TREATMENT UPDATE

Clinical Considerations and the Evolving Role of Maintenance Therapy in Advanced Non-Small-Cell Lung Cancer

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This activity is intended for physicians, registered nurses, and other healthcare providers who are interested in learning about clinical advances in maintenance therapy approaches in the treatment of patients with non-small-cell lung cancer.

GOAL

The goal of this activity is to provide participants with a detailed overview of the evolving evidence regarding the role and clinical considerations for using maintenance therapy for the treatment of patients with non-small-cell lung cancer to improve outcomes and quality of life.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the role of maintenance therapy in patients with advanced non-small-cell lung cancer
- Compare clinical trial data supporting the use of maintenance therapy after first-line chemotherapy in patients with advanced non-small-cell lung cancer
- Integrate maintenance therapies into the clinical management of patients with advanced non-small-cell lung cancer based on histologic and molecular disease features
- Apply management strategies for preventing and treating adverse events associated with non-small-cell lung cancer maintenance therapies

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Clinical Considerations and the Evolving Role of Maintenance Therapy in Advanced Non-Small-Cell Lung Cancer

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The Definition of Maintenance Therapy in Advanced NSCLC

In this roundtable, Corey J. Langer, MD, FACP; Mark Socinski, MD; Howard (Jack) L. West, MD; Beth Eaby-Sandy, MSN, CRNP, OCN; and Victoria Sherry, MSN, CRNP, AOCNP, focus on the evolving role of maintenance therapy following first-line treatment of advanced non-small-cell lung cancer (NSCLC). In their discussion, the physicians provide an in-depth analysis of current and emerging treatment options available for use as maintenance therapy and share the criteria they use when managing patients with NSCLC who are eligible for maintenance therapy in their own practices. Other areas explored by all panelists include key toxicities and supportive-care strategies for patients receiving specific maintenance therapies, cost/reimbursement considerations with use of agents in the maintenance setting, and the overall cost-effectiveness of the maintenance therapy approach in NSCLC.

Corey J. Langer, MD, FACP: Let us begin with the definition of maintenance. Dr. Socinski, how do you define maintenance therapy in advanced NSCLC, and how has the definition evolved?

Mark Socinski, MD: I define it as prolonging the duration of therapy in those patients who have demonstrated some degree of sensitivity after 4 cycles of first-line treatment. This sensitivity entails lack of disease progression associated with either a response or stable disease. Maintenance can involve continuation of 1 of the drugs used during the first 4 cycles, the classic example being continuation of bevacizumab. Alternatively, several trials have investigated various switch-maintenance strategies with pemetrexed, erlotinib, docetaxel, and other agents where the maintenance component was not included in the initial 4 cycles of first-line therapy. This strategy is a consideration in approximately two thirds of patients.

There is a fair amount of patient drop-out during the first 4 cycles, either because patients progress or have difficulty tolerating therapy. Therefore, these maintenance strategies are not pertinent to all patients with advanced NSCLC but rather only to the subset of patients who demonstrate some sort of treatment sensitivity manifested as stable or responding disease.

Corey J. Langer, MD, FACP: Do you always consider maintenance therapy after 4 cycles of first-line treatment? Do you ever consider it after 6 cycles in select patients?

Mark Socinski, MD: I rarely treat to 6 cycles in patients. I typically stop after 4 cycles, unless of course patients are participating in a clinical trial requiring 6 courses of first-line therapy. I have given up the argument that 4 cycles are better than 6. If a clinician wants to administer 6 treatment cycles, then that is acceptable.

Corey J. Langer, MD, FACP: In fact, a trial that you led started the debate as to whether 4 first-line cycles were better than indefinite treatment.

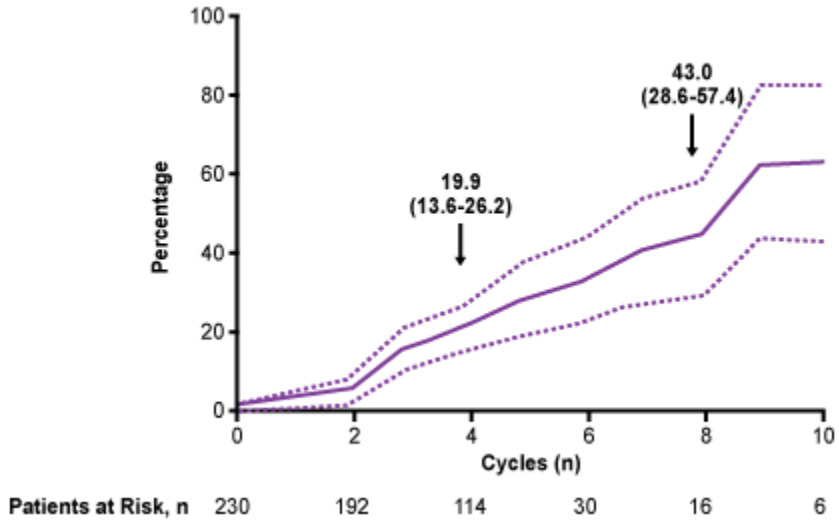
Mark Socinski, MD: Yes, my colleagues and I conducted a phase III trial comparing the efficacy of 4 cycles of carboplatin/paclitaxel vs continuous treatment with carboplatin/paclitaxel until disease progression in the first-line setting.[1] In total, 232 treatment-naive patients with stage IIIB/IV NSCLC and a Karnofsky performance score of ≥ 70 were randomly assigned to the 2 treatment arms. Overall response rates, median overall survival (OS), and quality of life were all comparable between the 2 arms (Table 1). The only notable difference between the arms was increased toxicity associated with continuous therapy. Specifically, the incidence of grade 2-4 neuropathy was 14% with 4 cycles of chemotherapy vs 27% with continuous chemotherapy (P = .02). Moreover, the neuropathy was cumulative, occurring in 19.9% of patients after 4 cycles of carboplatin/paclitaxel and in 43.0% after 8 cycles (Figure 1).

Table 1. Treatment Outcomes of the Phase III Trial Comparing 4 Cycles vs Continuous Carboplatin/Paclitaxel[1]

Outcome	4 Cycles Carboplatin/Paclitaxel (n = 114)	Continuous Carboplatin/Paclitaxel (n = 116)	*P* Value
Median no. of cycles delivered (range)	4 (0-6)*	4 (0-19)	
ORR, %	22	24	.80
[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	23	34	[illegible]
[illegible]	15	[illegible]	[illegible]

[illegible]; ORR, objective response rate. [illegible]
ent received 5 cycles and 2 patients received 6 cycles. [illegible]

Figure 1. Rate of cumulative neuropathy by carboplatin/paclitaxel cycle.[1] Kaplan-Meier methods used to account for patient dropout. Hatched lines represent 95% CIs.



Another reason why I administer 4 chemotherapy cycles in the frontline setting before maintenance therapy is because that was typically the approach taken in the positive trials of maintenance therapy.

Howard (Jack) L. West, MD: The findings from Dr. Socinski's very typical trial of 4 cycles vs continuous chemotherapy are partly limited by the fact that ongoing treatment with a platinum doublet containing a taxane leads to cumulative prohibitive neuropathy. Data from the French study by Perol and colleagues[2] suggest that there may still be value in continuing some first-line chemotherapy regimens beyond 4 cycles.

Continuation vs Switch-Maintenance Therapy: Which Is More Useful?

Mark Socinski, MD: Most studies of maintenance therapy in NSCLC administered 4 cycles of platinum-based therapy and then employed switch-maintenance strategies. These studies constitute the most positive trials arguing for a maintenance approach. Although it is possible to continue treatment with bevacizumab as maintenance, this strategy may not necessarily the best approach. Just because the ECOG 4599 study reported improvements in OS, progression-free survival (PFS), and response rates with bevacizumab maintenance following 6 cycles of carboplatin/paclitaxel[3] does not mean that this strategy provides value in lung cancer. However, phase III data from GOG 218 showed that bevacizumab maintenance therapy

following bevacizumab plus carboplatin/paclitaxel induction therapy significantly prolonged PFS in advanced ovarian cancer compared with carboplatin/paclitaxel alone.[4]

Corey J. Langer, MD, FACP: Yes, one of the unanswered questions in advanced NSCLC is whether there is true value in maintaining bevacizumab beyond the duration of chemotherapy.

Dr. West, which do you prefer: continuous maintenance or switch maintenance? And do you call it “switch maintenance’” or “early second-line therapy”?

Howard (Jack) L. West, MD: I use the term ”switch maintenance,” although the terminology is not really important; that is simply semantics. However, the concept of calling the strategy “maintenance” emphasizes the goal of prolonging the period of nonprogression for as long as possible and suggests the need for a longitudinally tolerable treatment approach.

There is a finite group of agents that lend themselves to the maintenance approach. Bevacizumab is one, and others include pemetrexed, erlotinib, and perhaps gemcitabine. It has been interesting to see some positive data emerging on the concept of continuation maintenance with gemcitabine, which does not have US Food and Drug Administration (FDA) approval for this indication.

My approach has generally been to continue treatment with bevacizumab, pemetrexed, or both agents as maintenance therapy if patients received these specific agents in the first-line setting. I would potentially put single-agent gemcitabine in the same continuous-maintenance category for patients with disease of squamous cell histology.

Ongoing therapy until progression has always been the treatment approach of choice in patients who receive a first-line EGFR tyrosine kinase inhibitor (TKI). Given the very limited number of effective treatments and lines of therapy in NSCLC, clinicians should be careful not to discard any treatments too soon. The concept of ongoing doublet therapy vs a fixed number of cycles in the first-line setting is potentially a different paradigm than the concept of stopping the doublet and continuing on with just a singlet comprising the right drug.

Current and Emerging Agents Being Used for Maintenance Therapy

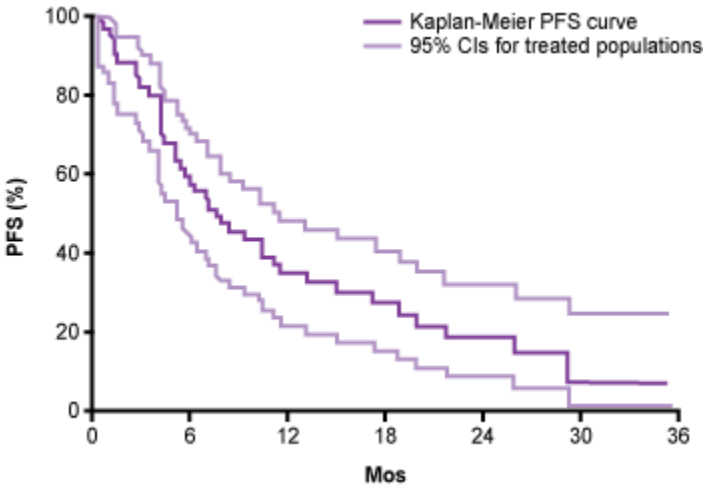
Pemetrexed Maintenance

Corey J. Langer, MD, FACP: Many clinicians use pemetrexed continuously following first-line therapy despite a lack of definitive data supporting the effectiveness and safety of this approach. Paz-Ares and colleagues[5] in Spain are currently conducting a randomized, double-blind, placebo-controlled trial of maintenance pemetrexed plus best supportive care (BSC) vs placebo plus BSC following first-line treatment with 4 cycles of pemetrexed/cisplatin in patients with advanced nonsquamous NSCLC.[5,6] Patients who do not experience disease progression following 4 cycles of pemetrexed/cisplatin are randomly assigned 2:1 to receive either maintenance pemetrexed or placebo. This study has a planned enrollment of 900 individuals and a primary endpoint of PFS. Initial data may be presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2011.

Based on encouraging phase II data from a trial conducted by Patel and colleagues,[7] my colleagues and I, with a fair degree of enthusiasm, have adopted continuous maintenance with pemetrexed/bevacizumab after first-line pemetrexed/bevacizumab/carboplatin. This was a study that evaluated the efficacy and safety of 6 cycles of first-line pemetrexed/bevacizumab/carboplatin followed by maintenance pemetrexed/bevacizumab in 50 patients with stage IIIB/IV nonsquamous NSCLC.[7] The ORR was 55% (95% CI: 41% to 69%), and median PFS and OS rates were 7.8 months (95% CI: 5.2-11.5 months) and 14.1 months (95% CI: 10.8-19.6 months), respectively, after a median follow-up of 13 months (Figure 2). However, it has never been proven in a large randomized trial whether continuing

pemetrexed/bevacizumab beyond the initial 4-6 cycles of first-line therapy is beneficial. Many of us think it is, but it is still unclear.

Figure 2. PFS with first-line pemetrexed/bevacizumab/carboplatin followed by pemetrexed/bevacizumab maintenance.[7]



Mark Socinski, MD: A study currently assessing this very approach is the PointBreak trial. This is a randomized, open-label phase III study of first-line pemetrexed/bevacizumab/carboplatin followed by pemetrexed/bevacizumab maintenance compared with first-line paclitaxel/bevacizumab/carboplatin—the current FDA-approved standard—followed by bevacizumab maintenance in patients with stage IIIB/IV nonsquamous NSCLC.[8,9] Patients may receive up to 4 cycles of first-line therapy before commencing maintenance therapy. Planned enrolment is 900 patients—450 per treatment arm—and the primary endpoint is OS. This is not a perfect trial given the different first-line regimens and the different maintenance regimens.

Another similar study is the 3-armed ECOG E5508 trial, which has a very nice design. This randomized phase III study will compare maintenance treatment with bevacizumab, pemetrexed, or both bevacizumab/pemetrexed following 4 cycles of first-line treatment with carboplatin/paclitaxel/bevacizumab in patients with stage IIIB/IV nonsquamous NSCLC.[10] Planned enrollment is approximately 1300 patients, and the primary endpoint is OS.

Corey J. Langer, MD, FACP: In the E5508 trial, the maintenance arms are continued indefinitely until either progression or untoward toxicity. As of July 2010, this study is not yet open, but it should open fairly soon, within the next 1-3 months.

One of the criticisms that my colleagues and I encountered at ECOG when we were designing this trial was the absence of a control arm consisting of no maintenance therapy. The E5508 study will compare different maintenance strategies, but it will not isolate the benefit of maintenance therapy in the context of a patient who has already received bevacizumab up front. To account for this, one of the proposals was to include an observation arm with no maintenance, with the initiation of bevacizumab/pemetrexed at the first signs of progression. However, this being the United States, that trial would probably never accrue adequately.

Gemcitabine Maintenance

Howard (Jack) L. West, MD: Before 2010, we really did not have much data for supporting gemcitabine maintenance in advanced NSCLC. There was primarily a smaller study by Brodowicz and colleagues[11] of the Central European Cooperative Oncology Group, which was published in *Lung Cancer* in 2006. This was a randomized phase III trial that sought to show a significant difference in the median time to progression in patients with stage IIIB/IV NSCLC who received gemcitabine maintenance vs BSC following first-line treatment with

gemcitabine/cisplatin. Numerically, the results clearly favored the maintenance gemcitabine arm over stopping therapy. Specifically, the Brodowicz and colleagues trial showed a 1.6-month improvement in time to progression with gemcitabine vs BSC (6.6 vs 5.0 months; $P < .001$) and a 2-month improvement in OS (13.0 vs 11.0 months; $P = .195$). However, the difference between the 2 arms for OS did not reach statistical significance. There were only 206 patients who were ultimately randomly assigned in a 2:1 fashion to ongoing gemcitabine or observation, so the study was underpowered regarding OS. Therefore, I would say that the results were still encouraging and that the absence of proof is not really proof of absence.

This study highlights one of the problems with these continuation trials: They end up being underpowered because they all require patients to start with the first-line therapy and attain at least stable disease before randomization, but nearly one half of the patients drop off before that time. This type of design contrasts with approaches that enroll patients after they have already received the first 4 cycles of therapy, which allows essentially 100% of the patients who were eligible from the beginning to be retained. The time point for the study start is very different between the 2 designs.

Corey J. Langer, MD, FACP: I agree. With most trials that start enrollment at the initiation of first-line treatment, there is going to be a natural attrition rate. The study design is a bit cleaner if patients are enrolled when they are declared to have stable or responsive disease following first-line treatment, although one must acknowledge that this does not reflect the entire patient population.

Howard (Jack) L. West, MD: More recent data lend stronger support to the benefit of gemcitabine maintenance therapy. Perol and colleagues[2] from France recently conducted the randomized phase III IFCT-GFPC 0502 study, in which 834 patients with stage IIIB/IV NSCLC were started on cisplatin/gemcitabine, and then patients who had not progressed after the first 4 cycles were randomized to either observation, continuous maintenance with gemcitabine, or switch maintenance with erlotinib. Therefore, this study directly compared no maintenance with continuation maintenance with switch maintenance.

Corey J. Langer, MD, FACP: This is probably the truest trial in that regard.

Howard (Jack) L. West, MD: Yes. This study did not include pemetrexed as maintenance, which is an approach that clinicians tend to favor more based on feasibility and presumption of benefit rather than true data supporting this strategy, at least not yet. However, the Perol and colleagues study at least provides a proof of principle. The data showed that patients who were randomized to either gemcitabine or erlotinib maintenance both had a significant improvement in PFS—the primary endpoint—in comparison with the observation arm, although the improvement was clearly more striking with gemcitabine (Table 2). Overall survival showed a trend toward being more favorable for both of the maintenance arms, but no significant differences compared with the observation arm were noted.

Table 2. Treatment Outcomes of IFCT-GFPC 0502 (Gemcitabine Maintenance vs Erlotinib Maintenance vs Observation)[2]

Outcome	Gemcitabine (n = 149)	Erlotinib (n = 153)	Observation (n = 152)
Median PFS, mos	3.8	2.9	1.9
▪ HR vs observation (95% CI)	0.55 (0.43-0.70)	0.82 (0.73-0.93)	
▪ *P* value	< .0001	.002	
Median OS, mos	12.1	11.8	10.7
▪ HR vs observation (95% CI)	0.86 (0.66-1.12)	0.91 (0.80-1.04)	
▪ *P* value	NS	NS	

HR, hazard ratio; NS, not significant.

Corey J. Langer, MD, FACP: The investigators implied that it was still too early to detect any significant differences in OS, but one wonders.

Mark Socinski, MD: Another impressive thing about the French trial is that the protocol dictated second-line therapy with pemetrexed for patients with progressive disease. I was rather impressed with the percentage of patients who were exposed to an approved second-line agent and also an agent approved for maintenance therapy. Specifically, 76.1%, 60.4%, and 63.2% of patients randomized to observation, gemcitabine maintenance, and erlotinib maintenance, respectively, went on to receive second-line pemetrexed, and responses were observed among 15.2%, 8.1%, and 11.9% of evaluable patients, respectively. To me, that was an interesting part of this trial.

Howard (Jack) L. West, MD: Absolutely. One of the criticisms of some published trials is insufficient crossover and exposure of the placebo or observation arm to subsequent equivalent therapy. This issue has to do with access vs timing. This concern was negated in the French study by ensuring that all patients were exposed to pemetrexed upon disease progression.

Corey J. Langer, MD, FACP: It is possible that an OS advantage with the maintenance approaches has not yet been observed in the French trial given the mandatory crossover to second-line pemetrexed in the event of progressive disease.

Howard (Jack) L. West, MD: Another point to make about this study is that the investigators showed impressive findings regarding the diverse subgroups of patients who benefited from maintenance therapy with both erlotinib and gemcitabine according to subset analyses. Very broad groups showed improvement in PFS regardless of the type of response to first-line therapy, adenocarcinoma status, smoking status, sex, and performance score. However, perhaps the greatest benefit with gemcitabine maintenance was observed in patients with an objective response to first-line therapy as opposed to stable disease (HR: 0.44 vs 0.68), which suggests to me that the full benefits of first-line therapy have not necessarily been achieved after 4 cycles.

Belani and colleagues[12] also recently conducted a phase III trial in which 519 patients with stage IIIB/IV NSCLC recline gemcitabine/carboplatin and then were randomly assigned to gemcitabine maintenance plus BSC or BSC alone. The findings showed no improvement in OS, the primary endpoint, or PFS, a secondary endpoint, between the 2 arms (Table 3).

Table 3. Treatment Outcomes of the Phase III Trial Comparing Gemcitabine Maintenance + BSC vs BSC Alone[12]

Outcome	Gemcitabine + BSC (n = 128)	BSC (n = 127)	HR (95% CI)	*P* Value
Median OS, mos	8.0	9.3	0.97 (0.72-1.30)	.838
Median PFS, mos	7.4	7.7	1.09 (0.81-1.45)	.575

The possible benefits of gemcitabine therapy may have been nullified by the specific patients enrolled in this trial. This patient population was very distinct demographically from the other populations that have been enrolled in trials of maintenance therapy. The median patient age was 67 years, and nearly two thirds of patients (64%) had an Eastern Cooperative Oncology Group performance score of 2. This population may bear a closer resemblance to a real lung cancer population, at least in terms of age. However, many clinicians tend to see patients with a better performance score.

To me, the discrepancy between this trial and the many recent trials that showed a benefit highlights the need to select the appropriate patients for maintenance therapy. The positive results from several recent maintenance studies apply to patients similar to those included in the trials and not those who are making an effort to get back to the clinic after first-line therapy, who will probably not be well served by receiving more therapy than they can go through comfortably.

Corey J. Langer, MD, FACP: The benefits of maintenance therapy are obviously going to be limited to patients with a reasonable performance scores, not those who have very tenuous functional status.

EGFR TKI Maintenance

Mark Socinski, MD: There are 4 trials that have investigated maintenance therapy with EGFR TKIs in NSCLC following 4 cycles of first-line therapy. Of these, 3 evaluated erlotinib (SATURN, ATLAS, and IFCT-GFPC 0502), and 1 evaluated gefitinib (EORTC 08021).

The SATURN trial[13,14] gained approval for erlotinib as maintenance therapy in advanced NSCLC in the United States. This randomized, placebo-controlled phase III trial randomly assigned 889 patients who did not have progressive disease after 4 cycles of platinum-based chemotherapy to erlotinib maintenance or placebo until progression or unacceptable toxicity.[1] The trial was positive for the primary endpoint of PFS (median PFS with erlotinib vs placebo: 12.3 vs 11.1), with an HR of 0.71 ($P < .0001$) (Table 4). The findings were also positive for OS, with an HR of 0.79. In Europe, erlotinib also is approved for use as maintenance therapy, but because the PFS and OS benefits were greater in patients with stable disease and fairly anemic in patients who responded to first-line therapy, the European indication is only for patients who have stable disease after initial chemotherapy.

Table 4. Comparison of Outcomes Among Phase III Studies of EGFR TKI Maintenance

Trial	Treatment Comparison	PFS HR (95% CI)	*P* Value	OS HR (95% CI)	*P* Value
SATURN[13,14]	Erlotinib vs *placebo*	0.71 (0.62-0.82)	< .0001	0.81 (0.70-0.95)	.009
ATLAS[15,16]	Bevacizumab + erlotinib vs bevacizumab + placebo	0.72 (0.592-0.881)	.0012	0.92 (0.70-1.21)	.5604
IFCT-GFPC 0502[2]	Erlotinib vs observation	0.82 (0.73-0.93)	.002	0.91 (0.80-1.04)	NS
EORTC 08021[17]	Gefitinib vs placebo	0.61 (0.45-0.83)	.0015	0.83 (0.60-1.15)	.2

ATLAS[15,16] is an analogous trial to the SATURN trial, except in the bevacizumab setting. In this randomized, double-blind, placebo-controlled phase IIIb trial, 743 patients with stage IIIB/IV NSCLC who did not have progressive disease following 4 cycles of first-line platinum-based chemotherapy plus bevacizumab were randomly assigned to receive maintenance therapy with bevacizumab plus erlotinib or bevacizumab plus placebo (Capsule Summary).[15] [coder: link to Clin Onc June 2009 8002] The HR for PFS was nearly identical to that observed in the SATURN trial (HR: 0.72; *P* = .0012), reflecting median PFS values of 4.76 months for bevacizumab plus erlotinib vs 3.75 months for bevacizumab plus placebo. The survival difference between the 2 arms was not significant. The prespecified primary OS analysis conducted at the time of PFS analysis showed an approximate 1-month difference in OS between the bevacizumab plus erlotinib vs bevacizumab plus placebo arms (14.4 vs 13.3 months, respectively; HR: 0.92; 95% CI: 0.70-1.21; *P* = .5604). Two post hoc analyses conducted after more deaths had occurred showed greater improvement in OS with the addition of erlotinib. In the last analysis, median OS was 15.9 months with bevacizumab plus erlotinib vs 13.9 months with bevacizumab plus placebo (HR: 0.90; 95% CI: 0.74-1.09; *P* = .2686). Still, the difference was not statistically significant.

Dr. West already discussed the phase III IFCT-GFPC 0502 study conducted by Perol and colleagues[2] that compared observation, continuous maintenance with gemcitabine, and switch maintenance with erlotinib in 834 patients with stage IIIB/IV NSCLC following 4 cycles of cisplatin/gemcitabine. For the primary endpoint of PFS, the HR for switch maintenance with erlotinib vs observation was 0.82 (95% CI: 0.73-0.93; *P* = .002), which was statistically significant. As mentioned, there was also a trend toward improved OS with erlotinib vs observation, as shown by an HR of 0.91 (95% CI: 0.80-1.04; *P* = NS).

Lastly is the EORTC 08021 trial conducted by Gaafar and colleagues,[17] which was stopped early because of poor accrual (planned enrollment: 598 patients). With only 173 patients, it is the smallest of any of the maintenance trials. Patients who had nonprogressive disease following 4 cycles of platinum-based chemotherapy were randomly assigned in a double-blind fashion to receive gefitinib maintenance or matched placebo until progression or unacceptable toxicity. The PFS HR for gefitinib vs placebo was 0.61 (95% CI: 0.45-0.83; *P* = .0015), which was statistically significant. The median values for PFS were 4.1 and 2.9 months, respectively. The HR for OS—the primary endpoint—for gefitinib vs placebo was 0.83 (95% CI: 0.60-1.15; *P* = .2) and was not statistically significant. The median OS values were 10.9 and 9.4 months, respectively.

Therefore, all 4 of these trials clearly show significant positive improvements in PFS with EGFR TKI maintenance therapy.

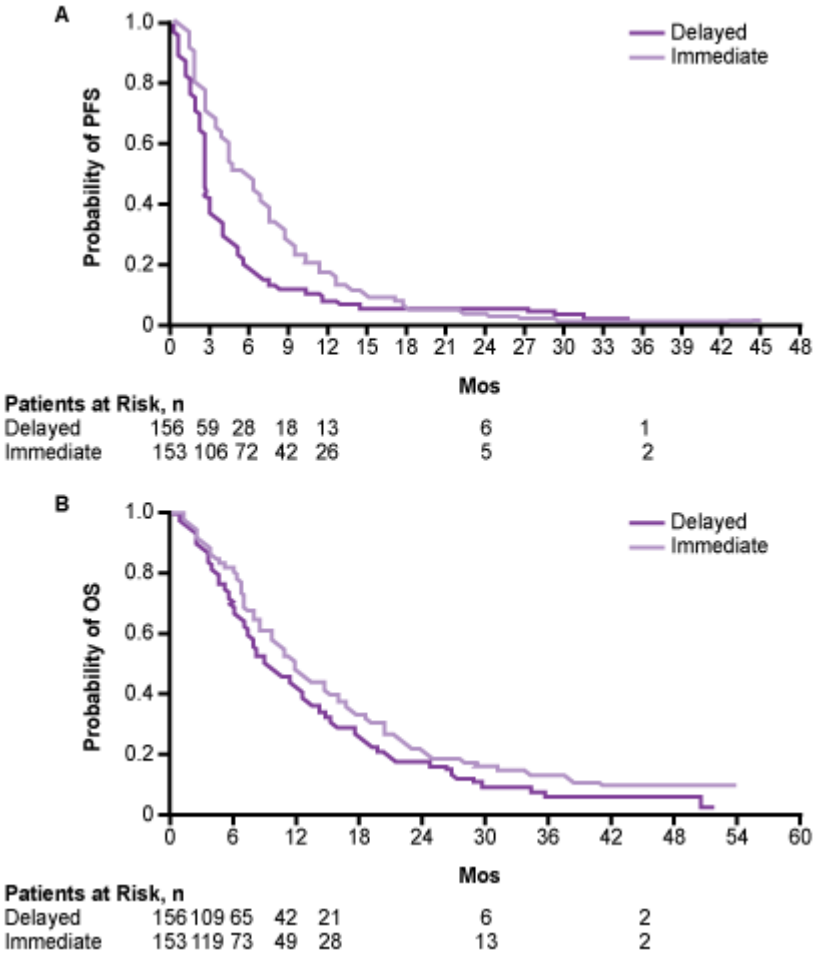
Regarding all the positive data from the many maintenance trials, the tone of this conversation has been that maintenance is the standard approach to treatment in patients with advanced

NSCLC, and I disagree. It is one standard, but I still think it is reasonable to allow patients treatment breaks, follow them with observation, and administer second-line therapy when needed. However, as a treating oncologist, I am attracted by the use of EGFR TKIs as maintenance therapy. These agents provide patients with a break from chemotherapy, they are generally well tolerated, and they are administered orally, unlike gemcitabine and pemetrexed, which allows patients to have fewer visits.

Docetaxel Maintenance

Corey J. Langer, MD, FACP: The randomized phase III study of docetaxel maintenance conducted by Fidias and colleagues,[18] in my opinion, started the modern era of switch maintenance. In this trial, 566 patients with stage IIIB/IV NSCLC received 4 cycles of first-line gemcitabine/carboplatin, then patients with at least stable disease were randomly assigned to receive immediate vs delayed docetaxel. Median OS—the primary endpoint—was greater with immediate vs delayed docetaxel at 12.3 months vs 9.7 months, but the difference between the 2 arms was not statistically significant (*P* = .0853) (Figure 3). Median PFS was significantly greater with immediate vs delayed docetaxel at 5.7 months vs 2.7 months (*P* = .0001). Essentially, I think this was an underpowered but ultimately "positive" trial.

Figure 3. Comparison of PFS and OS outcomes for immediate vs delayed docetaxel maintenance.[18]



Mark Socinski, MD: Yes, I agree with you.

Howard (Jack) L. West, MD: The main point is that this trial is certainly supportive of the same general trends seen in other maintenance studies, as indicated by a significant improvement in PFS and a trend toward an OS benefit of longer than 2.5 months. Moreover, these

improvements were seen despite the fact that approximately two thirds of patients (62.8%) in the delayed comparator arm crossed over to eventually receive docetaxel.

Corey J. Langer, MD, FACP: This may have been one of the reasons why this study did not show a survival advantage.

Howard (Jack) L. West, MD: Yes. Nonetheless, a 2.6-month survival benefit in absolute terms is certainly encouraging.

Mark Socinski, MD: The most impressive finding to me from the Fidias and colleagues study is the 7.6% difference in 1-year survival between the 2 arms (51.1% for immediate docetaxel vs 43.5% for delayed docetaxel). Let us not forget that this trial showed that receiving docetaxel, even if delayed, yielded comparable survival compared with immediate treatment.

Corey J. Langer, MD, FACP: This is one of the arguments for not necessarily embracing maintenance. Following patients closely and initiating second-line treatment quickly at the first sign of disease progression can ideally salvage those individuals without costing them any survival advantage while “preserving” a treatment holiday.

Individualization of Maintenance Therapy: Histology vs Markers vs Both

Corey J. Langer, MD, FACP: Dr. West, how do you individualize therapy for patients with adenocarcinoma vs squamous cell carcinoma?

Howard (Jack) L. West, MD: There are a wide range of therapeutic options available for adenocarcinoma. First, I find out very early on whether a patient has an EGFR mutation, either before first-line therapy begins or shortly thereafter. If a patient has an EGFR mutation, then I implement an EGFR inhibitor, namely erlotinib—again, either from the beginning of treatment or by transitioning it in.

Corey J. Langer, MD, FACP: If you find out that a patient is EGFR mutation positive and you have already started them on chemotherapy, at what point would you switch them over to a maintenance strategy, or would you wait and hold additional therapy in reserve?

Howard (Jack) L. West, MD: It depends on how well the patient responded to initial therapy. If they were started on carboplatin/paclitaxel/bevacizumab, I would probably proceed along the lines of the ATLAS trial and transition in the erlotinib. If they received pemetrexed first line and responded beautifully, I would probably continue to watch them closely and consider erlotinib at some point in the future when they develop disease progression.

For patients with adenocarcinoma who are EGFR wild type, I am quite comfortable administering maintenance pemetrexed or bevacizumab or both. If patients are in need of a treatment break, either physically or emotionally, I do not hesitate to offer that. I feel comfortable following such patients closely and being able to intervene promptly.

My general feeling is that if patients are able and they have responded well to first-line therapy, I am inclined to proceed with either an oral therapy or an every-3-week intravenous therapy as maintenance. This approach is typically very compatible with good quality of life. However, the appropriate course of management still requires an individual discussion with the patient regarding whether they would welcome a break from therapy or would be anxious being off treatment.

Corey J. Langer, MD, FACP: I have 2 more questions before I turn to Dr. Socinski. How do you treat patients with squamous cell carcinoma, and do you individualize the nature of maintenance treatment based on histology vs markers vs both?

Howard (Jack) L. West, MD: For squamous disease, I am inclined to use a similar approach as for adenocarcinoma but with different drugs. First-line pemetrexed and bevacizumab are not strong choices for patients with squamous cell histology because of efficacy concerns for pemetrexed and safety concerns for bevacizumab. Most often, I administer gemcitabine with either cisplatin or carboplatin as first-line therapy. For patients who are candidates for maintenance therapy after 4 cycles of first line chemotherapy, I am very comfortable continuing gemcitabine or switching to erlotinib or docetaxel as maintenance therapy.

Corey J. Langer, MD, FACP: Basically adapting a Perol approach, therefore.

Howard (Jack) L. West, MD: Yes, but at the same time, I feel very comfortable switching to erlotinib. I reserve switching a patient to docetaxel because I think this agent is a little more challenging in terms of quality-of-life adverse effects compared with these other choices.

Corey J. Langer, MD, FACP: Dr. Socinski, what are your strategies?

Mark Socinski, MD: I do not disagree with Dr. West. I typically use either carboplatin/paclitaxel or carboplatin/gemcitabine as first-line therapy in patients with squamous cell histology. If these patients are suitable for maintenance therapy, I typically administer erlotinib and reserve docetaxel for true second-line or third-line therapy.

Corey J. Langer, MD, FACP: You do not typically use docetaxel?

Mark Socinski, MD: No. Most of the patients with squamous cell carcinoma that we see in North Carolina are elderly male smokers, and many of them are not appropriate candidates for maintenance therapy. Also, going back to some of my earlier comments, using erlotinib in an oral strategy just seems to be a little easier for certain patients.

Corey J. Langer, MD, FACP: Ongoing smokers can and probably should receive a higher erlotinib dose.

Mark Socinski, MD: Yes.

Management of Toxicities Associated With Maintenance Therapies for Advanced NSCLC

Toxicities Associated With EGFR TKIs

Corey J. Langer, MD, FACP: Dr. Socinski made an interesting point that the toxicities of EGFR TKIs are, in some ways, much less severe than with chemotherapy. Do our 2 advanced practice oncology nurses agree with that assessment, particularly as clinicians often tend to use pemetrexed in NSCLC?

Beth Eaby-Sandy, MSN, CRNP, OCN: I think it definitely depends on the patient and whether they develop rash. Patients often view a rash as being just as problematic as other potential adverse effects because it is noticeable to others.

Victoria Sherry, MSN, CRNP, AOCNP: In addition, many patients believe that taking a pill will not yield as many adverse effects as receiving a drug intravenously. This is a common misconception.

The rash and diarrhea associated with EGFR TKIs significantly impact patient's quality of life. I find my patients have fewer adverse effects with pemetrexed maintenance.

Corey J. Langer, MD, FACP: How do you usually address these and other adverse effects with patients? Do you have prophylactic measures that you institute?

Victoria Sherry, MSN, CRNP, AOCNP: To prevent or ameliorate rash, I use a regimen for rash prophylaxis that the patient begins the day they start erlotinib. This regimen includes taking minocycline 100 mg twice daily for 2 weeks on and 2 weeks off. The cyclic use of minocycline helps to offset gastrointestinal upset in addition to applying a face lotion with an SPF ≥ 15 twice daily with the addition of hydrocortisone cream 1% at night. I emphasize that they should avoid sun exposure as much as possible and to wear a wide-brimmed hat and apply sunscreen liberally when they are outside. They are also instructed to take the medication on an empty stomach at night and to avoid taking PPIs or drinking grapefruit juice. My patients follow up with me in clinic 2 weeks after starting erlotinib for a toxicity check.

For symptom management of diarrhea, I instruct my patients to take over-the-counter loperamide. If that is ineffective, I prescribe diphenoxylate and atropine.

Corey J. Langer, MD, FACP: Is that usually at the first hint of diarrhea?

Victoria Sherry, MSN, CRNP, AOCNP: Yes, absolutely.

Corey J. Langer, MD, FACP: Are there any other issues with the EGFR TKIs?

Beth Eaby-Sandy, MSN, CRNP, OCN: In the maintenance or second-line setting, when my patients are started on erlotinib, they have a follow-up visit with me 2 weeks after starting the drug so that I can get an idea of exactly what side effects they are having. In the randomized phase III BR.21 trial of erlotinib conducted in patients who had received 1 or 2 previous chemotherapy regimens, the incidence of grade 3/4 rash was only 9% with erlotinib, which was managed with treatment interruption and symptomatic therapy.[19] Therefore, I do not administer preventive antibiotics for rash up front, which I know is sometimes used with monoclonal antibodies. The prevention strategies that I employ, many of which Ms. Sherry already mentioned, include having patients take their medication on an empty stomach, use moisturizing lotion, and avoid sun exposure as best they can. Treatment of rash depends on its grade. I offer topical treatments for grade 1 or 2 rash. Usually for grade 2 or 3 rash, I add oral antibiotics and possibly even a steroid if the rash becomes extremely uncomfortable for patients.

Corey J. Langer, MD, FACP: Do you find that the time of day at which patients take the medication makes any difference? Some of our patients seem to tolerate the drugs best when they take erlotinib 2-3 hours after dinner, at bedtime.

Victoria Sherry, MSN, CRNP, AOCNP: That is what I advise. I advise them to take the medication at night on an empty stomach.

Beth Eaby-Sandy, MSN, CRNP, OCN: Yes, many of my patients do well when they take the medication at night. I agree with that.

Toxicities Associated With Pemetrexed

Corey J. Langer, MD, FACP: Ms. Sherry, moving on to the other major maintenance drug, pemetrexed, tell us about some of the prophylactic measures you use in patients receiving this agent and what problems you have encountered.

Victoria Sherry, MSN, CRNP, AOCNP: The package insert for pemetrexed recommends premedicating the patient with a dexamethasone preparation the day before, day of, and day after chemotherapy to prevent a rash. My colleagues and I have found that the actual incidence

of developing a pemetrexed rash is low, and therefore, we avoid giving oral dexamethasone. Sometimes the adverse effects from the steroids are more difficult to deal with than the actual rash. We do give 8-mg intravenous dexamethasone the day they receive pemetrexed. Ms. Eaby-Sandy, do you still use this strategy?

Beth Eaby-Sandy, MSN, CRNP, OCN: I use this approach approximately 50% of the time. It depends on whether patients have diabetes complications, whether they have mood swings on steroids, or some other contraindication. I just do not see a lot of rash with pemetrexed.

Corey J. Langer, MD, FACP: My colleagues and I sometimes give dexamethasone as an intravenous dose on the day of pemetrexed administration.

Victoria Sherry, MSN, CRNP, AOCNP: Yes, we administer 8-mg intravenous dexamethasone.

Mark Socinski, MD: My colleagues and I generally give oral dexamethasone the day before, day of, and day after pemetrexed administration. If patients forget to take the dexamethasone, I am not concerned. I usually give them an intravenous dose of dexamethasone before they receive the pemetrexed. We do not see a lot of rash with pemetrexed, so I do not think that dexamethasone prophylaxis is terribly important.

Howard (Jack) L. West, MD: My colleagues and I do the same. We still prescribe oral dexamethasone the day before, day of, and day after pemetrexed administration, unless patients object. There are very limited data showi

Howard (Jack) L. West, MD: One underappreciated adverse effect of pemetrexed is eye irritation and swelling. Do you have patients that complain of this?

Mark Socinski, MD: I have a patient on pemetrexed right now who has slight periorbital edema. For this particular patient, we have treated through his periorbital edema. He has been able to tolerate the adverse effect, and it is not life threatening. His wife points it out every time I see him, but I respond by saying that his tumor is under great control. He is on the PointBreak trial and is receiving maintenance treatment with pemetrexed and bevacizumab. He has currently received 12 cycles of maintenance. To me, that is success.

Corey J. Langer, MD, FACP: I have seen eye problems of a different type in patients receiving erlotinib, such as conjunctivitis and the somewhat strange symptom of hypertrichosis, where the lashes grow excessively.

Beth Eaby-Sandy, MSN, CRNP, OCN: With pemetrexed, I have seen a couple cases of tearing

Beth Eaby-Sandy, MSN, CRI

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Victoria Sherry, MSN, CRNP, AOCNP: Yes, the nurses in our infusion room dip the urine on every patient receiving bevacizumab. I check a random urine every 3 cycles or if they are symptomatic.

Beth Eaby-Sandy, MSN, CRNP, OCN: I order a random urine protein every other cycle. If a patient has an elevated value, I have them do a 24-hour urine protein test prior to their next visit.

Corey J. Langer, MD, FACP: What about hypertension and headaches?

Victoria Sherry, MSN, CRNP, AOCNP: I find that hypertension is a much bigger issue than headaches. I will administer a diuretic or antihypertensive prior to treatment. Patients who are enrolled on a clinical trial have lower blood pressure parameters, and therefore, their treatment is more frequently delayed.

Corey J. Langer, MD, FACP: Yes, usually if a patient's blood pressure is higher than 150/90 mm Hg, study protocols dictate withholding therapy or using some medical manipulation to bring the blood pressure down.

Beth Eaby-Sandy, MSN, CRNP, OCN: Yes, I agree that it is more difficult to manage bevacizumab-associated hypertension when patients are enrolled on a clinical trial. When they are off study, I may give them an antihypertensive agent or delay the next treatment cycle. This is certainly something that comes up in the maintenance setting, since patients can be on bevacizumab for a long time.

I do not see headaches a great deal with bevacizumab.

Corey J. Langer, MD, FACP: I have certainly seen a few, but usually it responds to standard treatment.

An interesting sidebar from the ECOG study that compared paclitaxel/carboplatin vs paclitaxel/carboplatin/bevacizumab followed by bevacizumab maintenance was that patients who developed hypertension during the initial chemotherapy phase did better.[3] It appears that hypertension during the course of therapy with bevacizumab was a clinical surrogate for survival benefit. Development of hypertension was the equivalent of rash in the cetuximab trials. In some of the EGFR TKI trials, patients who developed rash demonstrated a 4-month or 5-month improvement in median OS compared with patients who did not develop rash.[22-24] So, yes, it is important to treat bevacizumab-associated hypertension, but it may not be such a terrible thing if it does appear.

I agree with what was said previously. I think outside of a clinical trial, we are not quite so steadfast and compulsive in our management of hypertension. We will often treat with bevacizumab if a patient's blood pressure is 158/91 mm Hg or something similar. However, in a trial, strict management is standard practice. Those sorts of readings would mandate the postponement of treatment until hypertension was under better control.

Dr. West, do you encounter that?

Howard (Jack) L. West, MD: Absolutely, both issues. The clinical trials have an extremely low ceiling on what is permissible in terms of elevated blood pressure. It is frustrating because these restrictions do not align with our real clinical concerns. Accordingly, outside of a clinical trial, we monitor and manage hypertension so that it does not increase out of control, but we are not so rigorous that we obsess over keeping it in the textbook normal range.

General Comments

Corey J. Langer, MD, FACP: Are there any other comments about toxicity management?

Beth Eaby-Sandy, MSN, CRNP, OCN: Another reason I think patients with lung cancer who receive maintenance therapy tend to do better than other patients, such as those on a treatment break, because they are seen more often by the nurse practitioner or oncologist when they come in for treatment, which allows us the opportunity to catch comorbidities or new metastases earlier and treat them.

Corey J. Langer, MD, FACP: Therefore, your argument is that it may not just be maintenance therapy per se that confers benefits to these patients; it may be the enhanced nursing supportive care as well. That is a very interesting point. At the 2010 ASCO meeting, a randomized phase III study presented by Temel and colleagues[25] was quite instructive. Patients with stage IV NSCLC were randomized to up-front palliative care integrated with standard oncology care vs standard oncology care alone. Early palliative care involved several strategies that nurses are typically involved with, such as promoting illness understanding and education, managing symptoms, and helping patients and their families cope with life-threatening illness. The group that received the integrated palliative approach in addition to therapy scored better on nearly every endpoint compared with the control group, whether it was depression, quality of life, hospice use at the end of their lives, hospitalizations, and intriguingly, survival (Table 5). I strongly suspect that enhanced nursing support is a hitherto, unmeasurable variable that often may occur in some of these trials, and I think unless you have a trial where patients are mandated to come in regularly for treatment, even if it is for a placebo infusion or a placebo pill, enhanced monitoring is definitely one of the considerations that needs to be acknowledged.

Table 5. Effect of Early Palliative Care on Outcomes in Patients With Stage IV NSCLC

Outcome	Early Palliative Care (n = 60)	Standard Care (n = 47)	*P* Value
Wk 12 QOL measures			
▪ Mean FACT-Lung score	98.0	91.5	.03
▪ Mean LCS score	21.0	19.3	.04
▪ Mean TOI	59.0	53.0	.009
Wk 12 psychological distress			
▪ Depression (HADS), %	16	38	.01
▪ Major depressive disorder (DSM-IV), %	3.5	17	.04
EOL resource utilization			
▪ Aggressive EOL care, %	33	54	.05
▪ Median days on hospice	11	4	.09
▪ Hospital/ER admissions within 30 days of diagnosis, %	39	55	.12
▪ Documented resuscitation preference, %	53	28	.05
Median survival, mos	11.6	8.9	.02

DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed; *EOL, end of life; FACT-Lung, Functional Assessment of Cancer Therapy-Lung Symptom Index; HADS, Hospital Anxiety and Depression Scale; LCS, Lung Cancer Symptoms; QOL, quality of life; TOI, Trial Outcome Index.*

Cost/Reimbursement Considerations With Use of EGFR TKIs as Maintenance Therapy

Corey J. Langer, MD, FACP: I think most clinicians use EGFR TKIs in the more formal second-line or third-line setting, but the reimbursement issues encountered when using these agents as maintenance therapies are probably the same in terms of whether patients can afford the deductible and/or the cost of these agents. What reimbursement issues have each of you dealt with?

Beth Eaby-Sandy, MSN, CRNP, OCN: I have not had a problem with reimbursement for EGFR TKIs in the maintenance setting as opposed to giving it in the second- or third-line setting for NSCLC. The general cost-reimbursement issue with any oral EGFR TKI is that patients who have Medicare are confronted with this situation very quickly and have to pay a large amount out of pocket. Alternatively, many patients automatically have a high copayment of 30% to 50% on their medications in general. That does not change whether the EGFR TKI is given as maintenance or second-line or third-line therapy; it still becomes an issue. Another potential issue is that if patients are receiving these agents as maintenance therapy, they may be on the medications longer than they would had the clinician waited until progression to prescribe the agents. Therefore, patients may have to face paying high copays for a long time, say 6-9 months or even longer.

Corey J. Langer, MD, FACP: Dr. West, are there any reimbursement concerns in Washington state regarding EGFR TKIs when used as maintenance?

Howard (Jack) L. West, MD: No, I would agree with Ms. Eaby-Sandy. I do not think that the insurance companies are asking at that level of granularity as to whether the agents are being used as maintenance therapy or as second-line therapy. Even if they did, use of these agents as maintenance is completely supportable, so it has been a nonissue.

Cost-Effectiveness of Maintenance Therapy for Advanced NSCLC

Corey J. Langer, MD, FACP: Where do you think maintenance therapy stands regarding topline cost-effective issues?

Mark Socinski, MD: I do not think that lung cancer is necessarily different from many other malignancies for which we have expensive drugs. In most situations, we can argue about the magnitude of the therapeutic benefit and its cost-effectiveness. I do not think that there are any data that address the cost/benefit of truncating first-line therapy at 4 cycles and then transitioning appropriate patients to erlotinib or pemetrexed as a single agent for maintenance. According to an economic analysis of the BR.21 trial, use of single-agent erlotinib in patients who had failed first- or second-line therapy was associated with an incremental cost-effectiveness ratio of $94,638 per life-year gained, which was deemed to be marginally cost-effective.[26] The investigators suggested that using molecular markers to predict response to targeted agents may help identify more or less cost-effective subgroups appropriate for such treatment. I do not think that clinicians are being completely irresponsible from a cost-effectiveness point of view by pursuing maintenance strategies with monotherapy in advanced NSCLC. At least, that is my sense of it. I do not know how others feel.

Howard (Jack) L. West, MD: Lung cancer does not exist in a vacuum. If we are going to weigh the cost-effectiveness of maintenance therapy, it needs to be weighed against other benchmarks. If clinicians give bevacizumab maintenance to breast cancer patients to improve PFS but not OS, with no evidence at all that it improves OS, and bevacizumab maintenance is given indefinitely for generally much longer periods of time than in lung cancer, I think we reach the potential implication that a life with breast cancer is more important than a life with lung

cancer. I certainly do not agree with that and think that is not the kind of message we want to send out to society.

Corey J. Langer, MD, FACP: I think it is safe to say that we have not seen much in the way of any formal cost-effective analyses in the maintenance setting. Recently, however, Klein and colleagues[27] reported an analysis including randomized trial data, Medicare reimbursement rates, and a retrospective claims database analysis that suggested pemetrexed may be cost-effective as maintenance therapy, particularly in patients with nonsquamous histology.

Howard (Jack) L. West, MD: Any cost-effective argument is more compelling when an OS benefit is seen in addition to a PFS benefit. What we can say about the maintenance trials that have shown a survival benefit is that the patients who have not progressed after the first 4 chemotherapy cycles are exactly the patients who seem the most likely to gain from further therapy. Regardless of whether the timing of subsequent treatment is critical, the data at least underscore that a 3-month to 5-month survival benefit can be achieved by giving additional therapy after the first-line setting. The flip side of this would be to assess the benefit of continuing treatment in patients who experience disease progression during first-line therapy.

There are certainly patients who derive considerable benefit from subsequent therapy after first-line treatment, and they will only benefit if clinicians ensure that they receive that treatment.

Future Directions in Maintenance Therapy for Advanced NSCLC

Corey J. Langer, MD, FACP: What are the future directions of maintenance therapy in advanced NSCLC?

Mark Socinski, MD: One of the issues that remains to be addressed involves identifying those patients who benefit from maintenance therapy vs those who can enjoy a treatment break. We need to understand whether we can differentiate between these groups of patients based on clinical and molecular characteristics or their response to first-line therapy.

I have been impressed with the consistent effect of the maintenance approach, and obviously, this begs the question of whether it is possible to enhance the benefits of maintenance even more. There may be an opportunity in either clinically enriched populations or molecularly enriched populations to be more innovative in the targeted therapy approach. For instance, there were intriguing data at the 2010 ASCO meeting with the addition of the ARQ 197 c-Met inhibitor to erlotinib in treatment-experienced patients with advanced NSCLC.[28] This combination may provide a benefit for patients in the maintenance setting. Another unanswered question right now is: Which patients who receive bevacizumab as first-line therapy really benefit from continuing pemetrexed with bevacizumab?

Corey J. Langer, MD, FACP: Yes, a 1-size-fits-all approach is not necessarily appropriate for patients. To add to that, clinicians need more insight into the patients who benefit from maintenance based on very basic factors such as sex and age, particularly for patients aged older than 70 years who may have more difficulty tolerating maintenance therapy. One of the reasons clinicians are able to give maintenance therapy in this day and age is because the drugs used for maintenance are a bit more conducive to continued use compared with those used in our previous, “older” therapeutic armamentarium.

Dr. West, do you have any comments about the future of maintenance therapy and what additional questions need to be addressed in this setting?

Howard (Jack) L. West, MD: I think we need to refine which patients are best served by these approaches. Just as Dr. Socinski said, other agents coming through the pipeline need to be tested in the maintenance setting. Minimally toxic oral agents or infrequently administered

therapies, potentially vaccines, are always an attractive consideration in the maintenance setting. However, as we saw with the Belani gemcitabine trial, not all patients will benefit from maintenance therapy, even with an agent or approach that has been demonstrated to be beneficial in another trial in a different demographic. Therefore, it is going to be important to look at which patients are best served by more therapy based on their response to previous therapy, performance score, and other considerations. In addition, clinicians need to be able to identify which drugs are best for which patients, probably largely using molecular factors. Use of EGFR TKIs in the setting of EGFR mutations is the leading example of this. I am hopeful, and I think many clinicians are, that in the next 3-5 years we will be able to better inform our decisions by using some increasingly tested molecular markers to help guide which of the many potentially active agents we might favor for a particular patient.

Corey J. Langer, MD, FACP: In the case of the EGFR TKIs, there may be a role for going beyond tissue markers and using just serum proteomics. That should be investigated.

Howard (Jack) L. West, MD: Absolutely**.**

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POSTTEST

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1. **According to the results of the phase III IFCT-GFPC trial conducted by Perol and colleagues, which agent elicited the best progression-free survival outcomes when used as maintenance therapy following 4 cycles of first-line treatment with cisplatin/gemcitabine**

   A. Erlotinib
   B. Gemcitabine
   C. Pemetrexed

2. **Which of the following agents has demonstrated favorable outcomes as maintenance therapy in non-small-cell lung cancer (NSCLC) patients with adenocarcinoma and EGFR mutations?**

   A. Erlotinib
   B. Gemcitabine
   C. Pemetrexed
   D. Bevacizumab

3. **Which of the following agents is not an appropriate option for maintenance therapy in a patient with NSCLC and squamous cell histology?**

   A. Erlotinib
   B. Gemcitabine
   C. Pemetrexed
   D. Bevacizumab

4. **Which of the following approaches would be appropriate to manage hypertension requiring medical intervention in a patient receiving bevacizumab maintenance therapy?**

   A. Dose reduction
   B. Stopping therapy
   C. Switch to another agent
   D. Delay in next treatment cycle

5. Results of the phase II study of pemetrexed in relapsed small-cell lung cancer conducted by Socinski and colleages suggest which of the following regarding prophylactic administration of vitamin B12 to reduce toxicity?

A. Vitamin B12 must be administered a week prior to pemetrexed initiation
B. Vitamin B12 can be administered the day of pemetrexed initiation
C. Vitamin B12 need not be administered prior to pemetrexed initiation

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