supportive care; NR, not reported.

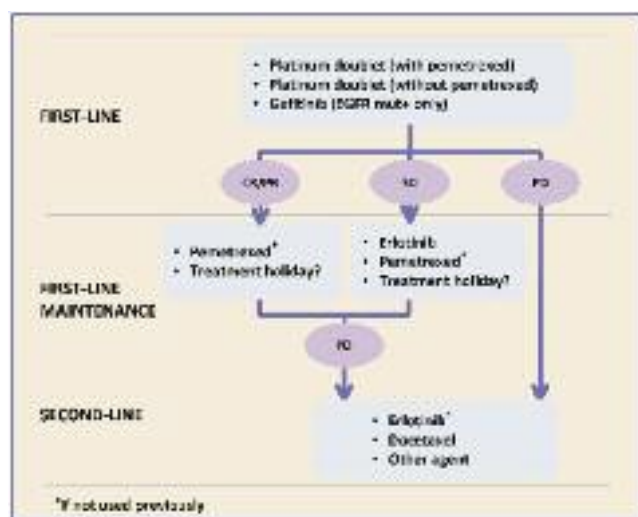


Figure 1: Potential treatment algorithm for NSCLC for UK physicians following the recent introduction of 1LM treatment. NB. Pemetrexed is only licensed for use in non-squamous disease.

1L chemotherapy. Data from SATURN show that erlotinib 1LM has shown benefits in all patients including those with squamous disease. For patients with non-squamous disease, both pemetrexed and erlotinib can be used. Patient preference is an important consideration in choosing which treatment will be most suitable for an individual. Common issues that concern patients include oral vs IV therapy, dosing regimen, home- vs hospital-based treatment, and toxicity profile.

Treatment-related adverse events most commonly associated with pemetrexed are fatigue and neutropenia [22,30]. Rash and diarrhoea are commonly associated with erlotinib [26, 31]. Pemetrexed must be administered intravenously and all patients require administration of pre- or concomitant medications, including supplementation with vitamin B12 (prior to and at intervals during treatment) and folic acid (during treatment) to reduce the risk of toxicity, and a corticosteroid on the day

prior to, the day of and the day after pemetrexed administration to reduce the incidence and severity of skin reactions [25]. Erlotinib is a once-daily oral therapy. Unlike cytotoxic chemotherapy, erlotinib is not associated with myelotoxicity, and most adverse events are mild or moderate [27].

The chemotherapy agents used as 1L treatment will also influence the choice of 1LM. Currently, using pemetrexed maintenance after using pemetrexed in a 1L regimen has not been confirmed as effective. A randomised, placebo-controlled phase III study of maintenance pemetrexed immediately following induction treatment with pemetrexed-cisplatin for advanced non-squamous NSCLC is currently underway and results are eagerly anticipated [32]. Until the results of this study are known, there is no evidence to recommend pemetrexed maintenance after 1L pemetrexed-cisplatin chemotherapy and these patients should be considered for erlotinib maintenance if they have SD.

A new concept when choosing 1LM treatment is the response to 1L chemotherapy. In both the SATURN and JMEN trials, patients with SD after 1L chemotherapy had a more favourable outcome to 1LM treatment compared with patients who had a CR/PR [24, 26]. SD accounts for at least half of all outcomes after 1L chemotherapy [21, 22, 26] and the evidence suggests that this substantial proportion of patients should be considered for 1LM.

Increasingly, the identification of predictive biomarkers in NSCLC will play an important role in treatment decision-making. For patients with activating EGFR mutations, an EGFR TKI is the most effective treatment and should be offered as 1L therapy. A pooled analysis evaluating clinical outcome in patients with activating EGFR mutations has demonstrated longer PFS with erlotinib (13.2 months) and gefitinib (9.8 months) than chemotherapy (5.9 months) [33]. Gefitinib is now licensed for 1L treatment in this subgroup of patients, although to date 1L gefitinib has demonstrated only a significant improvement in PFS, and not OS, in the subgroup of patients with EGFR mutations [28]. Results from an ongoing, prospective, phase III study of 1L erlotinib vs platinum doublet in EGFR-mut+ NSCLC (EURTAC), initiated by the Spanish Lung Cancer Group, are expected to be available in the near future to confirm the IPASS data [28] in a Caucasian population. A similar study in China (OPTIMAL) is also expected to report first findings later this year. EGFR TKIs are a clearly highly effective therapy for EGFR-mut+ tumours, but these patients comprise only a small percentage of the total NSCLC population and the majority of patients have EGFR wild-type disease. Nevertheless, for patients with stable, EGFR wild-type disease, a significant survival benefit is seen with erlotinib 1LM (HR 0.65, $p = 0.0041$) [34].

Implications of 1LM on the overall treatment pathway for NSCLC

The introduction of 1LM treatment offers patients an important new therapy option and oncologists must review the way the disease is treated. Instead of 1L chemotherapy, followed by a period of 'watch and wait' until disease progression and 2L treatment (assuming the patient is fit enough), a new treatment algorithm is emerging, as outlined below and summarised in Figure 1.

First-line treatment

Platinum doublet chemotherapy remains the standard of care for most patients. Pemetrexed is emerging as the treatment of choice for patients with non-squamous disease, with gemcitabine the choice for

squamous histology. For patients with EGFR-mutation-positive tumours, gefitinib may be an option.

First-line maintenance

For patients with non-progressive disease after 1L chemotherapy, current treatment options are pemetrexed (non-squamous disease, in patients not getting pemetrexed 1L) and erlotinib (SD), as discussed above.

Second-line treatment

The NICE-approved agents are erlotinib or docetaxel, although pemetrexed may be an option where it is funded (e.g. Scotland. In contrast, NICE does not recommend use of

2L pemetrexed in England and Wales). If not previously prescribed, erlotinib has become the 2L treatment of choice because it is effective across all patient subgroups (including EGFR wild-type tumours), is generally well tolerated, improves symptoms and, unlike docetaxel, is not associated with myelotoxicity [31].

Summary and conclusions

Maintenance therapy represents a new strategy to improve outcomes for patients with advanced NSCLC. There remains uncertainty as to whether or not the beneficial effect demonstrated by 1LM is due to use of early 2L treatment.

'Watch-and-wait' is no longer an automatic standard treatment option for patients who have SD following 1L treatment because the evidence shows a survival benefit of 1LM for these patients. If a treatment break is considered necessary, the patient should be closely monitored for any evidence of disease progression and 2L treatment started so that the opportunity for effective treatment is not lost. As implementation of 1LM enters routine clinical practice and a new treatment algorithm emerges, it is important for oncologists to ensure that the most effective treatment is prescribed for the appropriate patient at the right time. ■

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