Chemotherapy and Targeted Therapeutics as Maintenance of Response in Advanced Non-Small Cell Lung Cancer

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Non-small cell lung cancer (NSCLC) remains the most common cause of cancer-related death in the United States. Survival for patients with advanced disease remains meager with standard platinum-based doublet therapy even given initially. Improved efficacy and tolerability of third-generation chemotherapies and small-molecule inhibitors has prompted the evaluation of these agents in the maintenance setting in order to enhance current outcomes. Two separate strategies have evolved: the introduction of a non–cross-resistant drug immediately following first-line or induction chemotherapy (switch maintenance), or the continuation of the non-platinum partner initially introduced during induction (continuation maintenance). Here we review the available clinical trial data evaluating both maintenance strategies, and offer our assessment of their contemporary clinical implications and cost-effectiveness.
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Non-small cell lung cancer (NSCLC) remains the most common cause of cancer-related death in the United States.[1] Standard first-line treatment for patients with advanced disease typically includes platinum-based doublet chemotherapy, where the platinum agent (cisplatin or carboplatin) is selected based on patient performance status (PS) and oncologist preference, and the non-platinum agent is chosen based on factors such as the histology of the patient's tumor and side effect profile.[2,3] The goal of first-line chemotherapy is to improve survival, achieve maximal tumor shrinkage, ameliorate disease-related symptoms, and enhance patient quality-of-life, while balancing cumulative treatment-related toxicities. Most patients reach maximum benefit after three to four cycles of doublet therapy. Continued treatment beyond this may contribute little or no additional anti-tumor effect, and may instead cause increased treatment-related toxicity and worsened quality of life (QoL).[4] However, newer so-called "third-generation" chemotherapy given in the second-line setting can be tolerated for multiple cycles.[5] Therefore, American Society of Clinical Oncology (ASCO) guidelines recommend limiting first-line platinum-based chemotherapy to no more than six cycles,[6] and reserving additional therapies for after cancer recurrence. Several single-agent therapies, including docetaxel, pemetrexed, and erlotinib, have been approved by the US Food and Drug Administration for second-line use in NSCLC, based on improved survival outcomes post-platinum progression.[5,7,8]

Two separate approaches to maintenance therapy have been evaluated: the introduction of a non–cross-resistant single agent immediately following first-line or induction chemotherapy (switch maintenance), or the continuation of the non-platinum agent (or agents) initially introduced during induction(continuation maintenance). Both cytotoxic chemotherapy and molecularly targeted agents have been evaluated as potential maintenance strategies. In general, the goal of maintenance therapy is to render patients free from progressive disease and lung cancer symptoms for as long as possible using a well-tolerated regimen, without causing excessive toxicity or undue compromise to QoL. Evaluating just how well maintenance therapy achieves this goal has been more challenging than assessment of benefit in first- or second-line trials, not only due to heterogeneity in clinical trial design, endpoints

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selected and agents tested but also to the increasing economic considerations of treatment. While there is little doubt that maintenance therapy can prolong progression-free survival (PFS), and sometimes overall survival (OS), exactly which patients should receive it, what impact it has on QoL, and whether the benefit justifies the high cost all remain uncertain issues, even as maintenance therapy is increasingly adopted as standard practice.[9,10] This review will summarize some of the largest trials and most recent analyses evaluating both switch and continuation maintenance therapy for NSCLC, as they have helped inform our understanding of its true benefit and cost.

SWITCH MAINTENANCE

Switch maintenance, sometimes referred to as "early second-line" therapy, is supported by the Norton-Simon hypothesis—that sensitive cancer cells grow rapidly, while resistant cells grow more slowly, such that a successful treatment regimen will have an initial induction regimen to kill the sensitive cells, followed immediately by separate maintenance phase to eliminate the slower-growing, resistant cancer clones.[11,12] Accordingly, patients treated with a non–cross-resistant switch maintenance therapy should lead to improved survival outcomes, as second-line regimens have already been shown to improve survival. Summarized below are four large randomized phase III clinical trials that have informed our understanding of switch maintenance therapy (Table 1).

After unsuccessful attempts to demonstrate improved survival with maintenance therapy using second-generation cytotoxic agents vinorelbine and paclitaxel,[13,14] Fidias et al reported a significant benefit in PFS using switch maintenance docetaxel.[15] Five hundred sixty-six chemotherapy-naïve patients with advanced NSCLC were treated with carboplatin and gemcitabine, and all patients who had not progressed after four cycles (n = 398) were then randomized to receive "immediate" docetaxel maintenance therapy for a maximum of six cycles, or "delayed" docetaxel at disease progression. Patients who received immediate docetaxel remained progression-free longer than patients who received docetaxel at progression (5.7 months *v* 2.7 months, $P = .001$). There was also a trend towards longer OS for patients who received immediate docetaxel (12.3 months *v* 9.7 months, $P = .0853$), although the trial was powered to detect a significant difference in survival of 4 months. Patients did not report a significant difference in toxicity or QOL assessment using the Lung Cancer Symptom Scale (LCSS), whether they were treated with immediate or post-progression docetaxel.

The Fidias trial included a careful assessment of post-induction therapies, and demonstrated that most patients in the immediate docetaxel arm (145 of 153; 94.8%) received maintenance treatment, while only a little more than half of patients in the delayed docetaxel arm received second-line therapy after disease progression (98 of 156; 62.8%). In a subgroup analysis evaluating only those patients who received docetaxel in each arm, there was no measurable survival difference between the arms (median OS, 12.5 months in both groups), suggesting that receiving docetaxel at all, rather than the timing of its administration, was most important. However, because patients randomized to the delayed docetaxel arm were more likely to experience clinical deterioration that precluded second-line therapy, the Fidias trial results suggest that maintenance therapy ensures patients are exposed to additional non–cross- resistant treatment, which may explain the survival benefits measured.

A second large phase III trial that has informed understanding of switch maintenance was the JMEN study,[16] in which 663 patients who had not progressed after receiving four cycles of platinum-based therapy were randomized to pemetrexed or best supportive care (BSC) in a 2:1 study design. Like in the Fidias trial, patients who received switch maintenance pemetrexed remained progression-free lon-

Table 1. Switch Maintenance Trials

Study	N (pts)	Maintenance Arms	PFS (mo)	HR	*P* Value	OS (mo)	HR	*P* Value
Fidias et al[15]	309	Immediate docetaxel	5.7		.0001	12.3		.0853
		Delayed docetaxel	2.7			9.7		
JMEN[16]	663	Pemetrexed	4.3	0.50	<.0001	13.4	0.79	.012
		Placebo	2.6			10.6		
SATURN[18]	889	Erlotinib	3.0	0.71	<.0001	12.0	0.81	.0088
		Placebo	2.8			11.0		
ATLAS[19,20]	768	Bevacizumab /erlotinib	4.8	0.72	.0012	15.9	0.90	.2686
		Erlotinib	3.7			13.9		

Abbreviations: pts, patients; PFS, progression-free survival; HR, hazard ratio; OS, overall survival.