



## ASCO 2011 Highlights: SCLC, Early Stage NSCLC, and Mesothelioma Dr. Mary Pinder-Schenck

### **Dr. West:**

Hello and welcome. My name is Dr. Jack West, and I'm a Medical Oncologist in Seattle, Washington and also the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. Today, we're doing a program on the Lung Cancer Highlights from ASCO, the Annual Conference of the American Society for Clinical Oncology, held in June of each year. This live webinar, as well as the podcast materials to be produced from it, are the product of a partnership between GRACE and the LUNGeVity Foundation.

I'm very pleased to be here today with Dr. Mary Pinder-Schenck, who is an assistant professor in the Department of Thoracic Oncology at the H Lee Moffitt Cancer Center and an expert in lung cancer. She'll start off the program by talking about some of the ASCO presentations on small cell lung cancer, early stage non-small cell lung cancer, and even a little bit on mesothelioma. Thanks so much, and I'll turn it over to Mary.

### **Dr. Pinder-Schenck:**

Thank you so much Jack for having me. I think, you and some of the other faculty on GRACE have already done a pretty good job of preparing everyone for the sad reality that no really earth-shattering results were presented, especially in early stage lung cancer, at ASCO this year. I do think there were some very interesting presentations, none the less, in early stage non-small cell and mesothelioma and I'm going to talk about each of those diseases, in turn.

Although small cell lung cancer doesn't get the same level of attention that non-small cell lung cancer does, it is actually still a big problem. Although it only accounts for 13-15% of the cases of lung cancer that we see, when you think about the very large number of lung cancer cases that we see every year, small cell lung cancer ends up being more than 20,000 and onwards of 30,000 cases a year. Unfortunately, most of the patients who have small cell lung cancer are diagnosed with extensive stage disease. And small cell lung cancer is sort of strange compared to other cancers, in that we tend to commonly stage it as either limited stage, meaning that the cancer is confined to the chest and specifically to one half of the chest; or as extensive stage, which means everything else including metastasis to the other lung or to other organs. Most patients are advanced when they present.

These can be very easy to treat initially. So, patients will come in feeling very poorly. They may have lost a great deal of weight, they may have shortness of breath, and we typically treat patients first line with either carboplatin or cisplatin and another drug called etoposide, and usually patients do really well initially. They feel better. Most of them have substantial shrinkage of their cancer, and some even go into a remission, or have all of their cancer disappear from their scans.

The problem with small cell lung cancer is that, eventually, the disease relapses, and when it does, it's much more difficult to treat. So although a lot of patients may be up for additional therapy when their cancer relapses, we really have limited therapies in that setting. The only standard therapy at this time is a drug called Hycamtin, or topotecan. This drug is really only effective in patients who have what we call *sensitive relapse*. That means that their cancer has relapsed greater than three months after they have completed all of their initial chemotherapy, the

platin and etoposide. In patients that have cancer that relapses sooner than that, it's not a very good drug.

This is the National Comprehensive Cancer Network guidelines for therapy for small cell lung cancer. You can see that topotecan is considered the preferred agent for relapsed small cell in times where it is greater than two to three months after completion of initial therapy. The big problem with topotecan though, for those of us that treat patients, is that it can be really difficult to give. Number one is the infusion schedule, which means that the drug is given IV for five days in a row. Now the drug is available in an oral form, which is equivalent in terms of effectiveness and that sort of takes away that inconvenience of having the patient come in for five days in a row. But the oral form also has, like the IV form, significant toxicities. And most of us that treat a lot of patients with small cell lung cancer tend to have to give a lot of dose reductions to allow our patients to tolerate it. The drug is particularly difficult in terms of causing anemia and low platelets. Patients will often require transfusions in the course of therapy.

I'd also like to point out, on the current slide that's displayed, that topotecan really is not a superb drug. So, this is a study that compared topotecan to a previous regime that was used a long time ago in small cell lung cancer therapy, and that's a regimen called CAV. This study shows that topotecan really wasn't any better than CAV in terms of how long patients lived. Topotecan really was approved, or accepted, by the fact that patients had improved symptoms control, so things like shortness of breath and quality of life compared to CAV.

We're getting to a study that was presented in the oral abstract session, which are considered to be the most important sessions at ASCO. This was Dr. Jotte's study, a randomized phase III trial comparing our current standard, which is topotecan, and in this trial was administered intravenously, with amrubicin. I know a lot of you at GRACE are fairly familiar with amrubicin, because there have been earlier trials, phase two studies that were presented with amrubicin, and amrubicin is also used quite a bit in Japan. So many patients that have small cell lung cancer know that the drug exists, and we've been waiting for quite some time for the results of this phase III trial.

So this is basically a gold standard to help us compare a standard drug to a new drug. The primary end point, or what this trial was looking to show, was an improvement in overall survival for patients that had small cell lung cancer and had completed their first line chemotherapy and then progressed. This trial allowed patients with sensitive and refractory disease to enter the trial -- they weren't excluded on the basis of that. But the patients did have to have a good performance status. They had to be pretty healthy and ambulatory in order to get on the trial. I'd also point out that the infusion schedule for amrubicin is a little more convenient than topotecan.

Unfortunately, when Dr. Jotte presented the results, we did not see a difference in overall survival between the two groups. So the overall survival for amrubicin, the median overall survival, was 7.5 months. For topotecan, it was 7.8 months. Whenever we compare, in a phase three trial, two treatments, we always look at something called the P value. That tells us whether we think there truly is a difference between the two treatments. If that P value is higher than .05, which it is in this case, it's about .17, then we don't consider there to be a significant difference between the two treatments. Now, in this case, you can really see that these two treatments were close enough that you probably wouldn't have felt that they were significantly different.

One interesting thing on this survival curve, you can see down here in white, these are the patients, the survival of the patients who were treated with topotecan. These are the patients in yellow who were treated in amrubicin. Although these curves are very, very close at the

beginning, you can see out here about 9 months into the time course that Amrubicin does seem to be a little bit better. We have patients here who are living longer and you can see that topotecan, by 27 months there were no survivors. Whereas, with amrubicin, we still had some patients who were surviving at that time.

When we compared overall survival in sub groups, we broke it down it down into sensitive patients who are up here at the top and refractory patients, who are down here on the bottom, what we found was that: overall survival was not significantly different between the patients that got amrubicin and topotecan who had sensitive disease, meaning that they had relapsed more than three months out. However, with the refractory patients, there was a slight difference in overall survival. You can see that patients that have sensitive small cell lung cancer have longer survival than patients who had refractory small cell lung cancer. That's certainly what we would expect. So for patients who had refractory disease, there was a small improvements from 5.7 to 6.2 months in the median overall survival. That just met what we would consider to be statically significant.

Response rates for the number of patients who experienced substantial tumor shrinkage was also higher in amrubicin. So, about 30% of patients compared to 17% of patients had substantial shrinkage of their tumor with amrubicin.

Progression free survival, which means patients who are living without their cancer getting worse, was better in amrubicin. Now again, the difference was not big. The progression free survival was 4.1 months for amrubicin and 3.5 months for topotecan. But that did end up being statistically significant. Again, you can see this separation of the two curves out in the later time period, and we can see that really, by twelve months, all of the patients on topotecan had progressed. Whereas with amrubicin, there were some patients who maintained a long duration of response.

Remember we talked about how topotecan was considered better than the previous regimen based on improvement in patient symptoms. Fortunately, most lung cancer trials are collecting information about how patients feel and what their quality of life is like. What we can see here is that amrubicin was substantially better than topotecan in multiple symptoms that are common in small cell lung cancer and non small cell lung cancer, for that matter. So, cough, patients showed more improvement with amrubicin. Dyspnea, or shortness of breath, pain, appetite, fatigue, and just overall well being.

So, my conclusions about this trial are that, unfortunately, amrubicin was not as good as we hoped it would be. So, we had hoped that amrubicin would replace topotecan based on better tolerability and better survival for patients. But unfortunately, in the group as a whole, we could not say that Amrubicin was better in terms of overall survival. Amrubicin looked a little better in terms of progression free survival and did look better in terms of symptom control. I'd also note that I didn't show the slide specifically, but amrubicin was better tolerated in terms of anemia and low platelets. Patients who were on amrubicin required fewer transfusions than patients who were on Topotecan. This is, as I said, certainly something that we see in clinical practice as being a real difficulty with topotecan. Amrubicin did have more infections in patients who had low white blood cell counts, specifically their neutrophil. This was ameliorated somewhat later in the trial when growth factors were allowed. But growth factors were not allowed in the first part of this trial. So we did see more infections because Amrubicin was harder on the white blood count.

Finally, amrubicin has a slightly more convenient schedule and there is also, we're being very careful to look at cardiac function because amrubicin is part of a class of drugs called anthracycline that can damage the heart and result in heart failure. In this study, amrubicin did not show any effect on the heart function of patients, so that's also encouraging. I think I would consider this drug as an option for my patients if it were available. I would certainly like it to be available because I do think that symptom control is a very big issue in patients with small cell lung cancer. They tend to have quite a few symptoms from their cancer. So I think this would be a nice option to have, but I think it is going to be an up hill battle for the drug to be approved in small cell lung cancer.

Next I'll just quickly go through the second small cell trial that was presented in the oral presentation. This goes along the other scheme that we see very frequently in small cell trials. We're either trying to find something new, or we're trying to add something new to our first line therapy to see if we can do better. Now, in my opinion, we probably can't do a whole lot better in terms of making more patients respond to the treatment because we're already doing pretty well there with first line. What we'd really like to see is a longer time to relapse or a longer survival in these patients. The way that this trial was designed is that the authors added a new drug called obatoclax to the standard therapy for small cell lung cancer, or one standard. Some would argue that cisplatin/etoposide is a preferred standard. The authors added a third drug to the standard of carboplatin and etoposide. Patients who were on the obatoclax were also given maintenance obatoclax. Then the control arm was just the usual carboplatin and etoposide. The authors actually chose as their primary end point improvement in response rate for the number of patients who showed substantial tumor shrinkage. So they actually wanted to see a 20% improvement in response rate to consider this a positive trial.

This drug is called a pro-apoptotic small molecule. Pro-apoptotic just means that it helps cells to die and specifically cancer cells. There were some good data from the lab and from some early studies that it might be useful in small cell lung cancer. So that's why the trial was designed.

As I said, the primary end point was response rate. They were also looking at progression free survival and overall survival. So unfortunately the trial did not meet that pre-specified end point.

You can see the response rates were... these are complete responses and partial responses for all the patients there. What you can see is that the response rate was 65% in obatoclax's arm and 54% in the carboplatin/etoposide arm. That was not statistically significant. Now the authors then added in the category of stable disease to the complete responses and partial responses. When they did that, they did the statistically significant difference between the two groups.

We can see here that the median progression free survival was 5.4 months for the standard arm and 6 months for the arm that included obatoclax. The P value was close but did not meet 0.05. Again, with overall survival, the p value just barely, did not meet statistical significance.

There was a trend towards an improved survival for carboplatin/etoposide and obatoclax with an overall survival of 10.6 months compared to 9.9 months in the standard arm.

One interesting finding that the authors noted was that there appeared to be fewer patients who were chemotherapy refractory in the arm that received Obatoclax. That is an interesting finding because the patients who have the roughest time are those that do not respond to that initial chemotherapy. In that case, it can be very difficult to treat their cancer. In many cases, they may not have success with any therapeutic option.

What you can see is that there were 25% of patients who were refractory compared to 40% in the standard arm. The authors, again they broke this down a little bit by sensitive and refractory disease to see if there was any difference in how well the patients did. You can see that, if the patients were refractory, these are these lower curves; which, of course, if they are refractory, we expect them not to do as well and there really was not a difference. However, in the patients that had sensitive disease, and this could only be determined after they were treated, we had no way of knowing this at the outset, the patients who were treated with Obatoclax had a median survival of 15.4 months compared to 12.8 months. Now when we're breaking patients down, we have smaller groups. So we tend to have lower ability to detect whether or not our findings are significant. So although there seems to be a trend, and it may look like this number is a large difference, our p value was actually not significant.

And so, my commentary, my conclusions about this trial is that there were some very interesting findings. One of which being the decrease in the number of patients that were refractory. They were treated with obatoclax. But it did not meet the end point of improved response rate. I think that was a very ambitious end point to try and think you would have 20% more patients with substantial tumor shrinkage just based on the addition of a third agent to a pretty powerful regiment. I think it will be interesting to see whether certain subsets can be defined on the basis of molecular markers and whether we can try to tease out which patients may do better with this agent. I'd like to point out that, overall, it was pretty well tolerated. The patients did have some reactions which could be considered either a side effect or a benefit. They had some euphoria during the infusion. So, other than that the drug was pretty well tolerated.

So, not a very harmful drug, but also doesn't appear to be particularly helpful for the large population of patients with small cell lung cancer. This trial points out there have been many similar trials in small cell lung cancer where we've added a third drug to platinum and Etoposide and that seems to be the formula; just add whatever drug of the day that seems promising. Although this study does have some rationale for using the drug in small cell, I think that we really have to revisit the idea of just trying new drugs in unselected patients with small cell lung cancer.

I'm going to pick up the pace a little bit because I want to be able to get to adjuvant therapy. I'd just like to say that we always ask the Cisplatin or Carboplatin question and there was one abstract that demonstrated that Carboplatin and Cisplatin were essentially equivalent first line treatment of small cell lung cancer. This was a meta-analysis, or putting all these large trials together to try and come up with an answer.

As far as what the future holds for small cell lung cancer, again I think we need smarter trial design, immunotherapy which has proven very effective in melanoma. Maybe one avenue that we can pursue. I think we need to work on treating our limited staged small cell lung cancer patients with better regiments that can be used in combination with radiotherapy. Finally, I think we need to explore other pathways. One of these is the insulin like growth factor pathway. Another is something called Hedgehog and finally proteins and enzymes that are involved in DNA repair.

So moving on to early stage non-small cell lung cancer, I've kind of lumped our stage ones and two with our threes in this presentation because there really wasn't a lot more Stage III or locally advanced non small cell lung cancer. I'd like to just quickly review that, for early stage lung cancer, these are patients who had their tumors completely removed. Platinum based chemotherapy is the standard of care if they have lymph node involvement at the time of surgery.

For tumors without lymph node involvement, if the tumor is larger than 4 cm, then we do consider adjuvant chemotherapy. There are also some specific situations where we have a smaller tumor and we would still consider chemotherapy. For instance, if the tumor looks particularly aggressive under the microscope. But that remains controversial. In general, for very small stage I cancers, we really think adjuvant chemotherapy is something that we should really be doing in clinical trials.

This is the National Comprehensive Cancer Network list of chemotherapy regimens for adjuvant chemotherapy. Over here are the published chemotherapy regimens. So these are the drugs that we have large randomized trials that support a benefit for adjuvant chemotherapy. You can see that the most common drugs are cisplatin and vinorelbine. Over here these are regimens that have shown effectiveness predominately in patients with Stage IV disease. Essentially for patients with stage IV disease, or metastatic cancer, regimens like cisplatin and gemcitabine or cisplatin and pemetrexed and of course carboplatin based regimens have replaced these regimens. We rarely use cisplatin and vinorelbine or cisplatin and etoposide for patients with metastatic cancer.

But they are still the drugs that have the most evidence behind them for adjuvant therapy. So, I'm going to talk about a study by Dr. Kreuter. This was a European study basically that was trying to decide whether it was feasible to use cisplatin and pemetrexed, or Alimta, is the trade name of the drug. The authors weren't trying to see if cisplatin and pemetrexed were better than cisplatin and vinorelbine in terms of survival of patients. They were just trying to see whether it was going to be easier to deliver this new drug combination, more feasible for patients and doctors to deliver the drug. So patients either got cisplatin and vinorelbine, which is actually used quite a bit in Europe, or cisplatin and pemetrexed, which I would argue is used quite a bit here in the U.S. These were patients with Stage IB through IIIA non-small cell lung cancer. They had to have a good performance status and they had to be considered by their doctors to be candidates for cisplatin.

The authors defined feasibility as a regimen that wasn't going to cause undue death. That would be very serious. We wouldn't want that. That patients weren't going to withdraw prematurely because of the regimen and that we weren't going to see a lot of bad side effects -- things that would cause hospitalization.

One thing I'd really like to point out is that you can see a very large percentage of the patients were Stage IB. We know that in stage IB patients, it's really those with the larger tumors where there is a suggestion of benefit. So many other trials have shown that patients with smaller tumors don't appear to benefit from adjuvant chemotherapy. So I think later this may be an issue. The other issue is that this trial was designed before we knew that pemetrexed did not really have efficacy in patients with squamous cell carcinoma. However, this trial actually included a substantial portion of patients with squamous cell carcinoma. So when the efficacy results are eventually released, that may have an impact.

Basically, the authors found that cisplatin and pemetrexed is a very reasonable combination. So the feasibility was actually 95% compared to 75% for cisplatin and vinorelbine. So that was very encouraging. There were very few severe events in the patients, particularly in that group. You can see that only 15 patients stopped therapy early. Whereas 41 patients stopped therapy early in the cisplatin and vinorelbine arm and most of the patients who were on cisplatin and vinorelbine stopped therapy early because the toxicity according to the protocol and the treating physician was unacceptable. At this time we really haven't been following the patients in the study long enough to know whether or not one regimen is showing signs of being superior. You can see that

only one patient has relapsed on the cisplatin and pemetrexed arm. Only three patients have relapsed on the cisplatin and vinorelbine arm.

We really can't say anything about the efficacy at this point. What we do know is that cisplatin and vinorelbine was more toxic and we especially saw that in terms of white blood cell counts. I think that most of us, from our practice with Stage IV patients, know that cisplatin and pemetrexed is a pretty easy regimen to give.

So I think, in conclusion, there were no surprises, although it's nice to see that it's feasible to give this to patients that have had surgery. I think when the final results of the trial come out, it may be hampered by the fact that there were a large number of squamous patients that we don't expect to benefit from Pemetrexed and a large number of patients with Stage IB. Finally, I think that many of my colleagues are already doing this in the adjuvant setting, and that kind of gives me a segway to my next presentation, which is just Dr. Heather Wakelee's update on the ECOG 1505 adjuvant trial.

Now, the ECOG 1505 adjuvant trial allows physicians to choose from one of several chemotherapy regimens and then randomizes patients to either standard chemotherapy with one of those regimens or standard chemotherapy plus a year of Avastin, or bevacizumab. Now we already know that Avastin has activity for patients with non-small cell lung cancer who are metastatic. So this is the trial that showed us that bevacizumab, or Avastin, added to carboplatin and paclitaxel chemotherapy showed an improvement in overall survival from 10.3 months to 12.3 months and an improvement in progression free survival.

So on the basis of that trial, Dr. Wakelee and colleagues designed a study to test whether bevacizumab improves outcomes for patients with early stage lung cancer. So this is a huge trial, 1,500 patients. They have to stages IB through IIIA, already resected and it only allowed patients who had tumors larger than 4 cm. Patients either get chemotherapy for four cycles or chemotherapy for four cycles and Bevacizumab. And as you can see, as I said in the U.S., cisplatin and pemetrexed is already fairly well accepted and is actually included as one of the four possible regimens that physicians can choose from on this study. So Dr. Wakelee just presented an update.

What you can see is that, already, 636 patients have been accrued to the study. So we still have a long ways to go. One interesting thing is that there were actually more women than men on the study and that's unusual for lung cancer trials. So, we will have a fairly good representation on how women do with this regimen.

You can see the distribution that about 24% of patients had Stage IB lung cancer and then varying amounts of other resected lung cancer. The majority were adenocarcinomas, but still a large proportion of squamous cell carcinomas.

This just shows you what drugs that oncologists are choosing. Vinorelbine was one of the most popular choices, second to cisplatin and docetaxel. Pemetrexed was kind of a late entry. This was only added in 2009, as we got more data for patients in the metastatic setting. And again, only non-squamous patients can use pemetrexed. So I think this likely to represent a greater proportion of patients once the study meets its final accrual.

Dr. Wakelee presented the data on toxicity. We don't have any data yet because we haven't met the accrual for survival. But we do have data on toxicity. Basically there were no unacceptable or big surprises in terms of toxicity. Hypertension was more common in patients who were on

bevacizumab, and that's a known side effect. Proteinuria was more common in patients who are on bevacizumab. But again, a known side effect of bevacizumab. Neutropenia, a bit more common, and we saw that in the stage IV trial as well. So that was not a surprise. There were seven deaths on the standard arm and ten deaths on the bevacizumab arm. Not a big difference there and, actually, not a significant difference. There were no surprises in terms of the causes of death. Specifically, there was no big problem with hemorrhage, which was something that everyone was concerned about with Bevacizumab.

So, I'd like to just quickly present a couple of abstracts that were not in the oral presentations. Just two abstracts on adoption of adjuvant chemotherapy for non-small cell lung cancer in elderly patients. There was one study from Canada that looked at adjuvant chemotherapy in the elderly. This is important because many of our patients with lung cancer are elderly, and that is defined by some as over 65, and by others as over 70. We're not quite sure what to do with those patients, sometimes, for adjuvant chemotherapy because our large clinical trials typically included young patients. So, the Canadian study basically looked at two different periods in Canada's history. One was in the early part, 2001-2003 and then 2004 and later and found that as chemotherapy started to be adopted amongst elderly patients, it was used more frequently as time went on. Survival improved in that group of patients. Then, an American study that looked at our Medicare SEER database, which includes information on treatment of patients who were over the age of 65, also found that there was an improvement in patients who received chemotherapy who were elderly compared to those who did not receive chemotherapy after surgery. Interestingly in Canada, cisplatin regimens were by far more commonly used and in the U.S., carboplatin regimens were more commonly used.

So I think you have to take these trials with a grain of salt because, of course they're not randomized and physicians tend often to give chemotherapy to people that they think can tolerate it better. Those may be the people who would've done better regardless of whether they had gotten chemotherapy. So we have to take it with a grain of salt but I think it certainly provides us a comfort that we're not doing harm to elderly patients with good performance status if we give them chemotherapy.

And then finally there was one really interesting presentation from Sloan Kettering Cancer Center where the authors looked at patients who were treated with adjuvant EGFR tyrosine kinase inhibitors like Tarceva or Iressa. There were not many patients because this isn't an approved strategy. There were only 22 patients in this study. But it was quite interesting that the authors found that, even for patients who relapsed either on or after they had stopped their adjuvant tyrosine kinase inhibitor that they could still respond once their cancer relapsed. So this goes along with some data that we have in the metastatic setting from Dr. Sequist where we've seen that patients may be on a drug like Tarceva and then become resistant and relapse and then may go for a period off of treatment and then respond to the drug again.

Finally, I'd like to conclude the section on adjuvant therapy just by quickly going through what I think are the directions of the future. That's basically looking at biomarkers. So things like ERCC1 and RRM1, which are markers of DNA repair. We've seen from earlier trials that this may help us determine who needs chemotherapy and what kind of chemotherapy.

So this is a trial that is ongoing looking at stage I cancers. We also have a trial that is looking at both EGFR mutation status and ERCC1, which is, again, the DNA repair enzyme and assigning patients to therapy based on those biomarkers. So this is a customized trial.

Another customized trial looking at BRCA1, which many of you may be familiar with from breast cancer. So the investigators in this trial are going to be looking at customizing adjuvant chemotherapy based on that biomarker. And again thymidilate synthase, which is involved in response to pemetrexed, and ERCC1. So I think you're going to see a lot more customized adjuvant trials and that really is where the future is. I also wanted to quickly note that with all the new mutations that we're seeing in Stage IV lung cancer, I think it's only a matter of time before we see many customized adjuvant trials looking at treating these mutations differently.

So, in the interest of time I'm going to just move along to mesothelioma. There wasn't a lot happening in mesothelioma. This is a cancer that is primarily caused by asbestos and is a cancer of the lining of the lung called the pleura. You can see right here a patient with a thickened pleura. Mesothelioma is not a very common disease. There are two to three thousand cases in the U.S. per year. But it's notoriously difficult to treat. Most patients are not candidates for surgery, and even those who are typically have relapse of their disease.

The majority of patients are treated with cisplatin and pemetrexed, and this regimen was established as the standard regimen based on a clinical trial that compared cisplatin alone to cisplatin plus pemetrexed. You can see that about a little more than 40% of patients had substantial shrinkage of their tumor with the combination of cisplatin and pemetrexed. The progression free survival was about 5.7 months and the median overall survival was about 12.1 months.

So this is our first line regimen. We really don't have a standard second line regimen for mesothelioma. We have two goals. One is to try and improve on the first line regimen so patients can do better. The second is to try and come up with other drugs that we might be able to use in the second line or greater setting. Unfortunately we didn't find any of those this year.

The first trial that I'm going to discuss briefly was a trial of maintenance thalidomide versus observation after chemotherapy with cisplatin and pemetrexed. Many of you may have heard of thalidomide because of its very infamous history of causing birth defects in children in the 1960s and 70s, and the drug was banned because of that. It's now been resurrected and shown some very significant effectiveness in a cancer called multiple myeloma. Mesothelioma is a cancer that has very high levels of vascular endothelial growth factor (VEGF), which is also the target of the drug Avastin. Thalidomide inhibits VEGF and it also has some other effects on the immune system. It was formerly used as a sleeping pill because it causes extreme sleepiness.

This trial randomized patients after they had received cisplatin and pemetrexed or carboplatin and pemetrexed to either observation, which would be the standard of care, or thalidomide. You can see here that basically these two curves from time to progression essentially overlap completely. So there was really no benefit to patients being on Thalidomide. The addition of that drug did not stop their cancer from progressing.

Then these are the overall survival curves. Again, if anything, it looks like the patients who were on Thalidomide did a little worse. Now that was not statistically significant, but certainly very disappointing when we're having our patients take another drug with no benefit and potential harm.

Then another drug, called cedirinib, which inhibits multiple VEGF receptors as well as other receptors within the cell, was given to patients with mesothelioma and unfortunately showed very disappointing results. This was just given as a single agent, so it was not recommended that this drug be pursued further.

There was one abstract that showed some promising results. This is actually a drug called SS1P, which is an immunotoxin. It was combined with pemetrexed and cisplatin in the front line treatment of pleural mesothelioma. This was not a randomized trial. This was actually a Phase I trial to determine the safe dose of giving this drug. But once the patients were receiving higher doses of SS1P, it does appear that the patients were having more tumor shrinkage than we would've expected historically. Now that doesn't mean that this is ready for prime time, but I think it's encouraging to see some signs of activity in mesothelioma. I think, in mesothelioma, there will be an increasing emphasis on trying to find biomarkers that might suggest certain treatments for mesothelioma.

We've actually have had some encouraging biomarkers that have been discovered recently. So I think that, in coming years, we will see some improvement in the treatment of mesothelioma, but again I think that simply adding a third drug like we are trying to do in small cell lung cancer is not going to be the route to success.

Thank you very much. I would like to turn it back over to Dr. West.

**Dr. West:**

We'll continue with a question and answer session in a later podcast.

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