



**Dr. George Simon**  
**Individualizing Treatment Recommendations in NSCLC**  
**Based on Molecular Factors**  
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*GRACE, the Global Resource for Advancing Cancer Education, is pleased to provide the following presentation by Dr. George Simon on Individualizing Treatment Recommendations in Non-Small Cell Lung Cancer Based on Molecular Factors. Dr. Simon is a medical oncologist and the Director of Thoracic Oncology at Fox Chase Cancer Center in Philadelphia, PA. Dr. Simon spoke at the GRACE Non-Small Cell Lung Cancer Patient Forum in Seattle in September of 2009, a program supported by OSI Pharmaceuticals and Swedish Cancer Institute.*

Lung cancer survival still needs a lot of improvement. So if you take all stages, all comers, it's about 17% that get cured and that differs based on the stage. If you're early stage, a higher proportion get cured. If you have advanced stage, a lower proportion get cured.

And in advanced stages of the disease, studies show that when you do one chemotherapy drug versus no drug, people live longer. So this is one drug versus the green is no drug and if you got no drug, the probability of living two years is 1%. And if you got one drug, the probability of living two years was 10%. This is a study done in the United States, and this is another study done in Poland that showed if they got no drug probability of living two years was zero percent; and if you got one drug there was 12%. So this and many other studies showed that one drug was better than no drug. And this and some other studies showed that two drugs was better than one drug. So gem/cis compared to cis two year survival from 15% to 3%, and this study looked at two drugs versus one drug and showed that 12%, two-year survival was 7%. So, so two drugs was better than one drug. And so it's easy to figure out what oncologists did next. If two is better than one, one is better than nothing, then three must be better than two.

So, they did many studies that looked at three drugs versus two drugs and the answer was not just a "no," it was "hell no," because by giving three drugs you did not increase efficacy. You increased toxicity.

So you have to step back and figure out there are so many different three-drug combinations is any particular so many different two-drug combinations, is there any particular two-drug combination better than any other two-drug combination. So this is one out of many randomized studies that asked that question, looked at many different two-drug combinations. And you can see that regardless of which two drugs you combined together, they're essentially all the same. They were pretty identical in efficacy.

This is where we were around 2000, when we added a third drug, it didn't make a difference. When you looked at various two-drug combinations they're all the same. So it was almost like we hit a stalemate.

We decided to pick chemotherapy based on a tumor's genetic profile. So we knew that certain markers would predict for the fact that a drug would work or not work. And then so we would do a biopsy. We would measure certain genes and then based on the expression of those genes, we would give them a specific drug or not give them a specific drug.

So we did this study called the Molecular Analysis Directed Individualized Therapy, its called this notorious acronym called MADe-IT that has been the brunt of many jokes. One of the markers that we looked at was ERCC1 that actually predicts for platinum resistance or sensitivity and the other marker that we looked at was RRM1 that actually predicts for Gemzar sensitivity or resistance.

Okay, so what we did was we did a biopsy and we measured, actually measured ERCC1 and RRM1 levels in tumors. And if the ERCC1 levels were low, we gave them platinum, cisplatin, carboplatin and if RRM1 levels were low we gave them Gemzar with the platinum. If RRM1 levels were high and ERCC1 levels were low, that means we had to give the platinum, could not give Gemzar so we give Taxotere®. So we give Taxotere® with the platinum. Now if platinum, ERCC1 levels are high, we could not give them platinum and if RRM1 levels were low we could give them Gemzar, could not give them platinum with the Gemzar; so we give Taxotere® with the Gemzar. Okay, and if they're both high, we could not give platinum, could not give Gemzar, so we were able to give Taxotere® or Navelbine®. So we used this tailored method and tried to show that the tailoring chemotherapy would actually improve survival. So this is what we call a "proof of principle" study. We did a phase II study when in every patient we actually tailored the treatment.

And what we found was that we got a response rate of 44%, and normally we should get a response of 25%. And we get a disease stabilization rate of 44%. And we call that the disease control rate, that is the response and disease stabilization added together to give you what's called a DCR (disease control rate) and that was about 88%. That actually looked pretty promising. That means eight or nine out of 10 patients actually derived benefit from the chemotherapy. And it's more likely to be about five or six, 50% of patients normally. So we have here pushing the numbers up to 80% or 90%.

And the median survival, that's about the halfway point, was 13.3 months and normally we would see mean survivals of nine months, ten months and here we're seeing median survivals more in the 13 month range.

So this appear to be promising. Again, before we make loud claims, we have to do what we call a phase III study.

Now currently we're doing this Phase III study. Phase III study means there are two cohorts of patients and we're comparing one cohort versus the other. And in the so called non-customization arm, what we would call the standard arm we would just give everybody platinum and Gemzar, and the other test arm or customization arm, we would tailor the chemotherapy based on the algorithm that I just showed you. And then pool those patients together and compare this cohort of patients to this cohort of patients and figure out who did better. So those studies are currently ongoing. It's a multicenter study.

Now, I'll talk briefly about targeted agents, previously we got drugs from nature. Okay, so platinum was basically the metal platinum, a salt of the metal platinum. Drugs like Taxol®, Taxol® comes from the Pacific Yew tree, the bark of the Pacific Yew tree.

And this is a tree called taxus bacata and this is where we get Taxotere® from, from, you know, we got it from nature.

Now in more modern times, we just design our own drugs. We make our own drugs. And this has been showed. So what we do is we figure out the protein that's a bad guy, okay. Based on research we try to identify one of these proteins and here this guy here -- ras and raf -- they're a bunch of bad guys, okay. We try to shut down the bad guy, okay. And the way you do that is you understand how that they work. So the first step is understanding how that signaling works. So here, there are two proteins. They kind of stick apart, they do nothing.

Then they attach to stuff that is circulating in the blood that activates those two proteins. Those two proteins come together. They then get activated, the switch gets turned on. That's called phosphorylation in our terms, and then a bunch of other proteins get activated. This activates this, this activates that. That activates that. And that activates that. And that activates that. And that leads to proliferation, meaning cancer cells start growing and dividing, and these are supposed to make, prevent cancer cells from growing and they get activated and they prevent cancer cells from dying. And that leads to, you know, growth and spread of cancer.

And so if you block this here, then all these unwanted effects get blocked and that's kind of the principle of how some of these targeted agents work. And they're going to intelligently design drugs. So these are drugs that are actually man-made from the ground up. They don't exist in nature, essentially.

One such drug is gefitinib works specifically works in EGFR mutation patients. And so this is another way of tailoring therapy. So one of the ways of tailoring therapy is studying the genes, which genes will work when, which drugs will work when a particular gene is up or down regulated and which drugs will work when specific mutations occur. And again, this is a study that showed that when you have a particular mutation using this drug gefitinib, one of those targeted agents made by man from the ground up actually works very well. It works as well as two conventional chemotherapy drugs, carboplatin and Taxol® put together.

And again if you have the mutation, the probability of responding to gefitinib is 71%, okay, that's pretty good. But if you don't have the mutation, the probability of responding to gefitinib is 1%. So it's like you know that this drug will work in that specific group of patients.

So lung cancer is the largest cause of mortality among cancers in the United States. And more women die of lung cancer than breast and all the gynecological malignancies put together. And it's still an orphan disease. And that's why this cartoon is very nice, it says it's not cured, it not an even in the race for a cure.

What we're doing well over time, so this is a publication from the Centers for Disease Control and this is from I think way back in 2003, now with more modern medicine there is a reason for hope. And there's about 5 million people, males and females now alive, about five years out in the United States and about 3 million people alive about ten years out from the diagnosis of their cancer and about 2 million people alive 10-15 years out from the diagnosis of the cancer. So, more and more people are now living with the cancer than dying of it. So cancer research is bearing fruit. We still have a long way to go and we need your support and advocacy for more research funds for deadly diseases like lung cancer.

I thank you for your attention.