Timing of Second Line Chemotherapy: The Transition to “Maintenance” for Advanced Non-Small Cell Lung Cancer (NSCLC)

Howard (Jack) West, MD
April, 2009

Hello and welcome to the GRACE video presentation on Timing of Second-Line Therapy: The Transition to “Maintenance” for Advanced Non-Small Cell Lung Cancer. My name is Dr. Jack West, and I’m a medical oncologist and the Medical Director of the Thoracic Oncology Program at Swedish Cancer Institute in Seattle, Washington. I also serve as the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

This video presentation is sponsored by Harvey and Bernice Janssen, trying to do what they can to help the lung cancer community.

The information provided here includes my own views and they are not necessarily those of the Global Resource for Advancing Cancer Education, nor those of the Swedish Cancer Institute. The contents of this program do not constitute medical advice, and they are intended to supplement but not replace input from an individual patient’s own medical team.

Just getting started, it’s important to bear in mind that the terminology here is still in development and that there are various and somewhat overlapping terms for the same process. The term “second-line therapy” generally applies to a new treatment being started after initial treatment. Some use the term “maintenance therapy” for an immediate transition after first-line treatment, while others feel that the term “maintenance therapy” implies continuing one or more of the agents that were started in the first-line setting. Other terms that have been used to describe an immediate transition from one treatment to the next are “consolidation therapy” or “sequential therapy.” I’m going to be a little loose here in using the terms “maintenance” and “early second-line treatment” interchangeably.

Older studies of immediate second-line therapy have generally been too small to provide clear conclusions, and only in the last few years have a couple of larger studies been reported in this setting.

The first is this one by Fidias and colleagues, which looked for a survival benefit from immediate versus delayed chemotherapy with docetaxel, also known as Taxotere® after four cycles of carboplatin and gemcitabine as first-line therapy for patients with advanced non-small cell lung cancer. Importantly, these studies highlight that only a slight majority of patients go through four cycles without progression or toxicity challenges and remain eligible for further chemo after randomization. In this study, one major issue is that the patients on the delayed Taxotere® arm were not assessed for progression until three months after their fourth cycle. With that long interval, more than a third of patients dropped out without getting chemo on the trial, so the comparison
ends up being one of the 95% of people getting immediate second-line therapy versus 63% getting delayed second-line therapy.

The results demonstrate a highly significant improvement in progression-free survival, doubling from a median of two months in the delayed Taxotere® arm to a median of four months in the immediate Taxotere® arm, as shown in the figure on the left. However, as highlighted in the figure on the right, the difference in overall survival was not quite statistically significant, with the P-value of .08 higher than the 0.05 cutoff for statistical significance though the absolute difference in median survival was 2.5 months longer in the arm receiving immediate Taxotere®.

This trial also indicated that the key difference in the two strategies is in the proportion of patients who actually received the intended treatment. When the survival results are limited to the patients who actually received additional chemotherapy after randomization, the median survival is the same at 12.5 months for both groups. The strong trend toward inferior survival in the delayed Taxotere® arm is directly related to more than third of patients in that arm who didn’t receive additional treatment after progression, generally due to a significant decline in performance status among these patients that precluded them from being able to benefit from more therapy.

A similar trial was conducted pemetrexed, also known as Alimta®. This study was sponsored by Eli Lilly and is sometimes referred to by the code JMEN by the sponsor company. It was conducted largely in central Europe and enrolled patients who had already received four cycles of first-line platinum-based chemo, any of the various regimens that didn’t include Alimta®. Patients were randomized in a two-to-one fashion to what was termed here “maintenance” Alimta® or placebo, each given every three weeks until progression. Because only patients who had not experienced progression after four cycles were enrolled, all 663 patients on the trial were randomized and able to answer the question of whether Alimta® immediately after four cycles of first-line chemo improved progression-free survival. Overall survival was a secondary end point in this trial.

The results of this study were very similar to the one in the previously described one with Taxotere®. Again, seen was a highly significant improvement in progression-free survival, the median in the recipients of Alimta® just over twice that seen in the recipients of placebo, and again about four months versus two months.

The curves for overall survival also appear very similar here to what was seen with the early versus later Taxotere® trial, though it’s important to emphasize that the results here are only preliminary. There was a nearly three-month absolute improvement in median overall survival with Alimta® compared to placebo, the P-value of .06 just above the cutoff for statistical significance. It is anticipated that more mature survival results will be presented at the annual ASCO conference in early June of 2009.

The results of this trial also showed a striking difference in outcomes when Alimta® was looked at divided by histology of non-small cell lung cancer. The primary end point of progression-free survival is highlighted in the columns of the left of the table here. You can see that the patients with non-squamous tumors, including adenocarcinomas, large cell carcinomas, or “other”, all share very similar improvements
with Alimta®, as highlighted in the red box. However, there is no benefit in progression-free survival for patients with squamous tumors, as shown in the green box.

The benefit in terms of response rate looked very similar, again with the superior results confined to the patients with non-squamous tumors within the red box, and no improvement in response rate seen among patients with squamous tumors in the green box at the bottom.

Finally, the overall results are quite striking with a full five-month improvement in survival for the patients with non-squamous tumors in the red box. However, not only was there no benefit seen among patients with the squamous tumor, these patients actually had a median overall survival that was two months worse with Alimta® than with a placebo. To me, these results clearly underscore that the benefit with Alimta® is concentrated in the patients with non-squamous tumors.

It’s important to note that there are some shortcomings in this trial. Most significantly, only 50% of patients on the placebo arm received any further active treatment. Although the actual rates of administering second line chemotherapy in the US aren’t much more than that, the trial really can’t be said to be a test of the timing of treatment when only half of the patients received any later therapy at progression, only 11% received Alimta®, 20% received Taxotere®, and about 12% received erlotinib, or Tarceva®. These are the FDA-approved agents considered to improve survival in this setting.

As previously noted, the survival difference remains preliminary and is expected to be reported with longer follow-up in mid-2009.

Finally, it’s worth noting that the targeted therapy Tarceva® has also been associated with significant improvements in progression-free survival in this setting. This has been reported when Tarceva® is given along with maintenance bevacizumab, or Avastin®, or given alone after four cycles of initial platinum-based chemotherapy. The full results of these trials have not yet been reported, but we anticipate seeing them at the ASCO 2009 meeting.

To summarize the current status of the field of early second line therapy, sometimes referred to as maintenance therapy, for advanced non-small cell lung cancer, two trials have demonstrated a highly significant improvement in progression-free survival for recipients of early chemotherapy, whether Taxotere® or Alimta®. The improvement in overall survival exceeds two months in absolute terms in both trials, but neither was quite large enough to be declared statistically significant. It’s fair to suggest that much of the improvement in results may well be attributable to far more patients actually receiving effective second line therapy if it’s administered early. Still, it appears that when a break, particularly one in the range of months, is introduced between stopping first line therapy and starting the next therapy, there is a greater risk of patients progressing and becoming too ill to benefit from further treatment.

Overall, an immediate transition to new therapy has not yet emerged as a clear standard of care, and the timing between first and second line therapy remains controversial. Nevertheless, I consider the results of these trials to be compelling
enough to strongly consider starting early second line therapy in patients in whom we’ve stopped first line treatment after four to six cycles.

It’s important to note, however, that these issues don’t apply to patients who are continuing on one or more of their initial first line agents, nor to patients who have progressed on first-line treatment. I would also say that patients who appear to have a very responsive or indolent cancer may do very well being monitored attentively rather than continuing on treatment indefinitely.

Finally, we’ve heard preliminary reports that Tarceva® is also associated with significant improvements in progression-free survival in a similar setting. Though we’re waiting on full results from these trials, in the meantime, I believe that this work supports the concept that any of our more active second line therapies, whether standard chemo or a targeted agent, can provide greater benefit if it reaches a broader population of patients, which is more likely to happen if it is given earlier rather than later.

You can find additional details on several topics within the subject archives at the web address www.cancergrace.org/lung. Members of GRACE can also leave comments and questions about this presentation at the web address in the middle of this slide.

Thank you for your interest.