



**NSCLC: First Line Treatment of Advanced Disease**  
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**December, 2009**

*GRACE, the Global Resource for Advancing Cancer Education, is pleased to provide the following presentation on First Line Treatment of Advanced Non-Small Cell Lung Cancer, by Dr. Alan Sandler, medical oncologist and Division Chief for Hematology and Oncology at the Knight Cancer Institute at Oregon Health & Science University in Portland, OR. Dr. Sandler spoke at the GRACE Non-Small Cell Lung Cancer Patient Education Forum in Seattle in September of 2009, a program supported by OSI Pharmaceuticals and Swedish Cancer Institute.*

Hello everybody. It's a pleasure to be here and thanks for inviting me, Jack, and for all the things that you've done with this program. So this is my first time speaking to this group and I asked for some advice. He said why don't you talk like you talk to your patients and whatnot. Geez, I should have thought of that on my own.

I thought what is it I'd like for you to take home from this little chat. Number one you should be very, very angry about, with your federal government about the fact that they could really probably the most harshest terms I could mention, not really care at all about lung cancer research. And that's really the bottom line. I can't say that with enough venomous thought.

So here's the NIH research dollar spent per patient death. This is from 2001; although the dollars per patient may have inched up slightly, the ratios are about the same. Lung cancer is about a \$1,000 per patient death as compared to colorectal cancer \$4,000, prostate \$8,000, breast cancer \$12,000 and HIV AIDS \$30,000. Now again, before I get anybody upset, I don't mean to be taking money from the other diseases of course. But I think if we spent a little bit more representative of what the impact of lung cancer, we might have the same results that we've seen in some of those other diseases as well. So that is the one part, the angry oncologist talking and I'll get off my soapbox. But that is something that if any of you would like to write your congressperson or senator that would be great.

So then I thought ,well what else do I want everybody to get out of this? Well, the other thing that is very simple and it's very clear is that chemotherapy actually works in metastatic disease. There essentially isn't really a patient out there who shouldn't have an attempt at chemotherapy when you have metastatic cancer except for those patients who are obviously so debilitated that they would not tolerate chemotherapy. But anybody who could actually tolerate it, and those are folks who are up and about, able to take care of themselves with minimal assistance which is still the majority of patients in this setting, because we're finding people earlier and earlier.

So these two columns are from the very original studies, from studies done in the 1970s where we compared in patients who have metastatic disease, so these are folks that

have diseases outside the chest, not a candidate for surgery, not a candidate for the chemotherapy and radiation that was just talked about and is in essence incurable -- so this is where we've gone. Basically about 10% of patients would be alive at one year if no treatment were done whatsoever in this group. And again I'm talking in terms of groups. There are those who do less well and those who do better.

Chemotherapy, the older chemotherapy in the 1970s that was done doubled the results: the number of patients alive at one year, and there were a few folks alive at two years. And then the newer and more modern chemotherapy that began in the early to mid 1990s tripled the results from no treatment whatsoever and about a 50% improvement from the old. We now have significant or measurable number of patients alive at two years. You have some patients alive at three years and beyond. So chemotherapy does work; it doesn't work nearly as well as we all would like it to work, but it actually does work.

The other aspect that I think people should know about is there's a lot of thoughts associated with chemotherapy, and how bad it is to receive chemotherapy and how patients feel when they're getting it. And the answer is, it's probably a lot better than what you think -- almost always -- and that's the talk that I have with my patients. As we think about the effects of chemotherapy, the horrors that we think about are far worse than the actual horrors, if you will, associated with chemotherapy. Virtually every single study that has ever looked at quality of life and that is to say how patients are feeling during chemotherapy, every single study has said that chemotherapy improves quality of life. This talks about survival, which I think is the number one most important thing, but it's also important how you're feeling when you're getting it.

In fact, that's the take home message from this talk: not only do you live longer with chemotherapy, but you actually feel better when you're getting it. And that even includes during the time you're getting it; not the time afterwards.

So this is a slide, basically this just shows that for a long period of time up until 1990 there wasn't much out there in terms of really approved agents for the treatment of lung cancer. Again, part of it was nihilism associated with lung cancer -- that pharmaceutical companies and folks just didn't do much in the way of research for it.

But since the early 1990s there's been really a plethora of drugs that are improved. You've seen these names before. The names aren't critical at all. It's just really trying to show you that there have been a number of drugs in a short period of time very recently that have approval for lung cancer, and really all of those are because they improve survival. They allowed patients to live longer and better. So that's really the story with chemotherapy.

Again, I often joke with my oncology colleagues that medical oncologists are not necessarily the sharpest tools in the shed with respect to sub-specialities. But we're very earnest! We're guilty of the, if two aspirin are good, three aspirin must be better. But, so we've done a lot of different things with those chemotherapy drugs. We've put

them in every different imaginable combination you can think of, often with very fancy acronyms and what-not. But basically what all these 20 to 30 years of research have shown us is that two drugs are better than one, getting three drugs are no better than two, and that the newer drugs are better than the older drugs.

We've also found that so-called *elderly* patients, defined as 20 years or older than the person speaking -- and in this case over the age of 70 -- that elderly patients as long as they're feeling generally well can get chemotherapy and do just as well as those folks in their 40s and 50s. Then even patients -- this is this PS2, which stands for performance status -- what you do in your day-to-day function. Are you able to take care of yourself, etc., and the performance status 2 folks are patients who are really starting to feel the effects of the cancer to some degree and they're not up and about as they normally would. Even those folks actually can benefit from modest amounts of chemotherapy.

So that's really what we've learned over the past 30 years. It works! And basically as you're giving two drugs, it almost doesn't matter what the names of the two drugs are. That's a trade secret that you really shouldn't be passing on to anybody else, but the fact is that's essentially the essence of it.

Now my slide I thought was kind of good until I saw Dr. Govindan's slide in terms of trying to show the confusion. Anyway the idea, the take home message is there's lots of different pathways and a lot of genetic abnormalities that are involved in every malignancy and lung cancer specifically and I think much like chemotherapy, that one drug isn't as good as two drugs. We're finding out that we had these targets. There's lots of different targets and we're trying what we call targeted therapy, the molecular targeted therapy which is where I'm going to go into next. The idea is, if probably just one of those in rare exception isn't really enough either. But it is a nice start and it's the only way you can get going is by looking at one and then seeing about adding others to the mix.

So I'm going to show you just three what we call *schemas*. These are the designs of the studies and these are three studies that have shown that these new targeted agents actually work, and so this is one that I was a part of that looked at adding a new drug called Avastin® which is an anti-blood vessel drug. It works by targeting a protein called vascular endothelial growth factor, which is a fancy name again of something that actually feeds and allows the tumors to promote new blood vessels to feed them. Tumors have to have new blood vessels to feed them if they get beyond, say, one centimeter or roughly about a third of an inch. And so the idea is, maybe if you eliminate those blood vessels, you can starve the tumor and have it at least stop growing, turning cancer into a chronic disease. And so this was the first attempt at using it with chemotherapy, and so half the patients and I think this also helps to illustrate the importance of clinical trials. We're not going to make advances without clinical trials. It's pretty much as simple as that. If we don't put people on clinical trials, we're actually going to go no further than we are right now.

So the idea of this clinical trial that was done: randomized patients to chemotherapy which was standard, or chemotherapy plus the Avastin®, which began with the chemotherapy and then continued until the cancer grew again. The bottom line is it worked. And there was an improvement in the survival with the addition of Avastin® to chemotherapy. And in this particular setting, over half of the patients were alive at one year. You'll remember that other table where it was 10% with no treatment, 30% with the better chemotherapy; now for the first time ever over half of the patients were alive with the addition of Avastin® at one year. We now had about 15% of patients alive at three years, where previously it was zero with no treatment, roughly about 5% or so with chemotherapy. So an advancement forward – it's not curative, but we're making progress.

This is another study that was done looking at a different drug: Erbitux®. Similar design, chemotherapy versus chemotherapy and Erbitux®, which is one of those antibodies against the epidermal growth factor receptor pathway. Suffice it to say that that's just a pathway that certain tumors are dependent upon for growth and development. So the idea being that in addition to chemotherapy you've got this antibody as well, and it too had a survival advantage. It was modest but the fact is it did. So that drug is being looked at for possible approval.

In the last one that I'm going to leave you with is one that's kind of interesting, and very much so for the non-smokers in the audience or listening on the web is this IPASS study. It looked at epidermal growth factor receptor tyrosine kinase inhibitor; those are the oral agents that attack the EGFR pathway. And so, what this study was done, it was done overseas, and it was in Asian patients who were never or light smokers, and compared Iressa®, the US sort of version is Tarceva®, to chemotherapy. Again, chemotherapy is the standard for patients with metastatic disease, and the thought was in these patients who were likely to have a mutation in that pathway, and therefore their tumor would be "addicted" to that pathway and maybe very much dependent upon it, that maybe this Iressa® would be as good or even better than chemotherapy. So, again, by a clinical trial, half the patients received Iressa® first, after the patients received traditional chemotherapy first, and what they found was there was a dramatic improvement in response rate and the time that the tumor went away and stayed away with the actual Iressa® over chemotherapy.

Overall, the survival of the two groups were the same. So it really wasn't so much of an "if" but more of a "when." I mean the idea was that that particular combination they did very well and patients were able to escape using chemotherapy for a period of time. When the Iressa® stopped working, they went on to get that chemotherapy, much like the patients who had chemotherapy when the chemo stopped working, they received the Iressa®. So it's really just sort of an order, but kind of fascinating that in a head-to-head competition, that just the pill with no side effects of hair loss or bone marrow effects, etc., actually worked as well as chemotherapy. They also found in that study that really, most of that benefit was only to the patients who had the mutation. That mutation occurs in about 60% of Asian patients who are never or light smokers;

probably only about 25%-30% of Caucasians who are never smokers. And only about 10% of the population as a whole if you look at all lung cancer patients.

So I think that that's part of the reason for showing that was just to kind of talk about the fact that we are taking steps forward beyond chemotherapy, although its probably not as fast as we would have liked and not as robust as we would have liked. But some evidence that things are moving in the right direction.

And then you know I had one slide that I didn't know whether I should show it or not. It doesn't really relate to my talk, but I actually was walking some at Oregon Health & Science University, which is again in Portland and I was walking, we have our hematology/oncology offices are the third floor, where oncology and on the second floor. So I was walking by this, apparently the office of psychiatry is down that way and so I happened to walk by and saw one of the offices and a sign outside were the offices of one of the psychiatrists. And it caught my eye and I just wanted to see what you all thought about it.

So Professor of Psychiatry, Director of the Traumatic Stress Program and then something I've never seen before Director of the Tortured Treatment Center of Oregon. I'm a little afraid to go in and knock on the door and just kind of see what goes on there.

So I'm sure we as oncologists have been accused of the same, but nonetheless, I think I'll leave you with that.