Second Line Chemotherapy for
Advanced Non-Small Cell Lung Cancer (NSCLC)

Howard (Jack) West, MD
March, 2009

Hello and welcome to the GRACE video presentation on chemotherapy for second-line treatment of 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. A transcript as well as a PDF file with copies of figures associated with this program are available at www.cancergrace.org/GRACEcasts.

This video presentation is sponsored by Mr. Alec Brindle, in loving memory of Pinky, who truly defined grace.

The information provided here includes my own views and they are not necessarily those of the Global Resource for Advancing Cancer Education or those of 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’s patient medical team.

One very important thing to consider is the goals of therapy in any situation of treating cancer. For second-line treatment of advanced non-small cell lung cancer we have goals of improving efficacy while also striving to maintain or even improve quality of life.

Just a few years after first-line chemo became clearly established for treating advanced non-small cell lung cancer, the potential value of second-line chemotherapy was tested in a randomized trial of docetaxel, also known as Taxotere, compared with supportive care alone. Because Taxotere is related to paclitaxel, also known as Taxol, which many patients receive first-line, this trial, which was conducted primarily outside of the U.S., excluded patients who had previously received Taxol. Patients who had received one or more lines of prior therapy were randomized to Taxotere initially dosed at 100 mg/m² IV every three weeks or supportive care alone, which was the standard of care at the time. However, halfway through the trial, the dose of Taxotere was lowered to 75 mg/m² IV every three weeks. That was because the higher dose was associated with unacceptable side effects, particularly lowered blood counts, a more than one in five chance of febrile neutropenia, which is fever in the setting of an excessively low white blood cell count, and a 10% risk of treatment-related death. The risk at the lower dose was much less.
The lower dose of Taxotere was associated with a clearly superior survival compared with supportive care alone, as shown on the panel to the right. In contrast, the higher dose of Taxotere was associated with a less impressive improvement and survival, as shown on the left. This benefit in survival was despite the fact that the response rate with Taxotere was only around 6%, although another 40% or so demonstrated prolonged stable disease. This study was among the first to suggest that patients could demonstrate improved survival in the absence of tumor shrinkage of more than 50%.

Importantly, the study also showed that Taxotere was associated with lower use of both narcotic and non-narcotic pain medicines, as well as lower use of other medicines used for treating cancer-related symptoms. In addition, patients who received Taxotere had a lower frequency of significant weight loss and less of a decline in performance status over time than the patients who received supportive care alone.

Another trial conducted concurrently enrolled 373 patients with previously treated advanced non-small cell lung cancer and randomized them to one of three arms: either of two doses of Taxotere every three weeks, or a third arm with an alternative chemotherapy of Navelbine or in a few patients, ifosfamide. Unlike the other trial, this one allowed patients to have received prior Taxol. As shown in the red box, the response rate with Taxotere was again rather low, just 11% with the higher dose and 7% at the lower dose of Taxotere and this compared with about 1%, a single patient who demonstrated a response on Navelbine. This difference was statistically significant between the pooled Taxotere arms, or either Taxotere dose compared with the alternative chemo, as shown in the green box. Despite the rather modest response rate, the survival was markedly superior for either Taxotere arm compared with the Navelbine or ifosfamide arm, as shown in the areas highlighted in red.

Looking at the actual survival curves, you can see that the median survival, the point at which half the patients had died, and highlighted in the red circle, isn’t very different among the three arms. Instead, the real difference appears in the approximately one-third of patients who have the longest survival, in whom the recipients of Taxotere at 75 mg/m² follow the top curve and demonstrated the best survival.

After these two trials were published within a few weeks of each other in mid-2000, Taxotere at 75 mg/m² every three weeks became the clear standard of care as a second-line treatment for patients with advanced non-small cell lung cancer and was approved by the FDA for this setting. Nevertheless, this is a challenging strategy for some patients, and one alternative approach is to give Taxotere on a weekly basis, generally with off weeks in between. Overall, the studies that compared weekly to every 3-week Taxotere have not demonstrated that either approach is clearly more effective, as illustrated by the results of these several comparative studies, generally clustering in the middle, without a clear superior result for either the weekly strategy that would be
represented by a dark square to the left of the vertical bar in the light blue area or the 3-week schedule represented by a dark box to the right of the vertical line. The overall results are represented by the diamond at the bottom and completely straddles the vertical line, suggesting equivalence.

A final important trial that was completed a few years later directly compared Taxotere every 3 weeks to pemetrexed, also known as Alimta, and also given every 3 weeks. This trial randomized almost 600 patients with advanced non-small cell lung cancer who had received one line of prior therapy. Both treatments produced remarkably similar response rates of approximately 9%, consistent also with the prior performance of Taxotere in earlier studies. As in the prior Taxotere studies, nearly half the patients also demonstrated prolonged stable disease -- again, almost completely identical between the two treatment arms in the trial.

Just as remarkable similar were the curves for progression-free and overall survival, which also reflect an identical median progression-free survival and one-year overall survival between Taxotere and Alimta. The appreciable difference and the leading reason that Alimta was approved as an alternative second-line therapy is that it was associated with a significantly lower drop in blood counts as well as lower risk of febrile neutropenia and infections in the setting of low white blood cell counts.

Very recently, however, the retrospective analysis of this study by histology of the non-small cell lung cancer tumor shows that recipients of Alimta, shown in the left part of the figure, did much better if they had a non-squamous tumor, as shown on the yellow curves. In contrast, recipients of Taxotere, shown on the curves on the right, did equally well regardless of the tumor histology. Further work in this arena led to the confirmation that the activity of Alimta is concentrated in patients with non-squamous tumors, and Alimta is actually now approved by the FDA in both first-line and second-line treatment of advanced non-small cell lung cancer, but only in patients with non-squamous tumors.

To review the highlights, the benefit of second-line chemotherapy for advanced non-small cell lung cancer was first established with the regimen of Taxotere 75 mg/m² IV every three weeks, which appeared superior to a higher dose that was associated with excessive risk of serious or even fatal side effects. Taxotere was demonstrated to improve survival compared with either supportive care alone or an alternative chemotherapy treatment, and this occurred despite the fact that only a small proportion of patients, about 10% or less, showed tumor shrinkage of 50% or greater. About half the patients of either a response or prolonged stable disease and this work strongly suggested that many patients were living longer, more because of delayed disease progression than because of major tumor shrinkage. Along with the improvement in overall survival, patients on Taxotere in one of these studies also experienced less significant cancer-related symptoms such as pain, weight loss and decline in performance status over time.
Very recently, Alimta has been compared directly to Taxotere and shown to have a remarkably comparable efficacy and less significant hematologic toxicity. A profile that led to its FDA approval as a second-line option for advanced non-small cell lung cancer. The most recent work with Alimta has consistently demonstrated that its activity is concentrated in patients with non-squamous histologies, and its FDA approval is now limited to that subset.

Targeted therapies such as inhibitors of the epidermal growth factor receptor or EGFR have also been studied in the second- and third-line setting and erlotinib, also known as Tarceva, is also an FDA-approved alternative. The EGFR inhibitors have been compared against single-agent chemotherapy options, and these and other targeted therapies are also being integrated with chemotherapy in an attempt to improve treatment outcomes for patients with advanced non-small cell lung cancer. Other standard chemotherapy agents are also being evaluated in this setting.

You can find additional details on several of these 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.