



**Angiogenesis in First Line Treatment of Advanced NSCLC:
A Focus on Avastin (Bevacizumab)
by Dr. Howard (Jack) West
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Hello and welcome to the GRACE video presentation of angiogenesis and the role of Avastin or bevacizumab in first line therapy 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 GRACE member Dr. Neal Burt, who is now without progression on chemo and Avastin for 18 cycles and counting.

A couple of disclaimers before we get started. 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 patient's own medical team.

Angiogenesis is one of the key critical components that allow a tumor to grow and spread. As shown in the progression from left to right on this slide, a small cancer can only grow to a few millimeters in size before it outstrips its blood supply and can no longer passively receive sufficient nutrition or adequately dispose of waste to its microenvironment. At that point, it needs to develop a blood supply to help with these processes before it can grow. Tumors secrete proteins to promote this process of developing new blood vessels, a process called angiogenesis. The most dominant of these is called vascular endothelial growth factor, or VEGF. Avastin is a monoclonal antibody that blocks the ability of VEGF to activate receptors on the lining of nearby blood vessels called endothelium. This blocks the angiogenic process.

A very important trial of Avastin in advanced non-small cell lung cancer came out of Vanderbilt University where they randomized about 100 previously untreated patients with advanced non-small cell lung cancer of any histologic subtype to receive first line chemo with Carbo and Taxol or the same chemo with Avastin at either a higher or lower dose. In this trial, patients on the higher dose had a much better survival than was seen in the lower dose and this led to the higher dose being adopted for further research in the U.S. This trial also identified the issue of the squamous subtype of non-small cell lung cancer being associated with a high risk of life threatening or fatal bleeding complications; specifically coughing up blood known medically as hemoptysis.

The subsequent larger randomized Phase III study known as ECOG 4599, more precisely assessed whether Avastin improved overall survival for patients with previously untreated advanced non-small cell lung cancer. Patients were randomized to up six cycles of Carbo and Taxol alone or with Avastin at the higher dose, and if

patients had not progressed after that point, those assigned to the Avastin containing arm would continue on Avastin alone as so called maintenance therapy until progression.

Importantly, based on the preceding trial, patients with squamous cell subtype of non-small cell were excluded as were patients with a history of hemoptysis, brain metastases, those on full doses of blood thinners, or with active cardiovascular disease. This was due to concern about the danger of potentially high risk of serious complications in these patients.

After several years of large trials of targeted therapies that failed to show a benefit for patients, this trial was considered a positive one and was presented by Dr. Allen Chandler at the Plenary Session of ASCO in 2005 and it was subsequently published in the prestigious New England Journal of Medicine, that was because it broke the negative pattern and established what many felt was a new standard of care. Carbo and Taxol with Avastin was associated with the more than doubling of the response rate, 34% improvement in progression-free survival and a full two-month improvement in the median overall survival compared with the same chemotherapy alone.

Importantly, however, Avastin was associated with some increased risk compared to chemo alone with 15 v. 2 treatment-related deaths seen in the two arms, respectively. Some of these were from bleeding complications which were less frequent with more careful patient selection, but still occurred rarely. Another treatment-related death was from an apparently higher risk of low blood counts and infection when Avastin was added to the Carbo and Taxol. Still, even taking these challenges into account, there was a two-month median overall survival benefit with the three-drug combination.

A subsequent subset analysis showed that side effects and treatment-related deaths were disproportionately seen in the subgroup of patients who were over 70, and those accounted for 24% of the trial population. Perhaps largely because of that, elderly patients did not experience a significant improvement in survival despite the fact that they had a markedly higher response rate when Avastin was added to chemotherapy.

A similar trial of chemotherapy and Avastin was subsequently conducted in Europe. In the so-called AVAiL trial for Avastin in Lung Cancer, there were a few key differences compared to the U.S.-based trial. The chemotherapy backbone was cisplatin and gemcitabine, a regimen very commonly used in Europe. In addition, the group not assigned to Avastin received a placebo with their chemo instead of chemotherapy alone. The AVAiL trial also compared the results of chemo with either the lower or the higher dose of Avastin. The trial enrolled a very similar population to the U.S. study in terms of eligibility restrictions and this trial also gave maintenance therapy to patients who hadn't progressed after six cycles of first line chemotherapy with Avastin.

Unlike the ECOG study that had a primary endpoint of overall survival, the AVAiL trial focused on progression-free survival of PFS as its primary endpoint. Both Avastin containing arms showed a statistically significant improvement in progression-free

survival compared to chemo alone and there was no suggestion that the higher dose was superior. If anything, the lower dose actually looked perhaps a little better.

However, very recent results of overall survival on the AVAiL trial showed that it was essentially the same in all three groups with a median of a little more than 13 months in all three groups. We don't yet have a clear way to reconcile these results with those of the ECOG trial except to say that the benefit of Avastin maybe specific to the chemo regimen that it's given with.

Importantly, there were no real surprises in terms of side effects which were actually quite comparable in most measures between the lower and higher dose of Avastin with cisplatin and gemcitabine.

In summary, angiogenesis appears to be an important process in the course of advanced non-small cell lung cancer. It's critical to note that the patients included in these trials with Avastin represent a limited subset of the overall patient population and I would estimate that to be about 40% of the general patient population with advanced non-small cell lung cancer. However, additional research suggests that patients with treated brain metastases and potentially those on blood thinners may receive Avastin safely so the eligibility issues are somewhat of a work in progress.

The first large trial with chemo and Avastin, ECOG 4599 came out of the U.S., used Carbo and Taxol as a chemo backbone and showed a significant improvement in overall survival and other efficacy perimeters though with some increased risk of potentially serious or even fatal side effects. These appeared to be most pronounced in older patients.

A second trial known as AVAiL conducted in Europe hasn't been published in final form, but showed a modest and statistically significant improvement in progression-free survival with either a lower or a higher dose of Avastin added to cisplatin and gemcitabine. However, no improvement in overall survival was seen with Avastin in this trial. Still Avastin is commonly used for eligible patients in the U.S. based on the American trial results.

There remain several key open questions such as why these two large trials produced different survival results. What should the optimal dose of Avastin really be? And what is the value of the maintenance portion of Avastin after the first six cycles with chemotherapy?

You can find additional details on several of these topics within the subject archives of 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 very much for your interest.