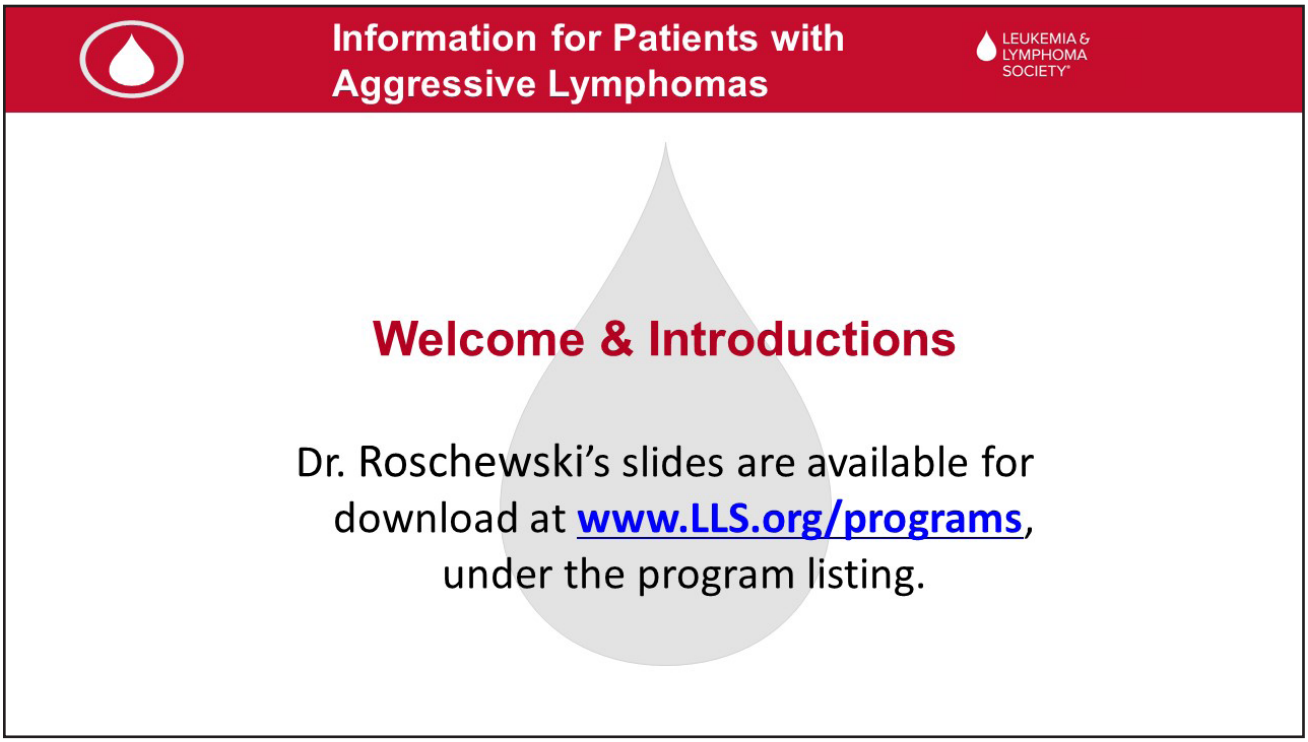


Slide 1: Welcome and Introductions

Lizette Figueroa-Rivera:
Hello everyone. On behalf of The Leukemia & Lymphoma Society, I would like to welcome all of you. Special thanks to Dr. Mark Roschewski for volunteering his time and expertise with us today.

Before we begin, we would like to play a recorded message and video from our President and Chief Executive Officer, Dr. Louis DeGennaro.

Dr. Louis DeGennaro:
Hello. I'm Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancer. For nearly 70 years, LLS has invested more than one billion dollars in scientific research to find better treatments and cures. We have played a pioneering role in the development of groundbreaking targeted therapies and immunotherapies that have led to increased survival rates and improve the quality of life for many blood cancer patients.

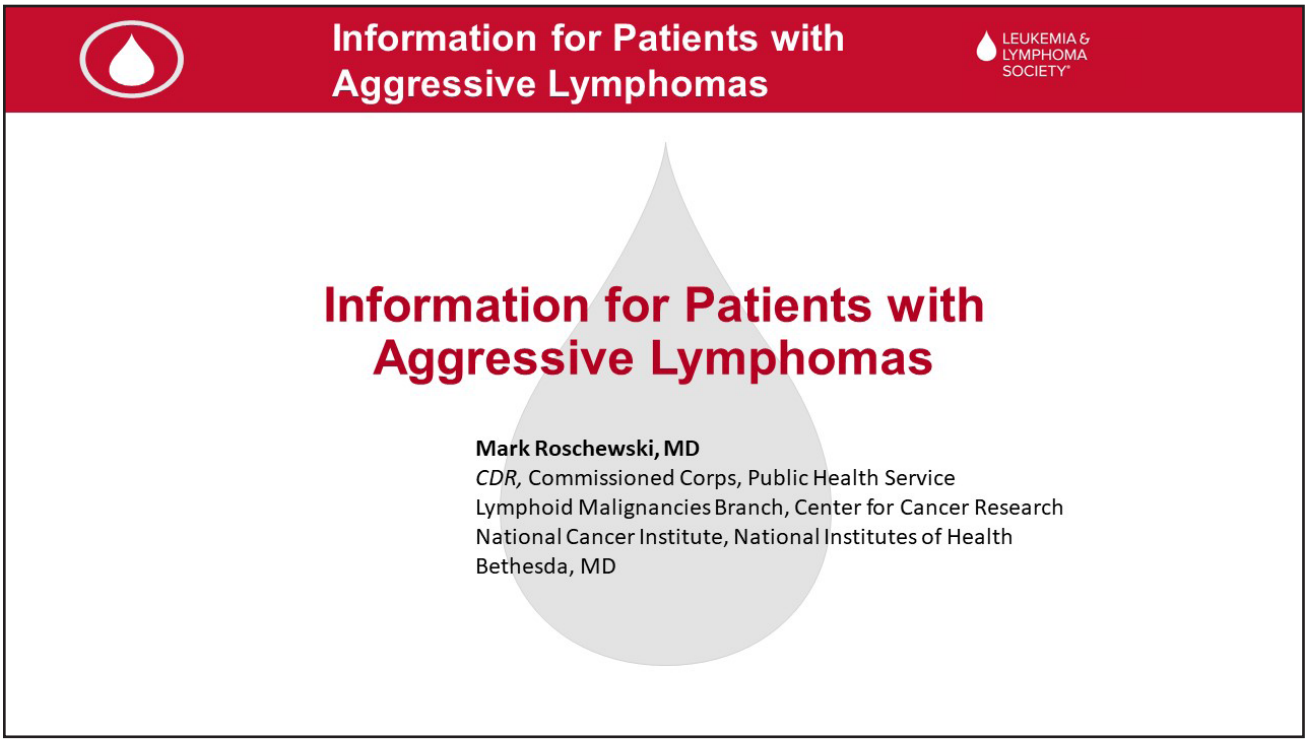
Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support. We also support blood cancer patients in their local communities through our 56 chapters across the United States. And, we fight for lifesaving policy changes at the state and federal level to ensure access to quality, affordable, and coordinated care.

We are committed to working tirelessly toward our mission every single day until we find a cure. We're fortunate to have esteemed key opinion leaders to present our programs. They each have volunteered their time and we appreciate their dedication to supporting our mission and commitment to caring for patients living with blood cancers.

Thank you for joining us today.

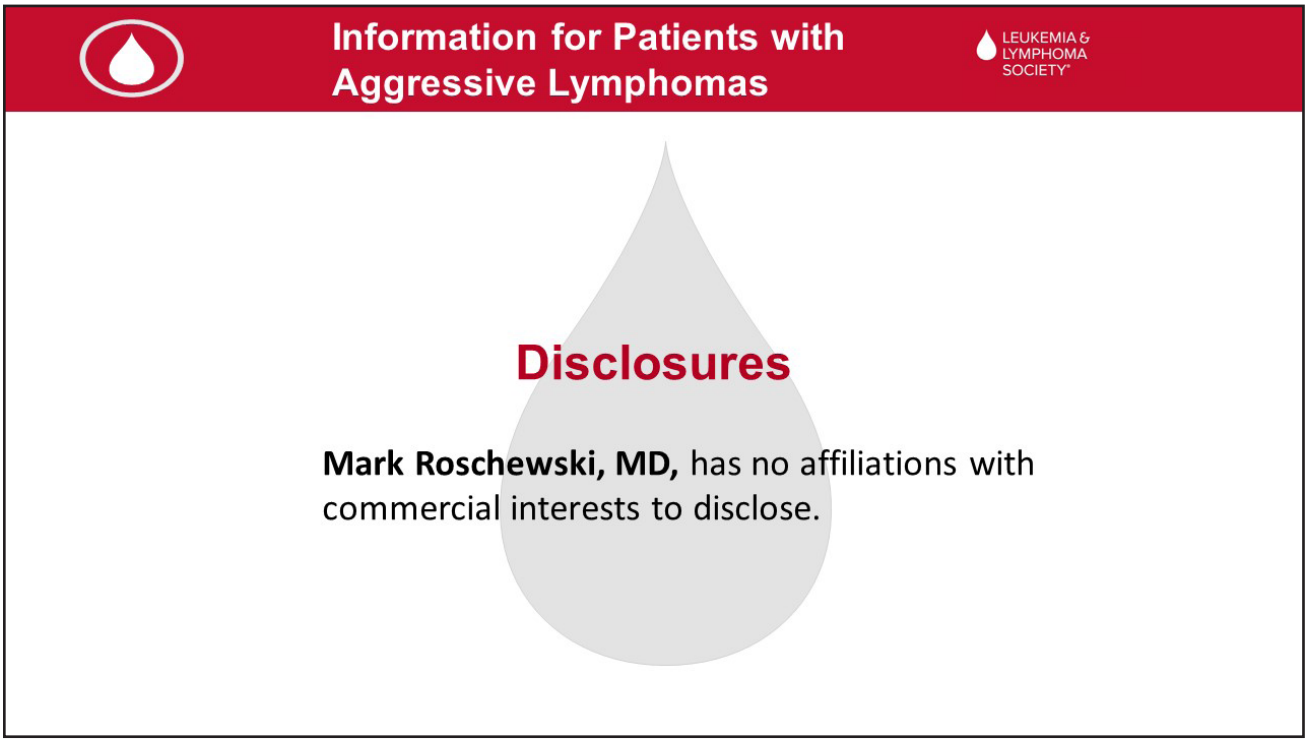
Lizette Figueroa-Rivera:
Thank you, Dr. Lou. And, The Leukemia & Lymphoma Society would like to thank Genentech & Biogen and Pharmacyclics, an AbbVie Company, & Janssen Biotech for support of this program.

I'm now pleased to introduce Dr. Mark Roschewski from the National Cancer Institute, National Institutes of Health in Bethesda, Maryland. Dr. Roschewski, I'm privileged to turn the program over to you.



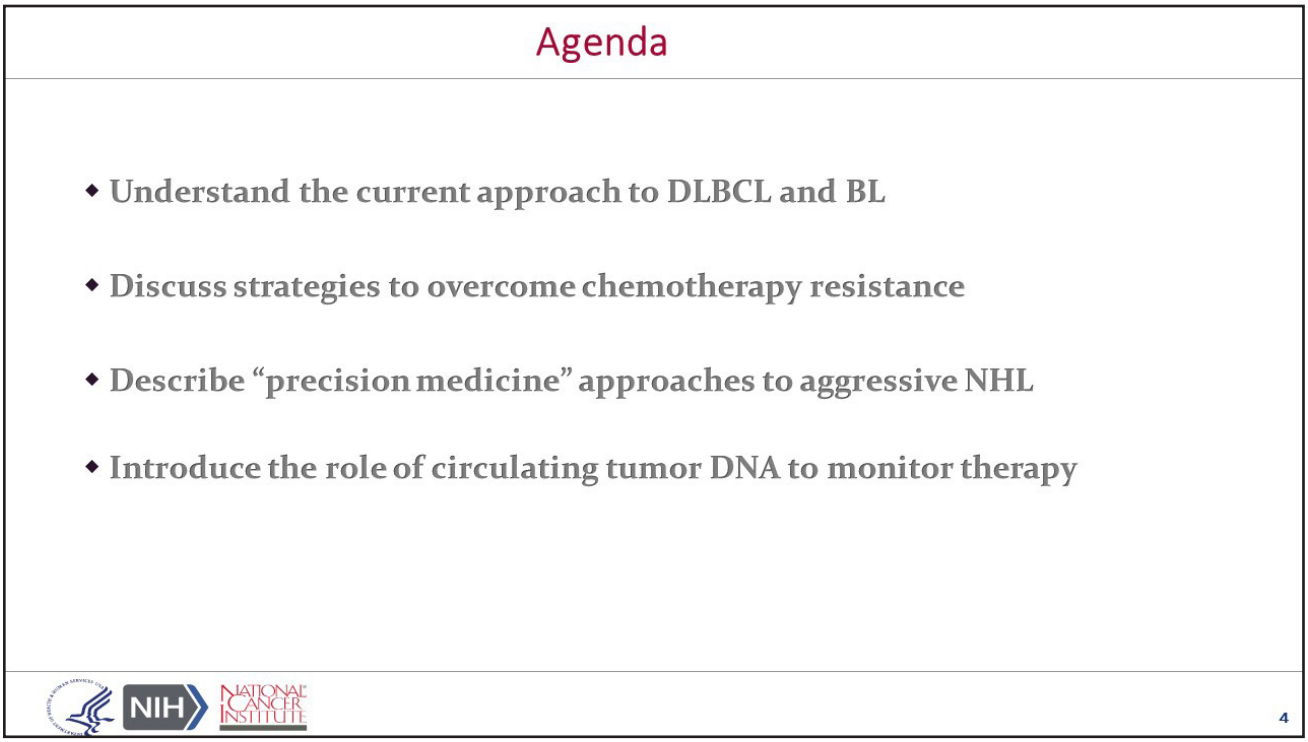
Slide 2: Information for Patients with Aggressive Lymphomas

Dr. Mark Roschewski:
Okay, thank you. It's a pleasure for me to be here speaking to all of you about aggressive lymphomas.



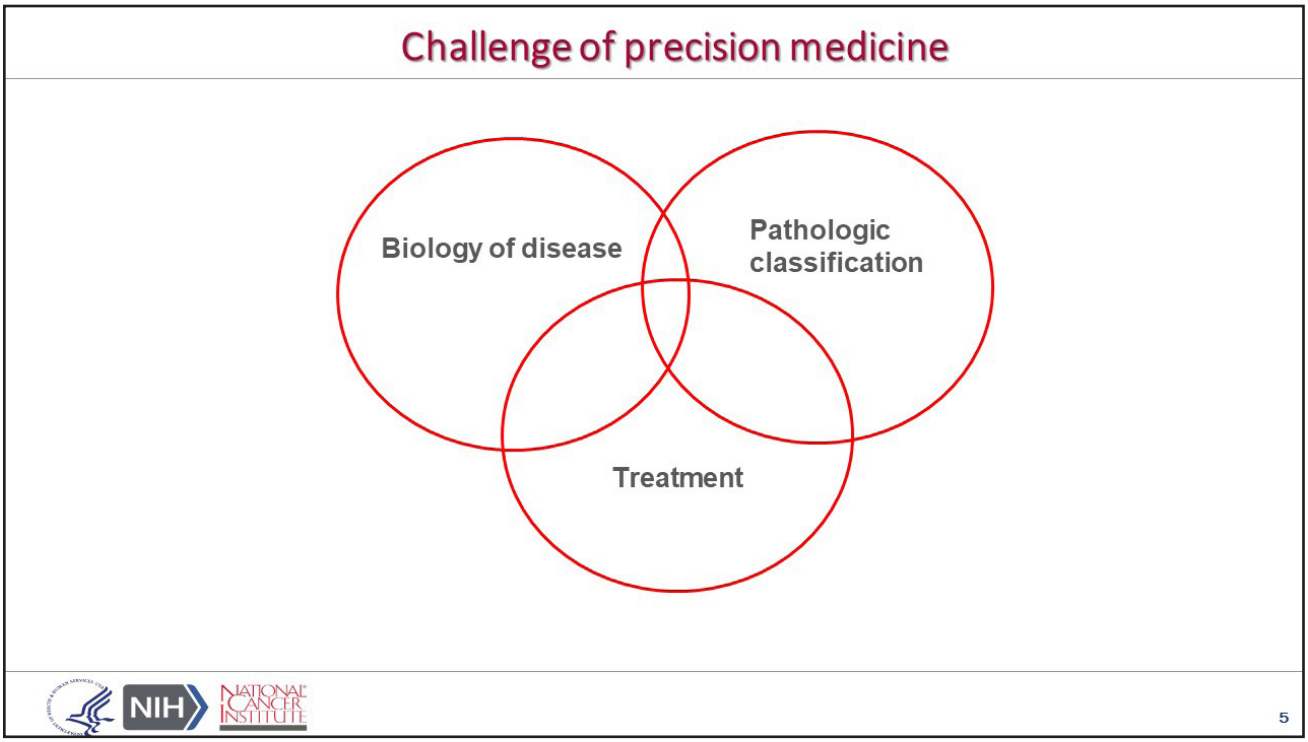
Slide 3: Disclosures

I have nothing to disclose financially.



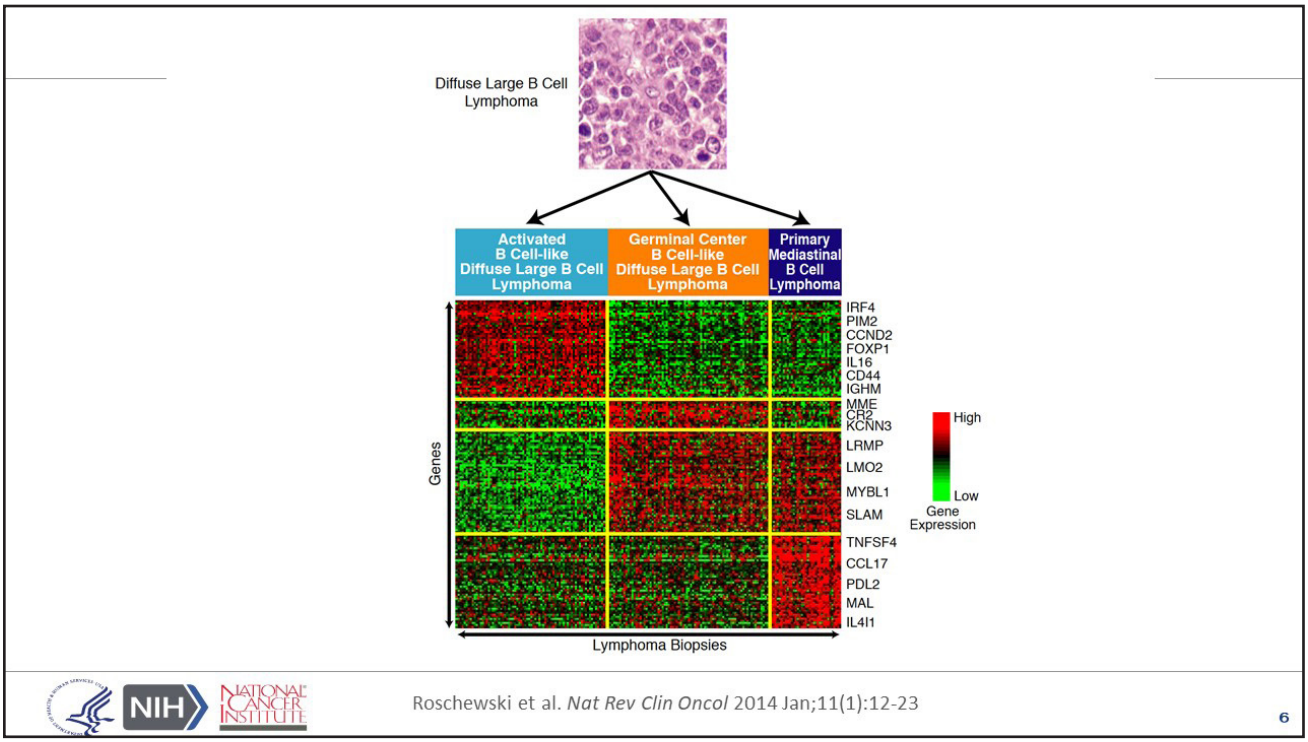
Slide 4: Agenda

What we're going to do is discuss how we as physician's approach patients with aggressive B cell lymphomas, such as diffuse large B cell lymphoma and Burkitt's lymphoma. Of course, some of the concepts that we discuss are applicable to other aggressive lymphomas that we need to focus on those, too. The thing that they have in common is that the goal for most patients is to achieve cure. And, it's true that chemotherapy, when given appropriately and intensively, can cure many of these patients. But of course, not all patients get cured, and we're in a time where we're trying to improve the cure rate by using precision medicine tools. So, the other thing I'd like to highlight is some of the strategies we use as physicians and researchers to then overcome the resistance we see with chemotherapy. We'll discuss this concept of precision medicine and hopefully I'll impress upon you the challenges we have moving forward. And, then finally, at the end I'd like to highlight, some newer things that aren't treatment that are coming that may eventually enable us to better inform our treatment decisions.



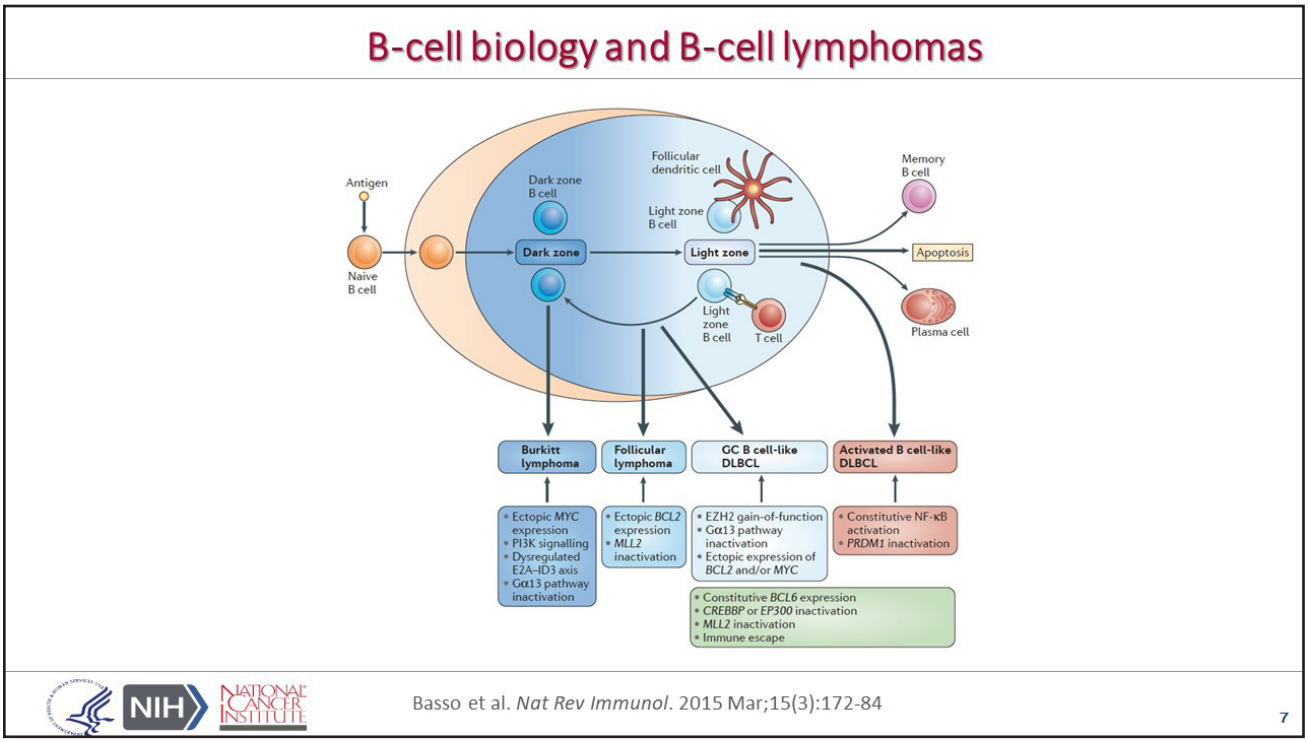
Slide 5: Challenge of precision medicine

So, this then diagram highlights some of the complications of precision medicine. That is to say, that of course we give treatment that's most effective and if we knew what the right treatment was, we would always select that for our individual patient. But, the problem is that we classify disease in a certain way based on the way it presents itself, the way it looks underneath the microscope, and that doesn't always marry up with the actual truth, and the truth being the biology of the underlying disease. If we knew exactly what the biology of the underlying disease was, it would be easier and more straightforward to design precision medicine treatments that attack the actual biology of the disease and not just the way we currently break these diseases down, such as classifications.



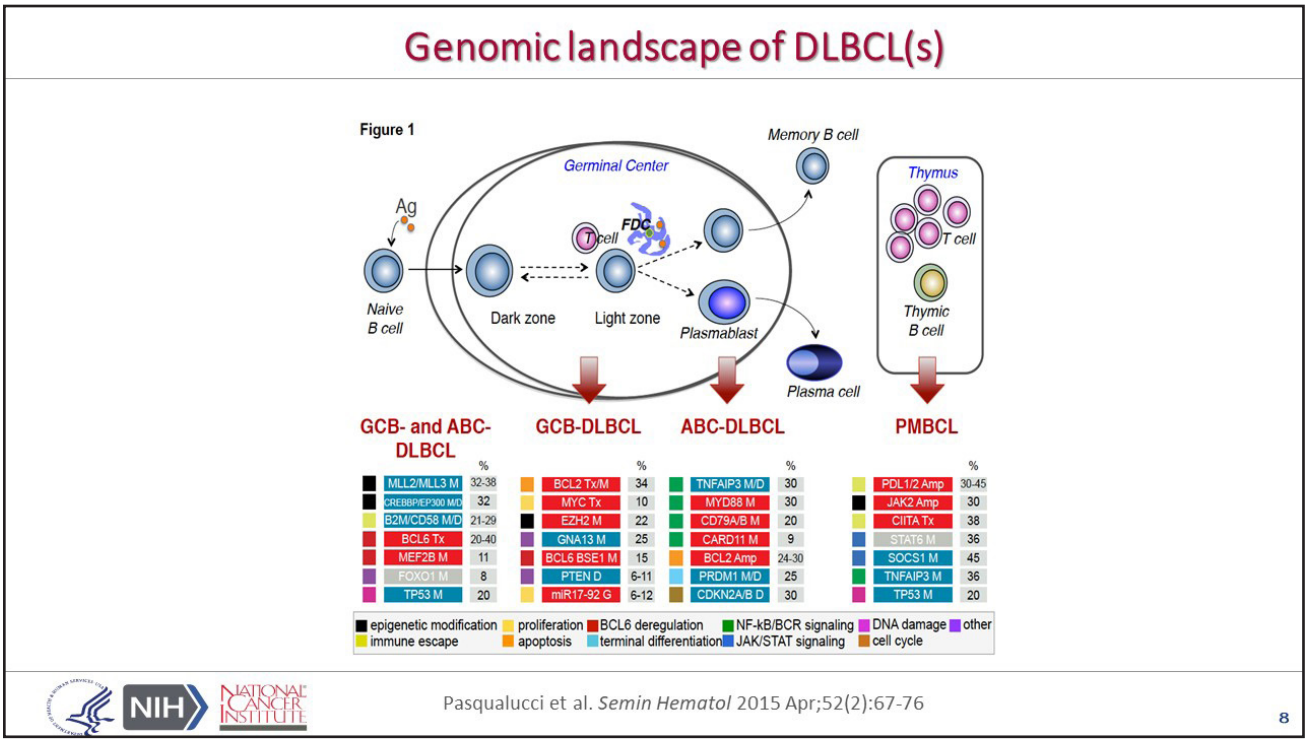
Slide 6: Diffuse large B-cell lymphoma

And, this is highlighted in this slide. So, what this is showing us is that even though tumors can look exactly the same underneath the microscope, highlighted at the top, if you actually use, in this case gene expression profiling, you can see that the molecular biology is different. And, so diffuse large B cell lymphoma actually is multiple different diseases. What is seen here in red is the expression of certain genes that identify the differences between an activated B cell-like diffuse large B cell lymphoma, compared to a germinal center B-like diffuse large B cell lymphoma, and something completely different, which is primary mediastinal B cell lymphoma.



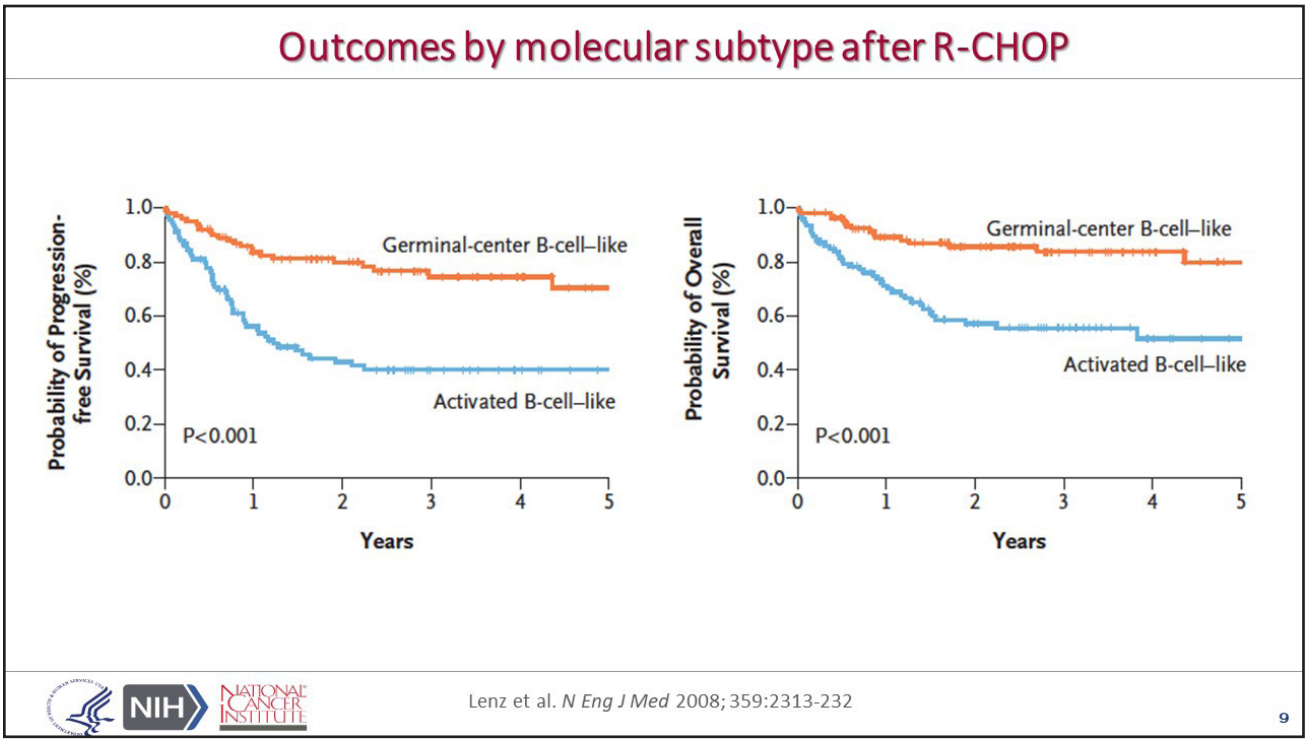
Slide 7: B-cell biology and B-cell lymphomas

And, one of the things that we do when we're trying to understand disease biology is we think about it in the context of what the cell was before it became malignant. So, what you're seeing here at the top is normal maturation of a B cell. So, of course, a B cell is part of our normal immune system, it goes through normal processes, at which it then becomes either a memory B cell or a plasma cell. And, what a B-cell lymphoma effectively is, is a normal B cell that has developed additional properties that it should not have, and that leads to malignant transformation and then the timing of which it turns into a malignant B cell defines what it looks like underneath the microscope and is currently how we classify diseases.



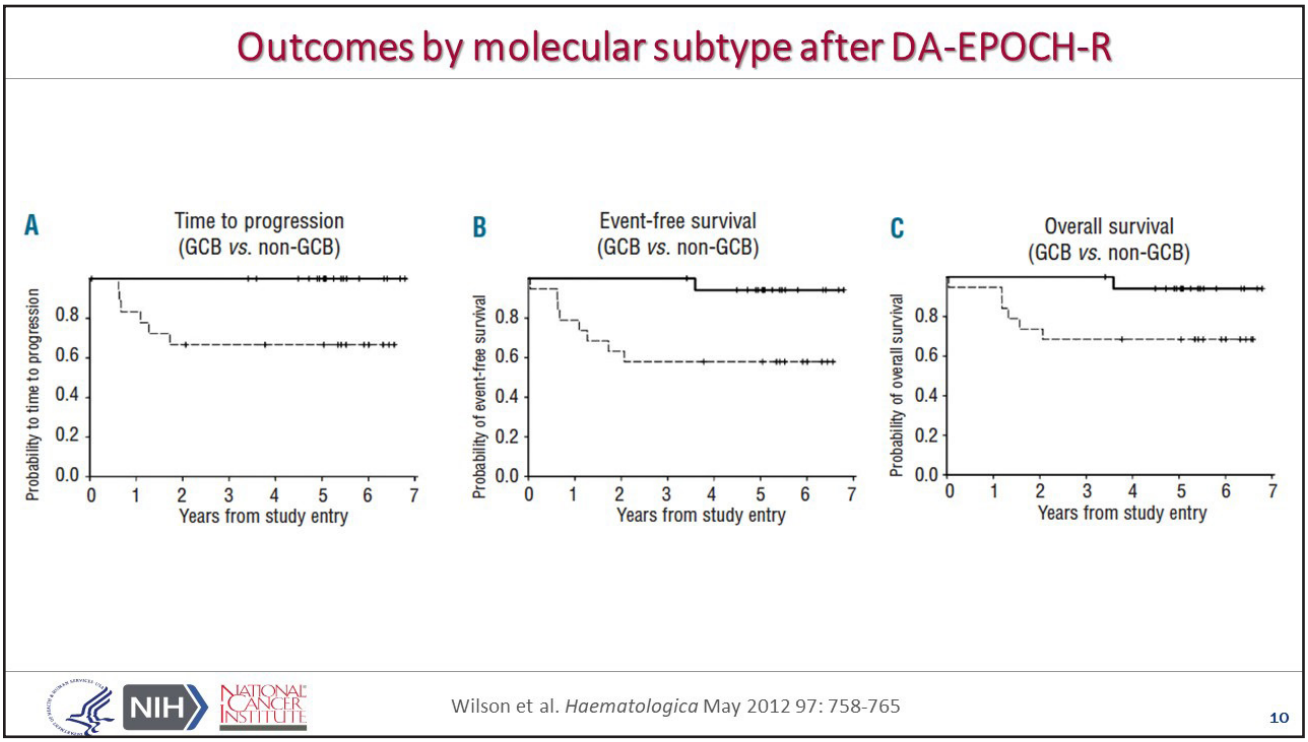
Slide 8: Genomic landscape of DLBCL(s)

This is another view of the same process. At the top, you see the B cell as it matures through a normal germinal center. And, what we're seeing here is that even diffuse large B-cell lymphoma can be broken down into multiple different subtypes based on gene expression profiling. And, if we actually look even more closely at the molecular biology with respect to individual mutations, we can see that highlighted below in the red and blue is that there are individual mutations that are shared across different entities and those that are unique and specific to different entities. And so, this becomes the challenge as we're trying to develop newer, better therapies and more precise therapies, is we have to understand that the biology we're dealing with here is quite complex and our understanding of that biology to this point is incomplete.



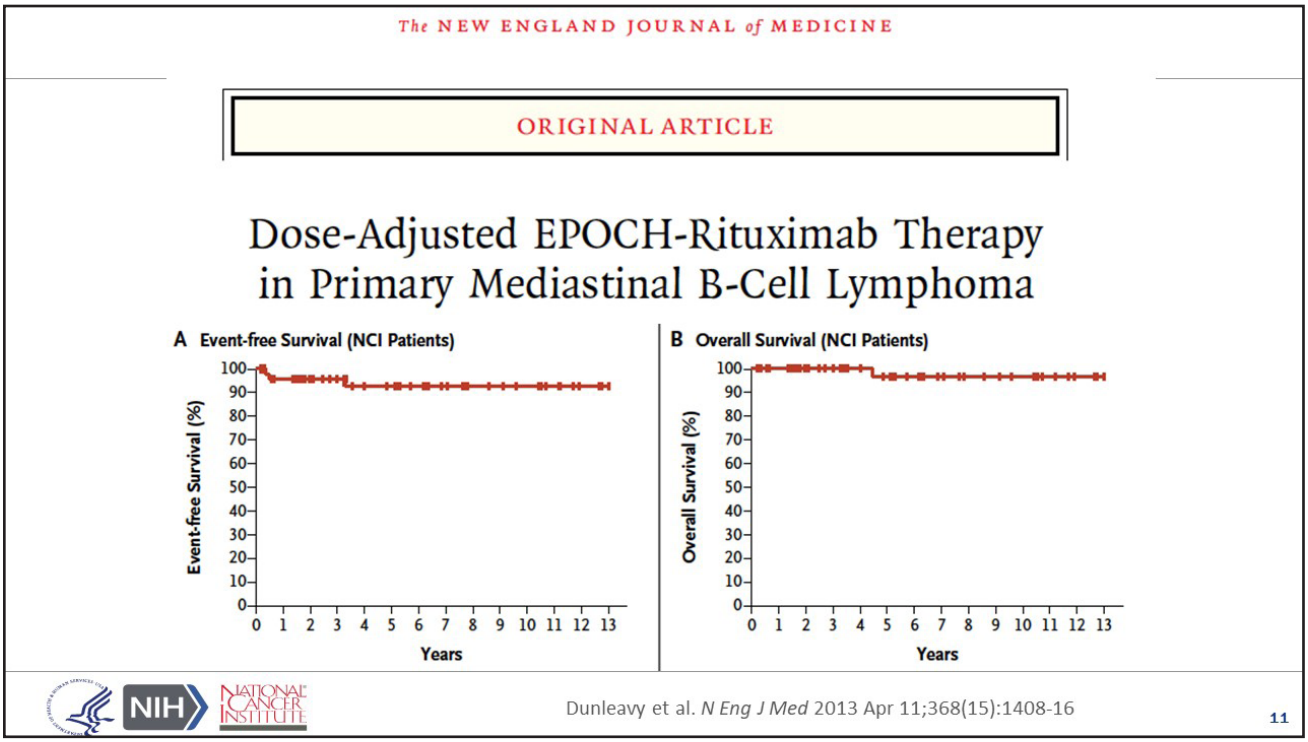
Slide 9: Outcomes by molecular subtype after R-CHOP

But, it matters. So, this shows us the ultimate outcomes, both progression-free survival as well as overall survival. You can see highlighted here, that if you have an activated B cell-like diffuse large B cell lymphoma and you're treated with R-CHOP, it's less likely that you will get a cure than if you have a germinal center B, at least in this paper that looked retrospectively.



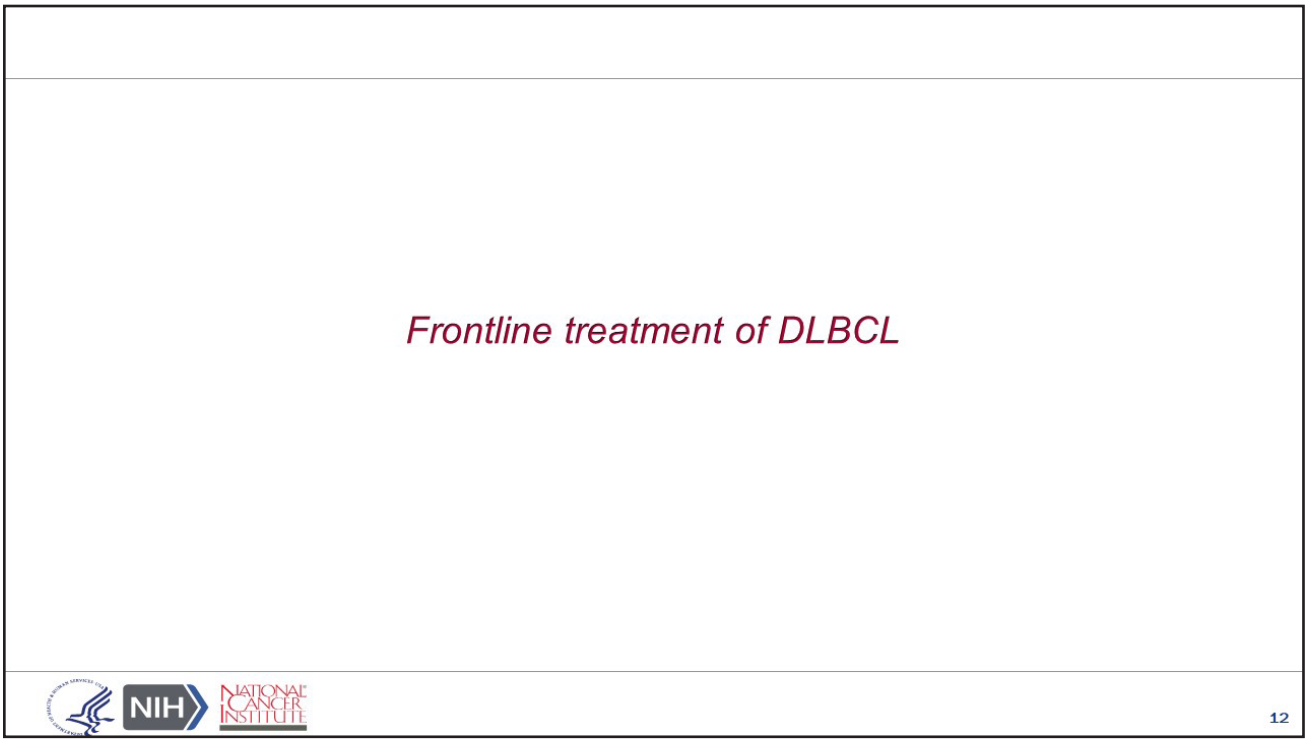
Slide 10: Outcomes by molecular subtype after DA-EPOCH-R

But, we also observed that in our prospective study, in a multicenter setting using the regimen we use here at the NCI, known as dose-adjusted EPOCH-R. And, what you're seeing on the top line is that those are germinal center B diffuse large B-cell lymphomas, and they do much better than the patients that have in this case non-germinal center B diffuse large B-cell lymphoma. So, again this highlights that not only is the biology different across diseases, but the treatment outcomes can be quite different, even when they're given the same therapy.



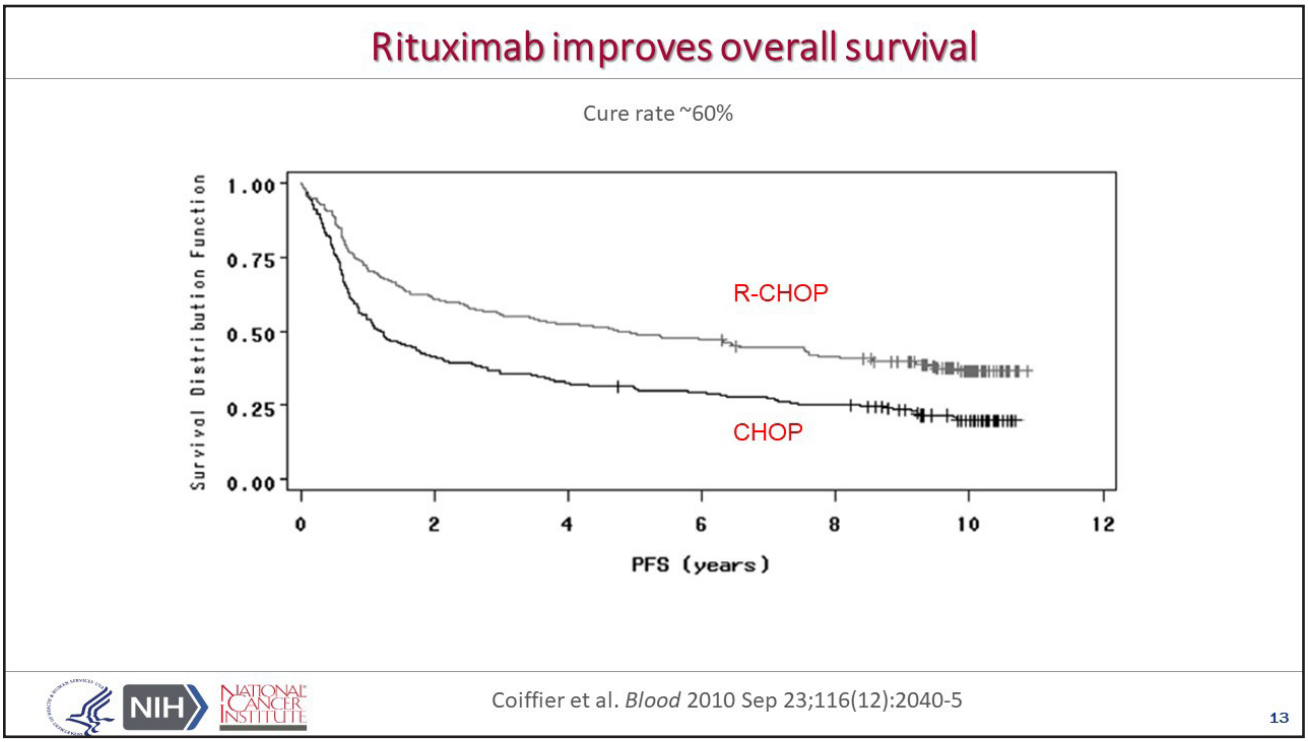
Slide 11: Dose-Adjusted EPOCH-Rituximab Therapy in Primary Mediastinal B-Cell Lymphoma

And, here's a third entity known as primary mediastinal B-cell lymphoma and this is 53 patients that were treated at our institution and you can see that most of these patients are cured when they're given the dose-adjusted EPOCH-R, and in many cases not even radiation. So again, this is a third entity that's now being defined, different molecular biology and different outcomes with similar treatments.



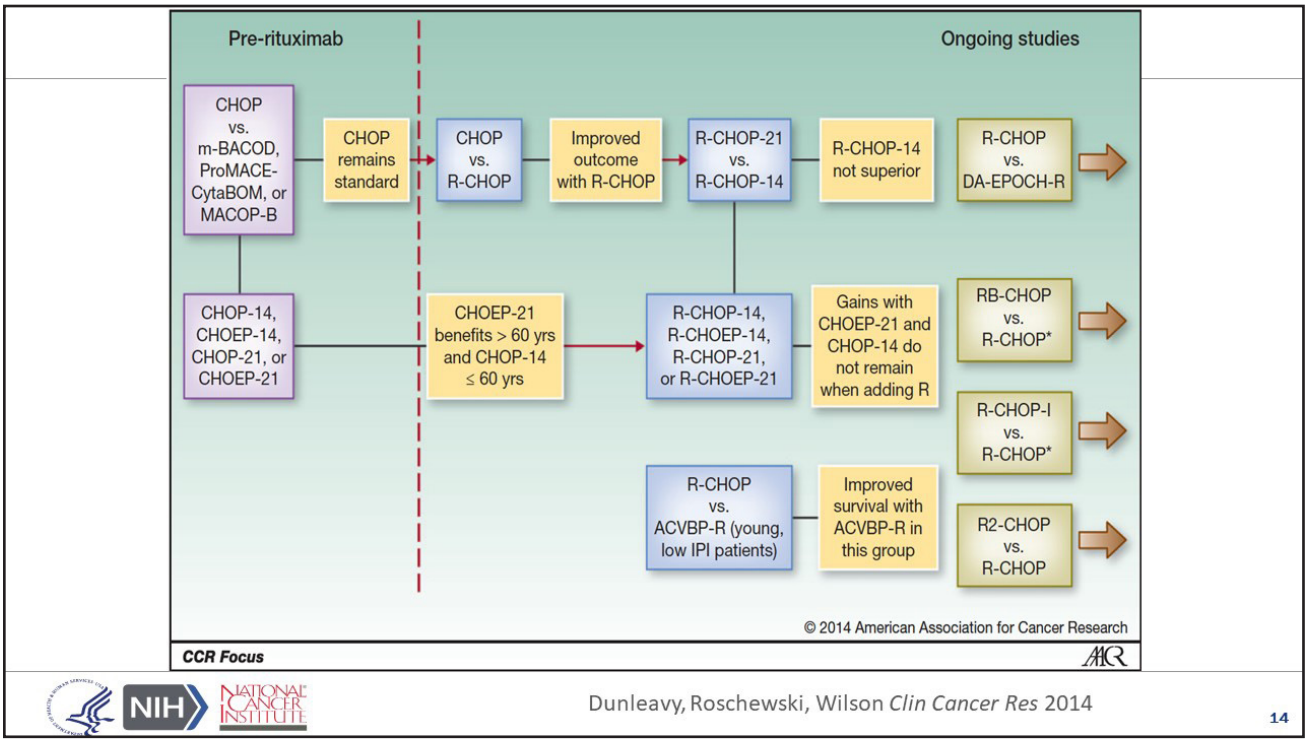
Slide 12: Frontline treatment of DLBCL

So, what does that mean for the way we approach patients now in an attempt to cure them?



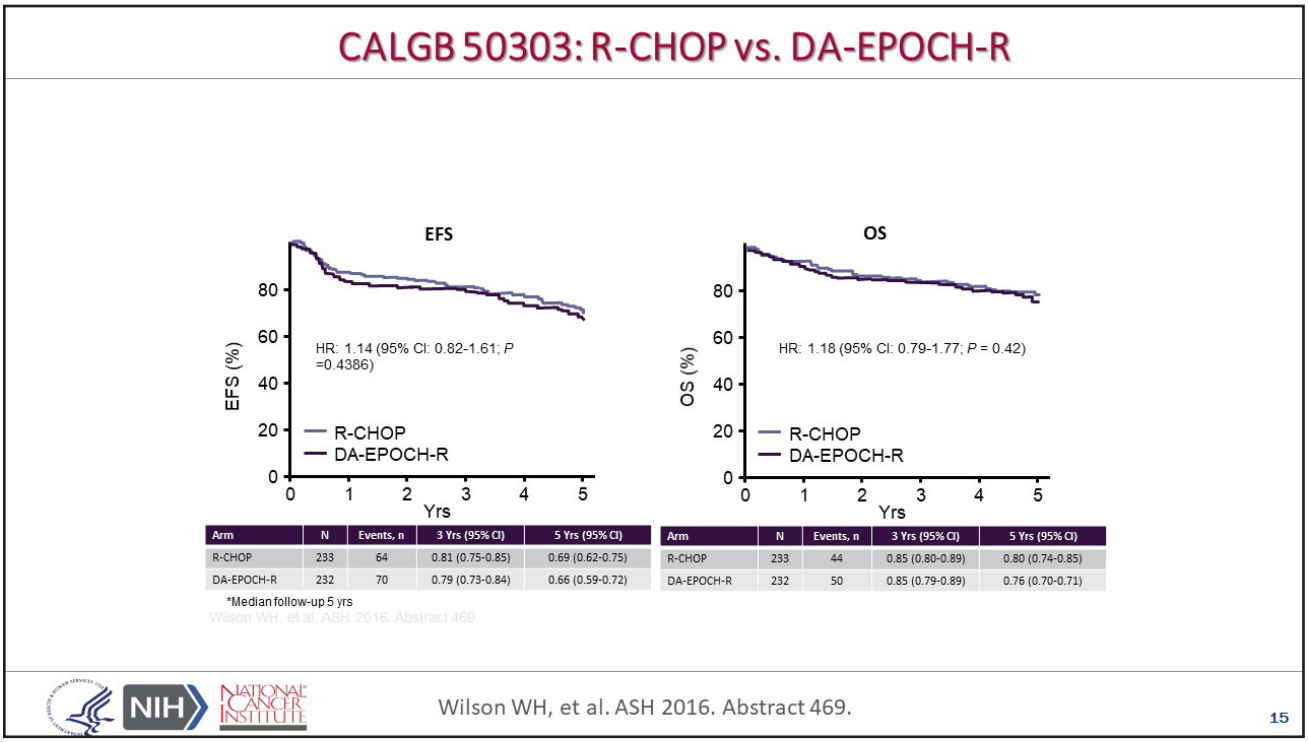
Slide 13: Rituximab improves overall survival

Well, the last transformative drug that really changed the way we approach patients was rituximab. So, this is the first study in older patients, patients over the age of 60, and this showed us a progression-free as well as survival advantage of about 15%. So, you can see that more patients were cured when given rituximab. But, you can also see that the curves started declining over time and we aren't curing as many patients as we would like. We estimate that the cure rate, all-comers with diffuse large B-cell lymphoma, is currently around 40%, and we're looking to move past that.



Slide 14: Randomized trials

There've been a number of randomized trials that have tried to improve upon the outcomes of R-CHOP and it's proven to be quite difficult. So, both more intensive regimens given every 2 weeks instead of every 3 weeks, additional agents, such as etoposide, and even things known as ACVBP, which is a highly intensive regimen, have been tried. And, the only regimen that has shown itself to be more effective than R-CHOP is the R-ACVBP, represented at the bottom. All other randomized studies, to this point, have been inconclusive or negative with the exception of these targeted therapy trials here, which are ongoing.



Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	64	0.81 (0.75-0.85)	0.69 (0.62-0.75)
DA-EPOCH-R	232	70	0.79 (0.73-0.84)	0.66 (0.59-0.72)

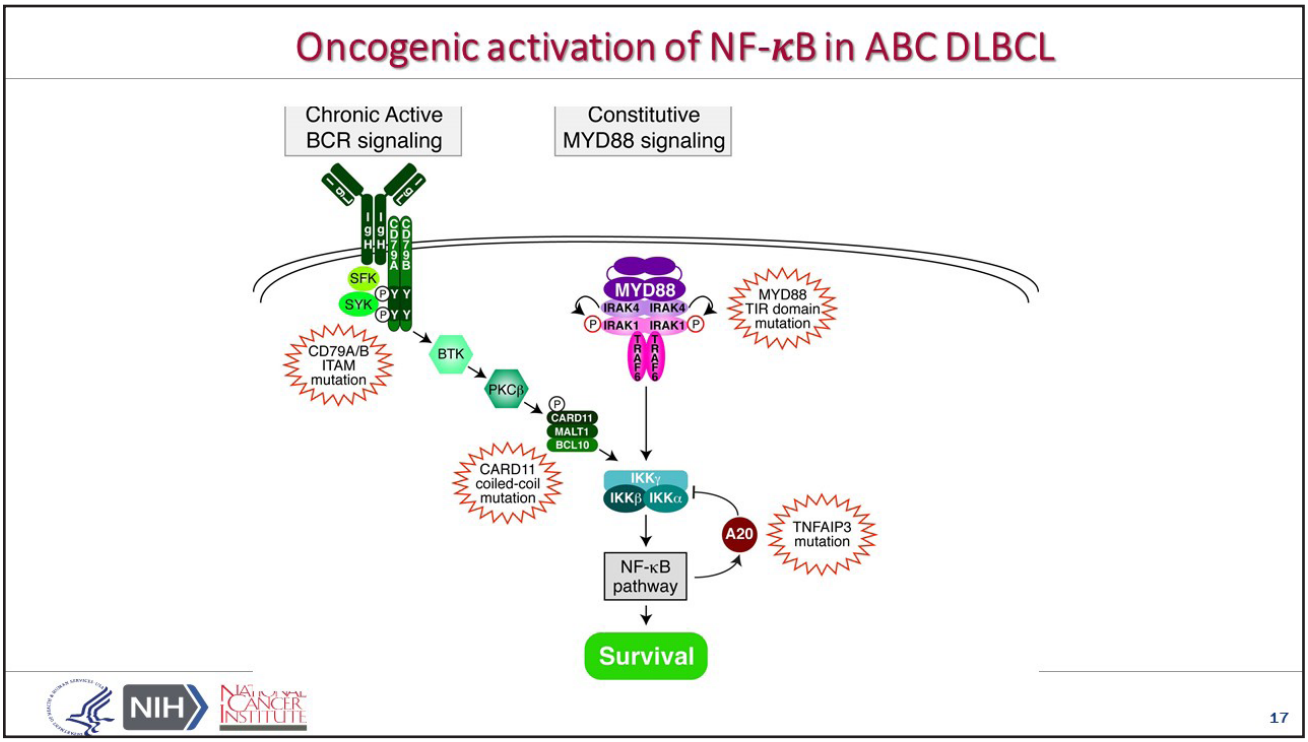
Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	233	44	0.85 (0.80-0.89)	0.80 (0.74-0.85)
DA-EPOCH-R	232	50	0.85 (0.79-0.89)	0.76 (0.70-0.71)

Slide 15: CALG 50303: R-CHOP vs. DA-EPOCH-R

And, this is the most recent randomized study that tested the outcomes of appropriate chemotherapy platforms. The regimen that we developed here, dose-adjusted EPOCH-R compared to R-CHOP, and in this case the study has been presented, not yet published, but it did show that there's no discernible difference between the outcomes, at least with respect to this study as you compare the outcomes here. So, there is no identifiable patient population that benefits from more intensive therapies dose-adjusted EPOCH-R.

Stage 16: Targeted therapy for ABC

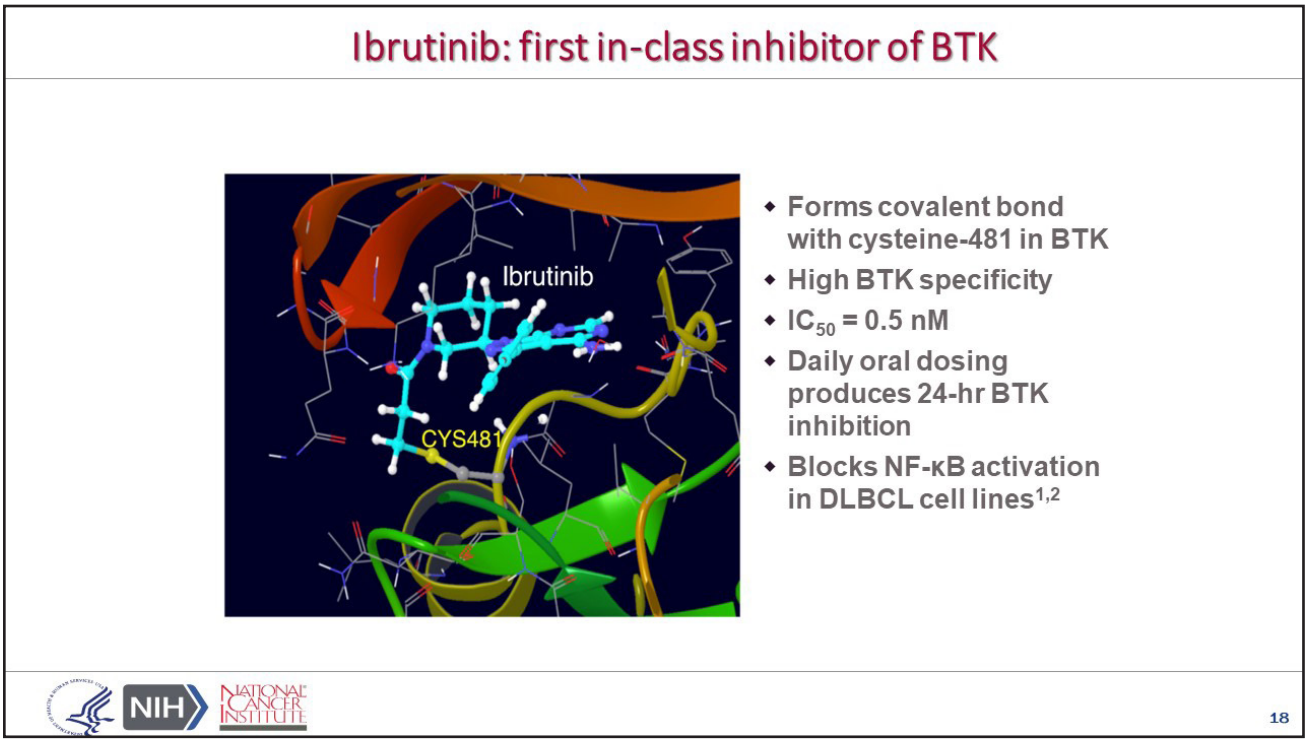
So, that's the platform and what we can say from that is that maybe 60% of patients are cured. And, one of the ways we can try to improve that cure rate or overcome the chemotherapy resistance that is intrinsic to some of these tumors is to actually target some of the things that are unique to them within given subsets of disease. So, I want to show you how we've applied that here at the NCI and how it's being applied at other centers as well.



Stage 17: Oncogenic activation of NF-κB in ABC DLBCL

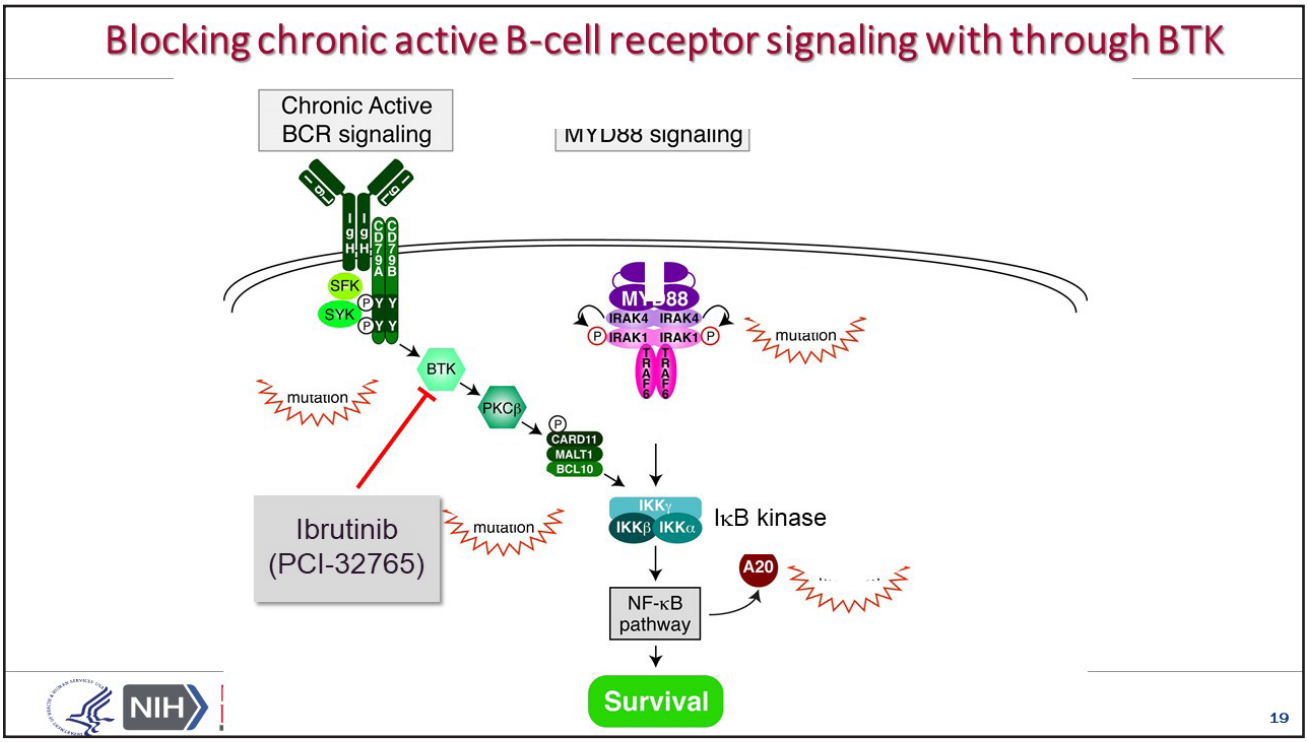
And, we'll focus on the worst counterpart here, which is to say ABC diffuse large B-cell lymphoma.

So, one of the ways that we think about the molecular biology is not simply on the basis of mutations, but we think about it in the way of pathways. And so, what you're seeing here is a normal B cell that signals down to the nucleus, represented by the NF Kappa B pathway. So, the NF Kappa B pathway is constitutively activated in all cases of ABC diffuse large B-cell lymphoma. But, what's different across different cases is the mechanism by which it's activated. So, you're seeing in stars here different mutations that occur and based on the mutation, it determines what the mechanism is by which the cell actually has a survival advantage. And, in this case, what's being highlighted is that there are some cases that actually have B cell receptor signaling that is chronically active or it's constantly turned on, and if that's a pathway that the tumor cells rely on for survival, then if you interrupt that pathway you can potentially result in cell death.



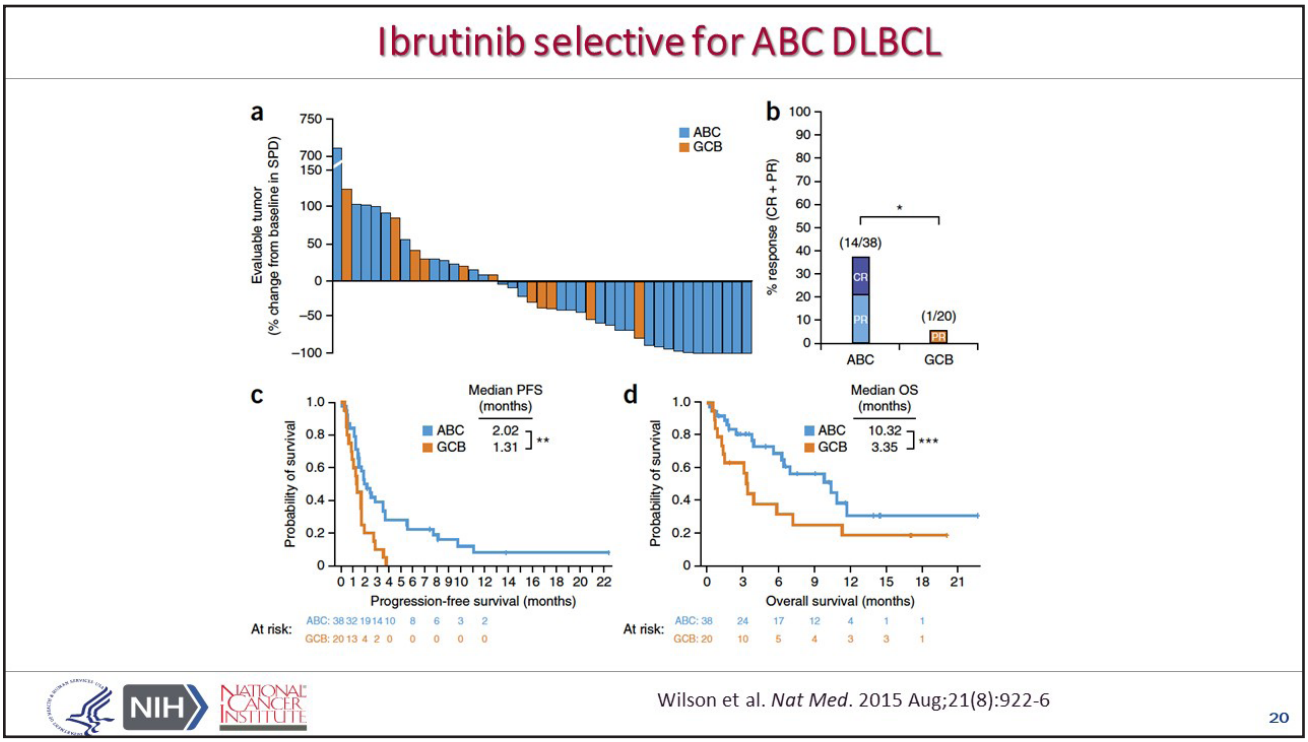
Slide 18: Ibrutinib: first in-class inhibitor of BTK

So, the first medicine that we studied here and has been studied in other settings is ibrutinib. And, ibrutinib is an oral medication, but it had other features that were highly relevant. That is to say it did work in cell lines, and it was highly specific to the pocket here of BTK. So, this is now targeting a very specific protein as opposed to chemotherapy, which is much more broad.



Slide 19: Blocking chronic active B-cell receptor signaling with through BTK

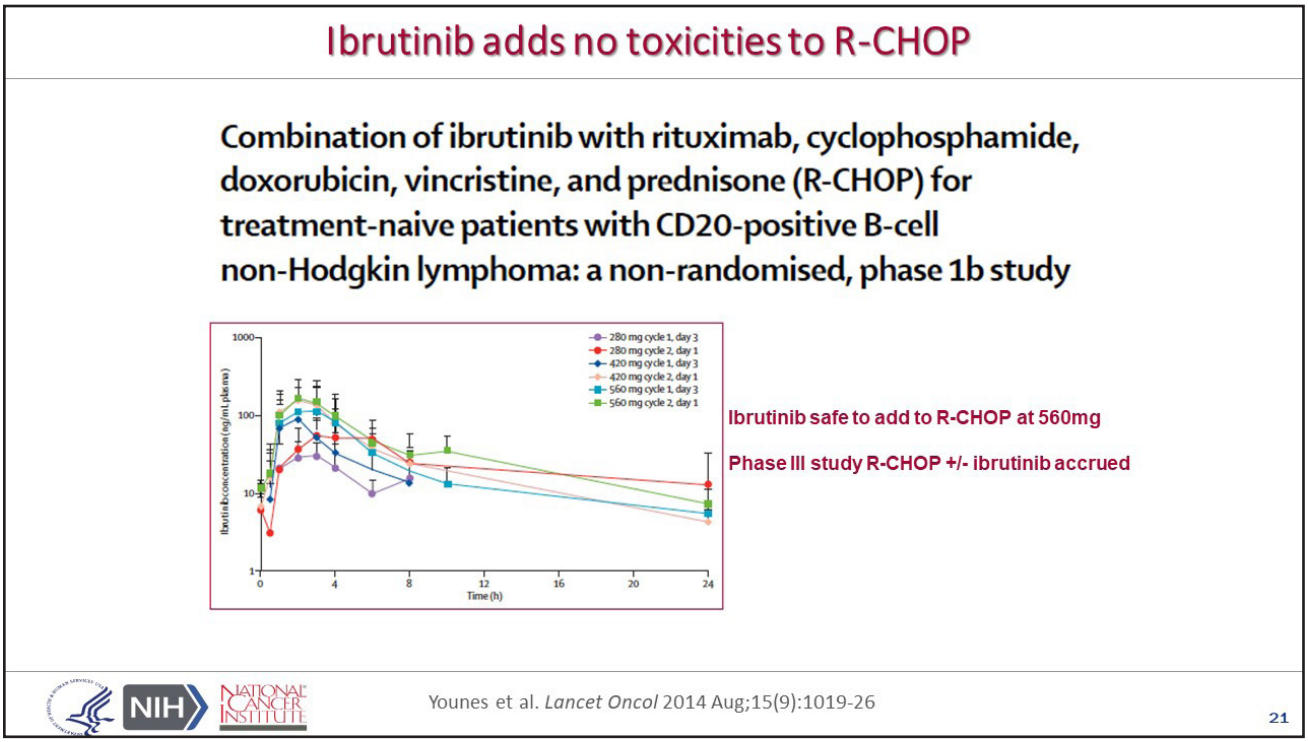
And here, this is depicted on how ibrutinib targets something known as the BTK pathway. So, in this way, we hypothesized that the use of ibrutinib would not only knock out BTK, but that the knockout of BTK in cases of aggressive lymphomas would actually result in clinical remissions.



Slide 20: Ibrutinib selective for ABC DLBCL

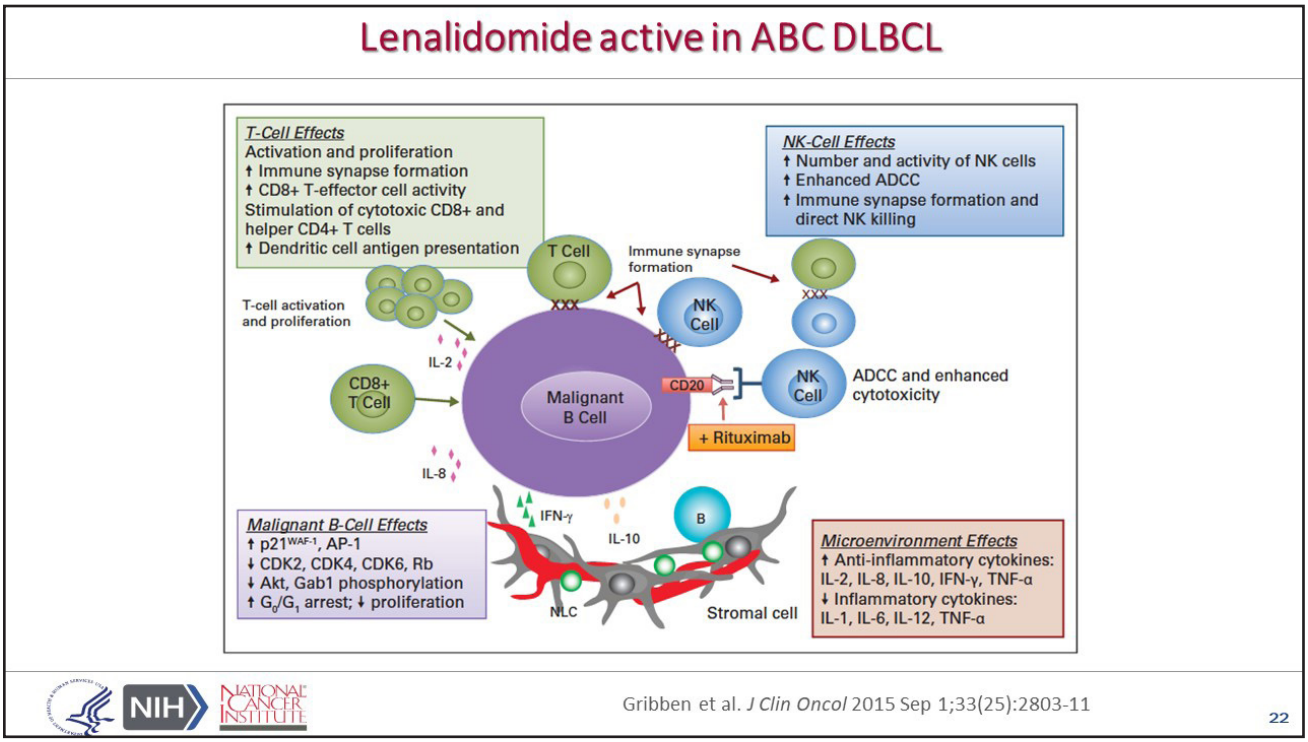
And, that is something that we observed. So, what you're seeing here is the result of a Phase II study that was performed in a multicenter setting that we led. At the top left, what you're seeing is a waterfall plot, which means that if the tumor cells shrink, that is depicted as the bars below the line, and you can see that many times patients had tumor cells that shrank with the use of just a singular medicine by mouth. And, in most cases, the tumor cells that shrunk or the patients with tumors that shrunk had ABC subtype as opposed to GCB subtype. And, that is consistent with what we had hypothesized prior to the study.

Also, you can see that if we look at patients that had deep remissions, that is to say either a partial or a complete response, almost all of them were in the ABC subtype, with 1 lone exception. But, the downside to this was cancer is quite complex, and the duration of response here was disappointing. The median progression-free survival with a single agent was only a couple of months, even though there was a difference in the 2 types of disease.



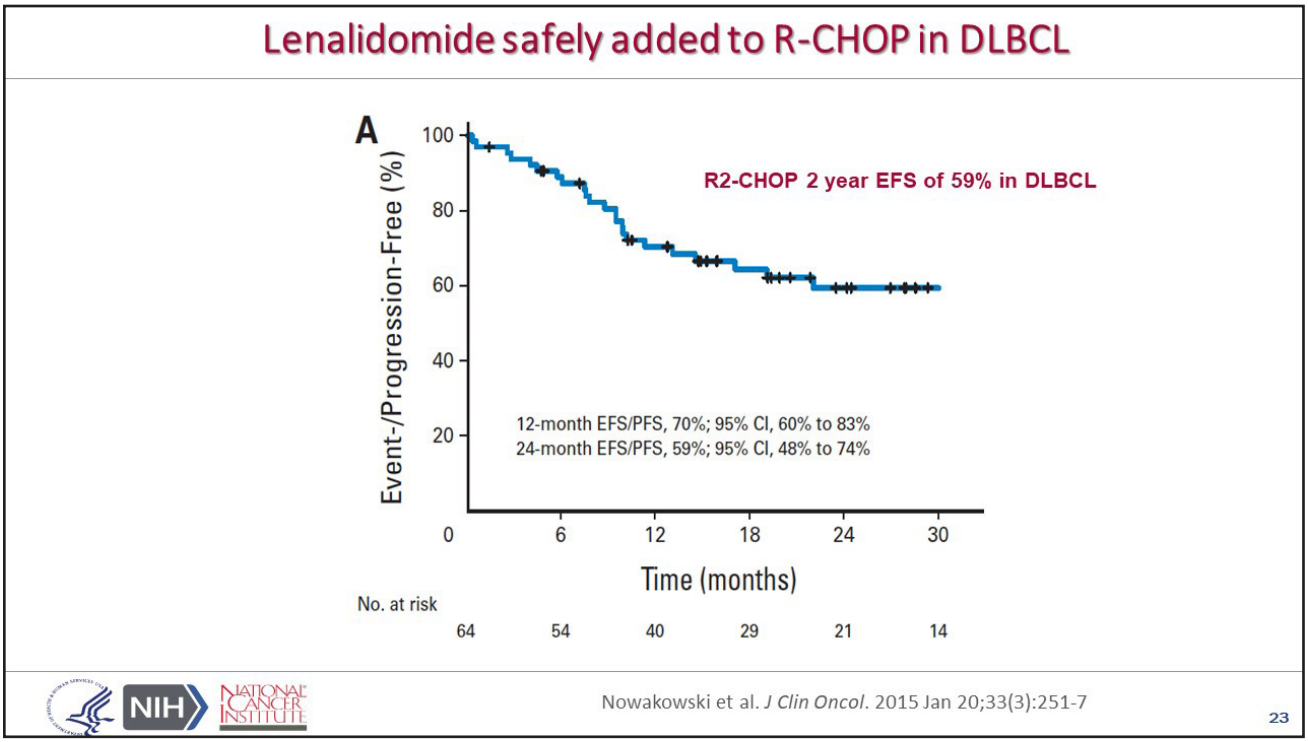
Slide 21: Ibrutinib adds no toxicities to R-CHOP

But, that doesn't mean patients can't benefit from the use of ibrutinib, particularly if it has some activity. And, the concept is perhaps it could be added to known curative chemotherapy to increase the number of patients that get a cure with the first time they get treated. And, this is a Phase I study that was launched after the results of our study to show us that if you give ibrutinib with R-CHOP it at least is safe. And, this Phase IB study formed the basis of what is now a randomized Phase III study, which has accrued all the patients and is waiting for the results to see if the addition of ibrutinib actually improves the number of patients that we can cure with R-CHOP-based chemotherapy.



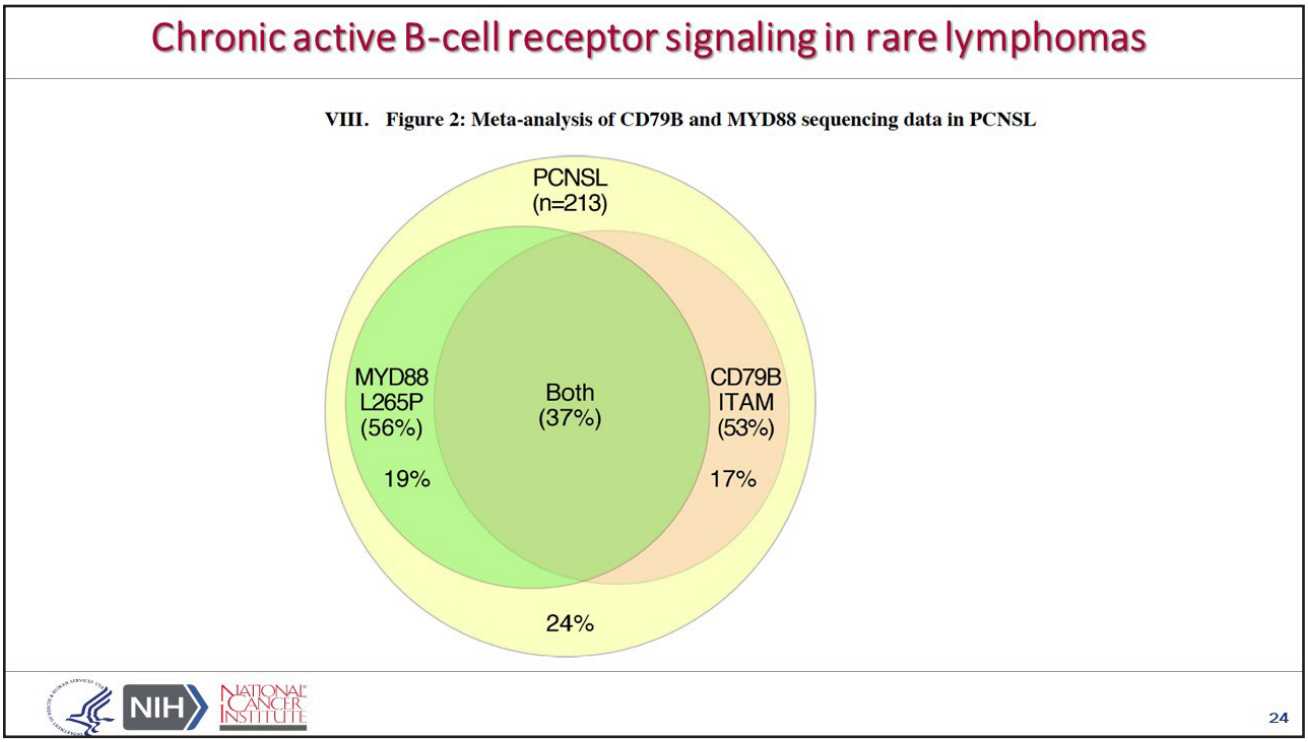
Slide 22: Lenalidomide active in ABC DLBCL

Another drug that is specific, even though it's less specific than ibrutinib, is known as lenalidomide. So, lenalidomide is also an oral medication. The major difference here is that it has more effects than simply to knock out BTK. It's what we call a medicine with pleiotropic effects, or things that affect a number of different cell processes, to include actually an effect on the patient's immune system both with known as natural killer cells as well as T cells. But, it also affects the tumor's microenvironment and does have some direct killing. We know that this occurs because patients with just single agent lenalidomide can actually have responses and those responses seem to be concentrated in patients with ABC large cell.



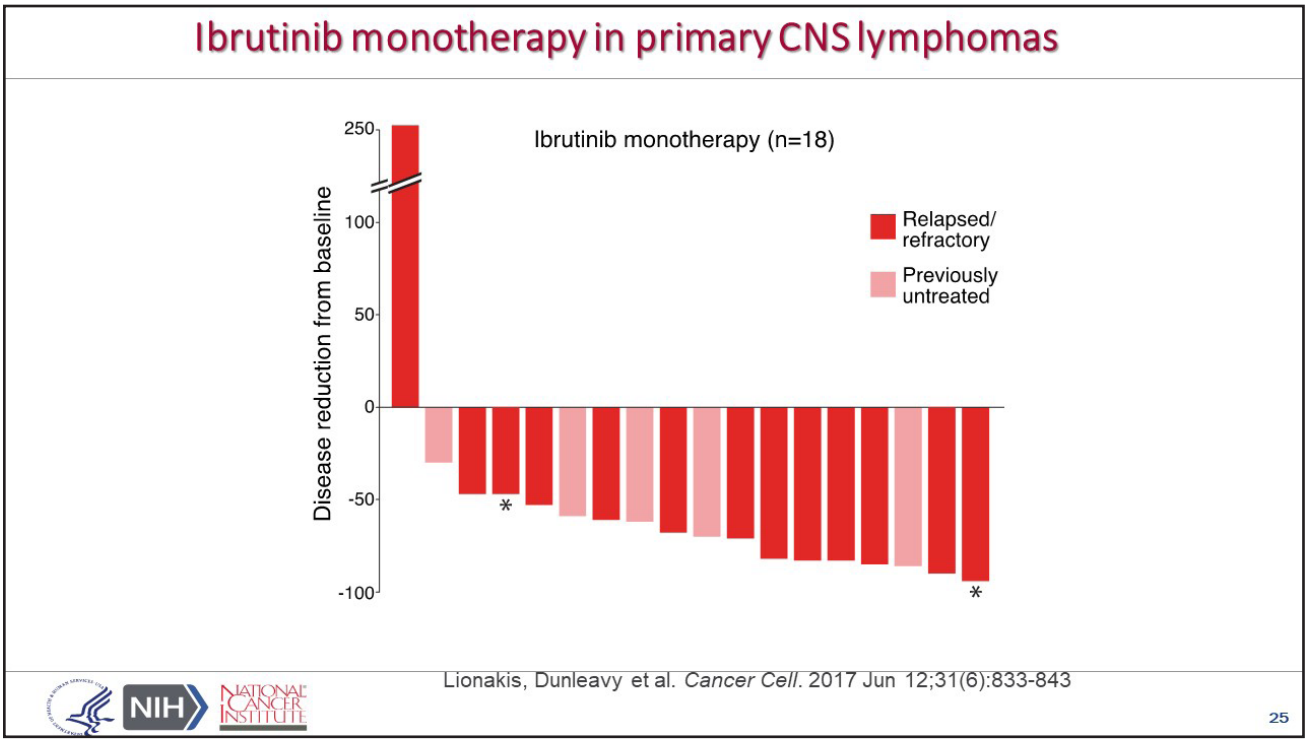
Slide 23: Lenalidomide safely added to R-CHOP in DLBCL

So, we also have learned with this Phase II study that was done, led by the investigators at the Mayo Clinic, that when you add lenalidomide to R-CHOP chemotherapy that the response rates are high, in this case event-free survival was around 60%, the toxicity is certainly manageable, and there are 2 ongoing randomized studies that are asking a question in slightly different ways: whether or not the addition of lenalidomide, also known as Revlimid®, added to R-CHOP, will actually improve outcomes and if so, in which patient populations does it improve?



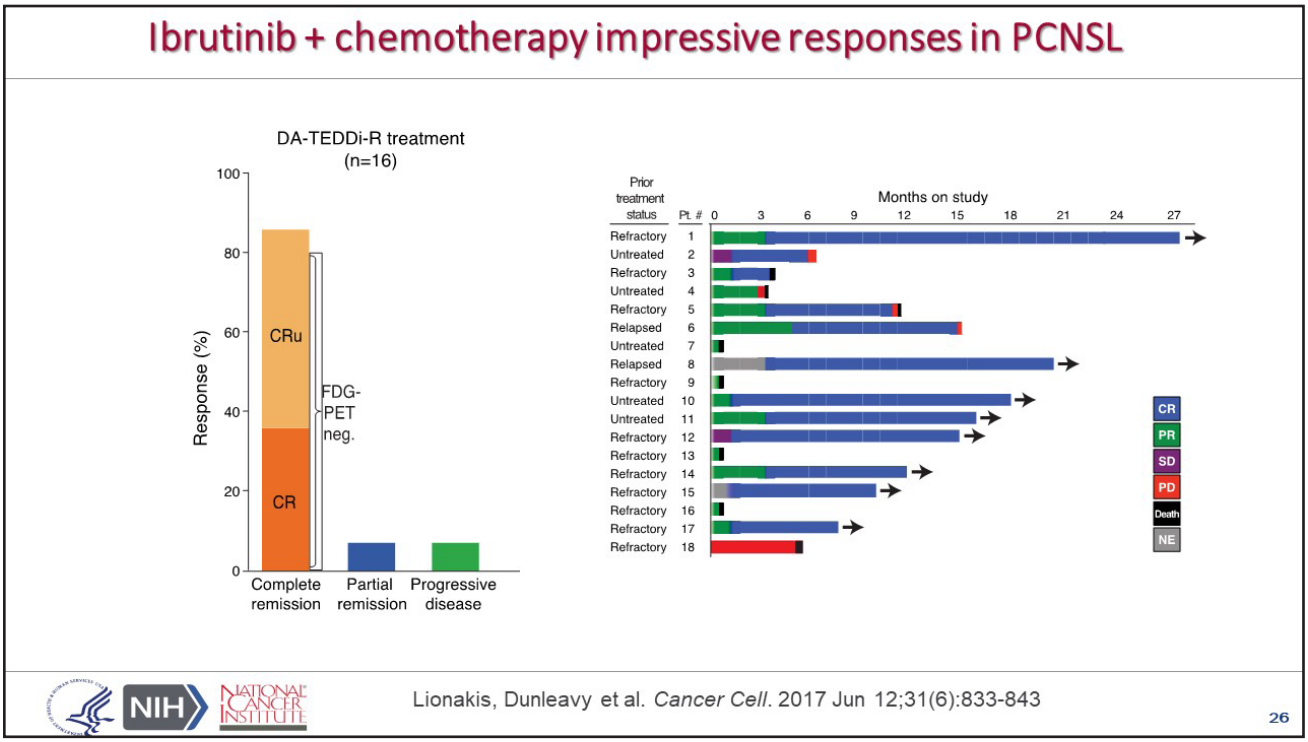
Slide 24: Chronic active B-cell receptor signaling in rare lymphomas

So, we took a different approach. We looked at the fact that we noticed that in patients that benefitted from ibrutinib, not only did they have the ABC subtype, but they seemed to have the presence of 2 individual mutations, that is MYD88 L265P, which is a very singular point mutation seen in about 20% of diffuse large B-cell lymphoma concentrated in the ABC subtype but more commonly seen in things such as diffuse large B-cell lymphoma that involves the central nervous system, otherwise known as primary CNS lymphoma. And, in our ibrutinib study, what we observed was that the coexistence of the MYD88, as well as the CD79B mutation, actually predicted for responses to ibrutinib. So, now we're getting closer to the idea that mutations or presence of molecular biology features that predict responsiveness to targeted agents. And, since this was more concentrated in primary CNS lymphoma, we actually took that to a clinical trial here in our institution.



Slide 25: Ibrutinib monotherapy in primary CNS lymphomas

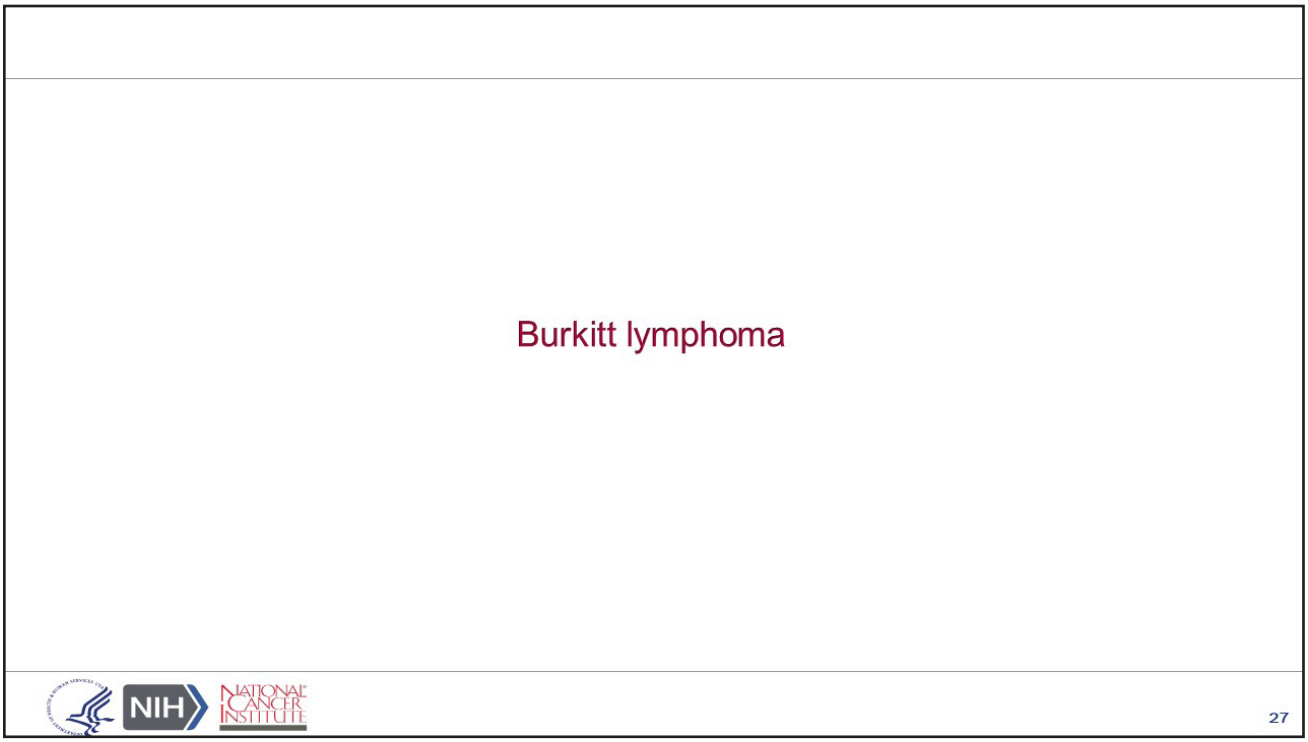
The way our clinical trial was designed is, we gave all patients with relapsed and refractory primary CNS lymphoma, ibrutinib monotherapy as a singular agent. And, what you're seeing here is a waterfall plot of how many of those patients actually responded to the single oral medicine by itself. And, with one exception, all patients had a reduction in their tumor, either both in patients that were relapsed or refractory, as well as the few patients that were previously untreated. So, we can now see that patients that get ibrutinib monotherapy, even when lymphoma is in their brain, can actually respond to the targeted medicine.



Slide 26: Ibrutinib + chemotherapy impressive responses in PCNSL

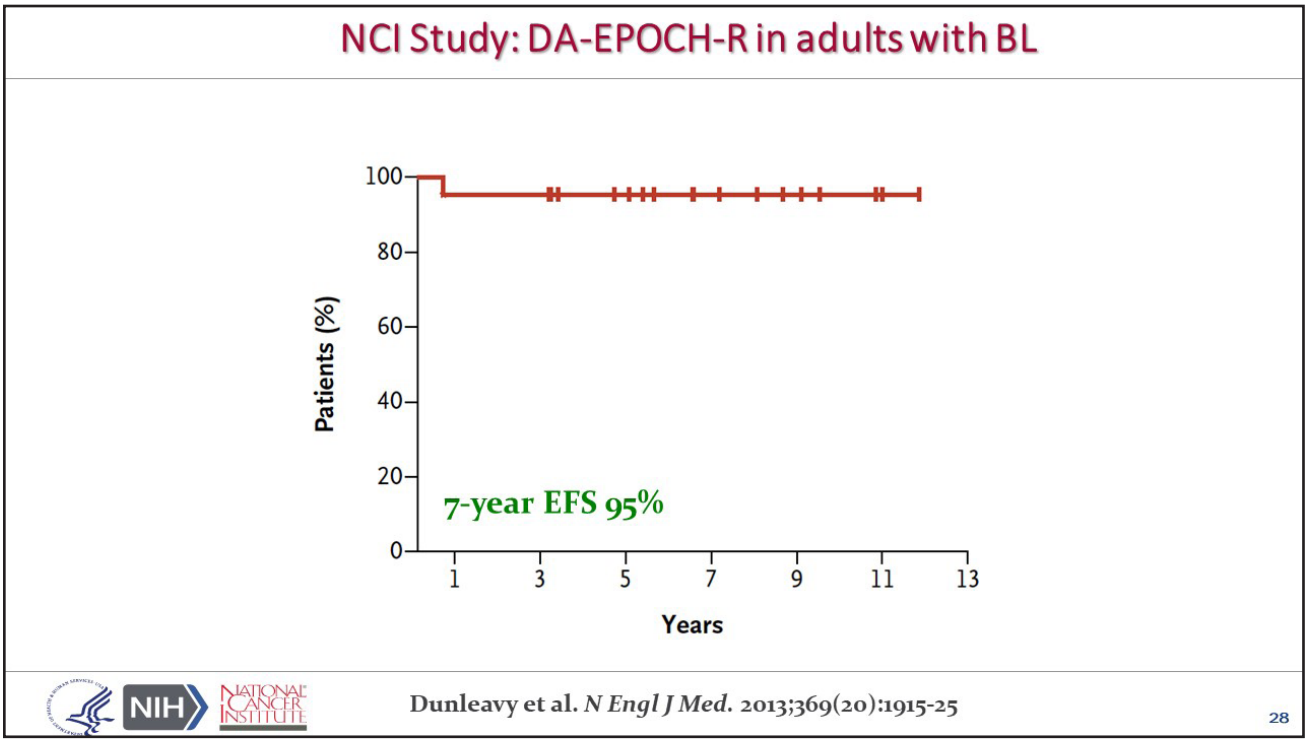
But, of course, response as I showed you in the previous study isn't good enough, we want to have deep responses and we want to have those responses last. So, after giving ibrutinib monotherapy, we took patients then to get chemotherapy in addition to ibrutinib, with the idea that, that chemotherapy plus ibrutinib might result in deepened responses. What we saw with this novel chemo regimen, known as TEDDI-R, which are multiple different chemotherapy medicines that cross the blood-brain barrier, is that most patients got a complete remission to that treatment and some exceptions here. What I want to show you here is this. That many of these responses actually lasted a long time, which is these arrows depicted here, meaning this is an ongoing response, without continued treatment. So, we were very impressed by the deep durable remissions given with ibrutinib plus chemotherapy.

Now, you will also see there were some troubles with our study. You can see very short timelines here. And, these were patients that had toxicity. And, that's the other side of the coin here with targeted therapies. As we try to improve therapies and we try to improve the cure rate and the number of times we lead to deep durable remissions, we have to remember that some of these medicines, even though they're very targeted, have a risk of toxicity that cannot be understated.



Slide 27: Burkitt lymphoma

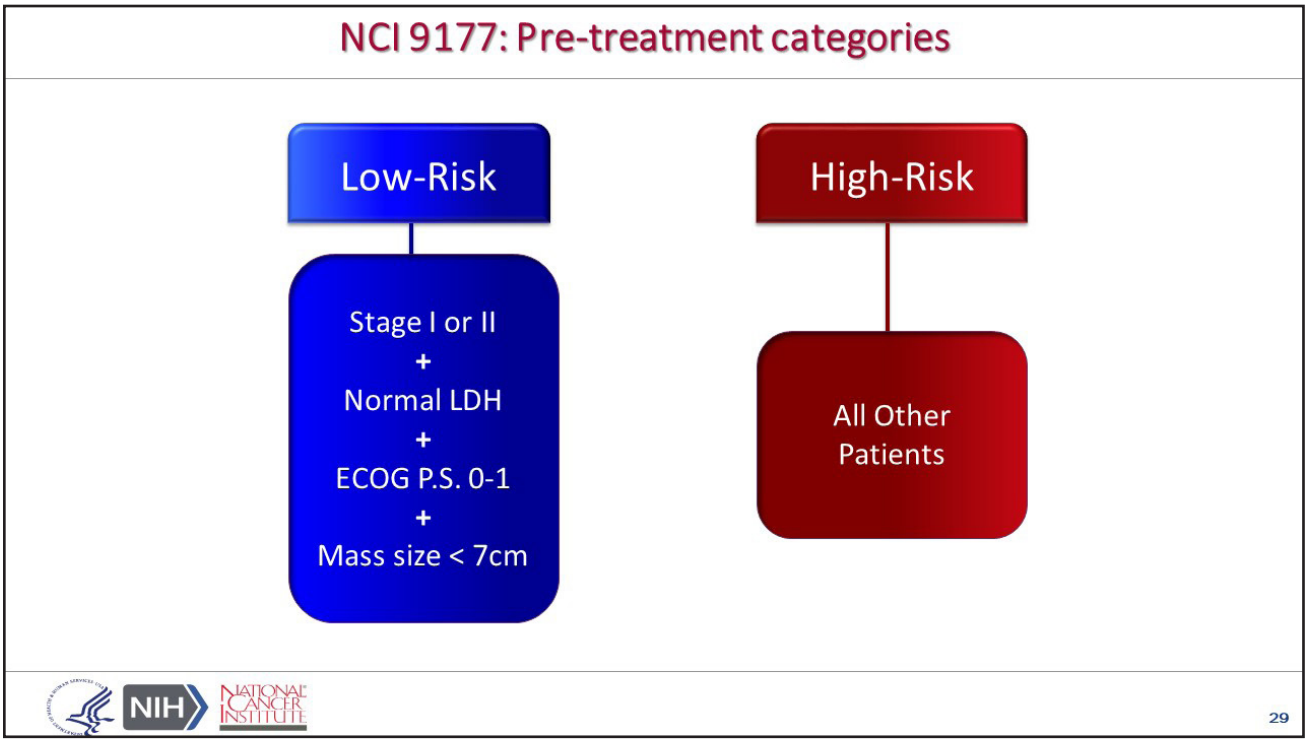
So, I'd also like to touch on Burkitt lymphoma.



Slide 28: NCI Study: DA-EPOCH-R in adults with BL

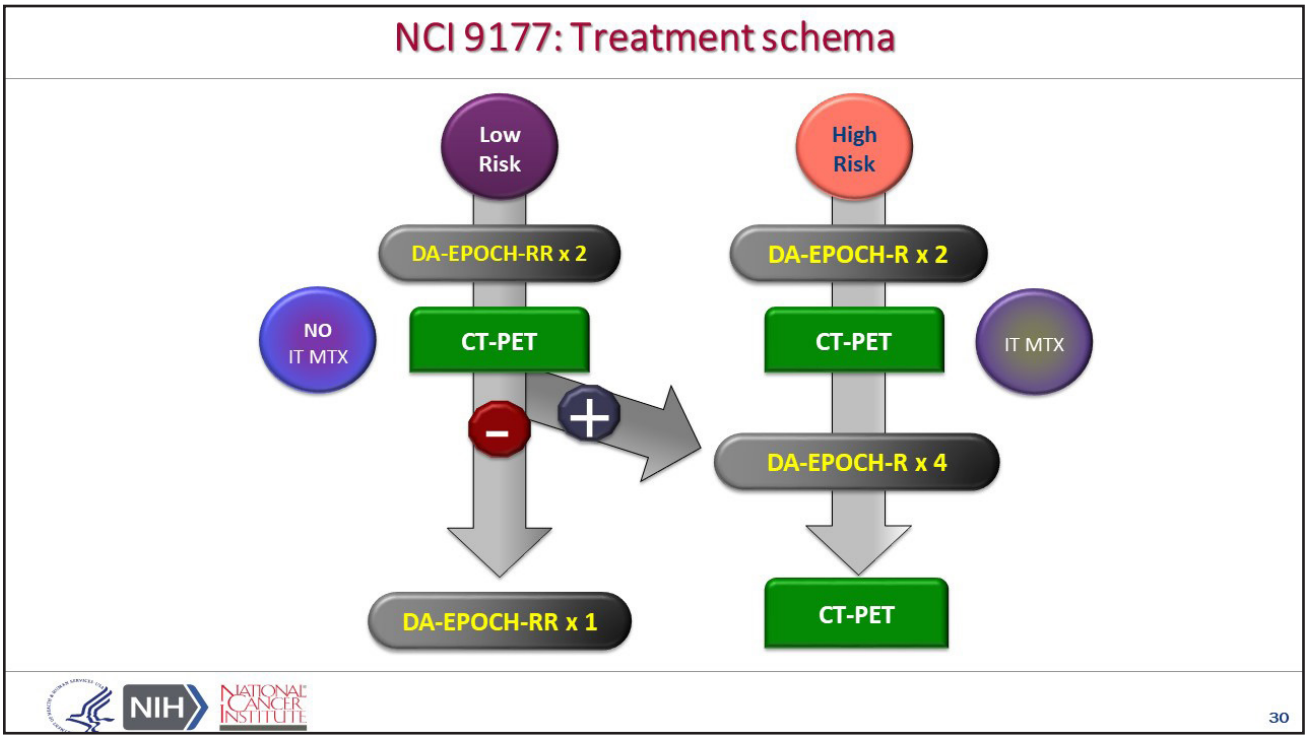
So, Burkitt lymphoma shares many properties with diffuse large B-cell lymphoma. It is considered even more highly aggressive than diffuse large B-cell lymphoma, which does make it susceptible to chemotherapy. And, it is highly curable, but it's not as easy to cure as patients get older. So, Burkitt lymphoma affects a number of pediatric patients. And, as we get older, particularly if we get even over the age of 35 or 40, the treatments given to those patients are much less able to be tolerated and so it makes it much more difficult to cure, even though the treatments are highly effective.

So, we sought at our institution to improve the cure rate. What you're seeing here is a small group of patients, about 30 patients that were treated at our institution, with dose-adjusted EPOCH-R and were all over the age of 18 with Burkitt lymphoma. And, you can see that in most situations we actually were able to cure them with dose-adjusted EPOCH-R. And, not every time do they even require 6 cycles of therapy.



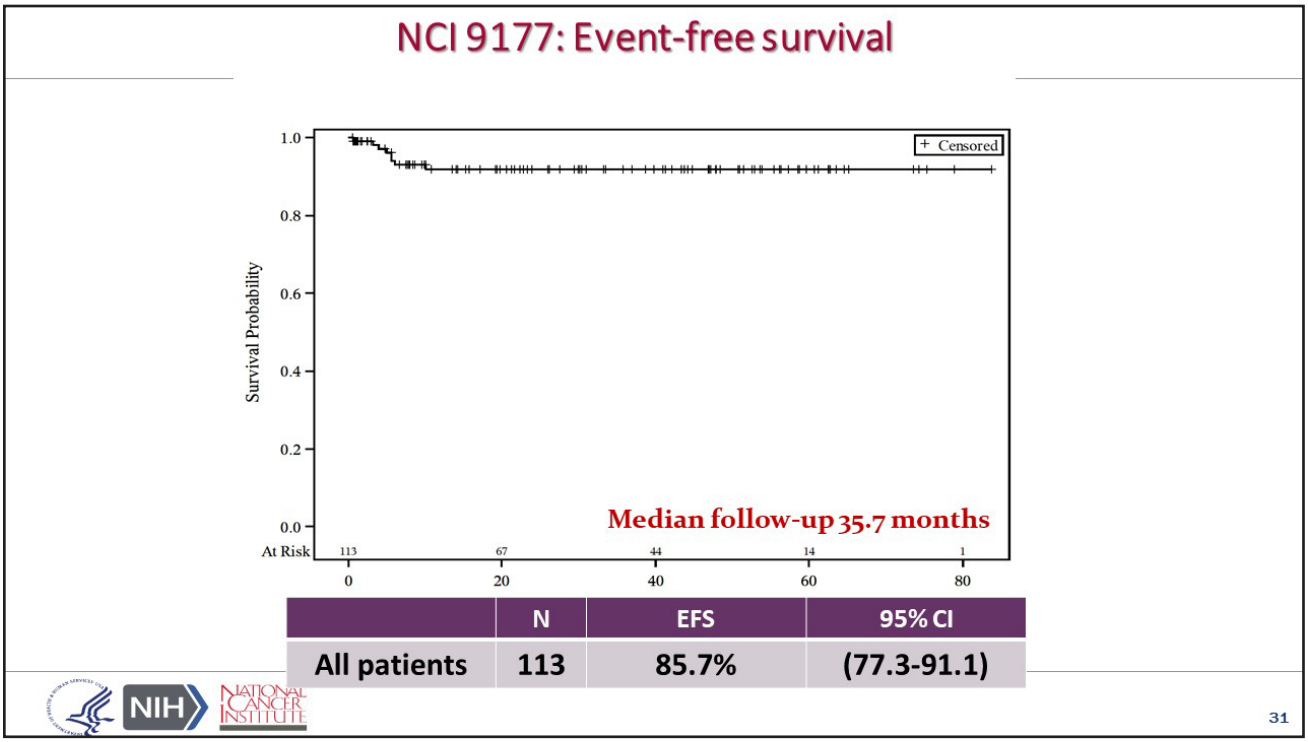
Slide 29: NCI 9177: Pre-treatment categories

So, we sought to validate that in a multicenter setting. And, so we just have completed a study in 24 different institutions in which we separated patients out into high- and low-risk features based on clinical features. Whether or not they had small amounts of disease and early stages, they were considered low risk. Whereas high-risk patients were considered those that did not have those features.



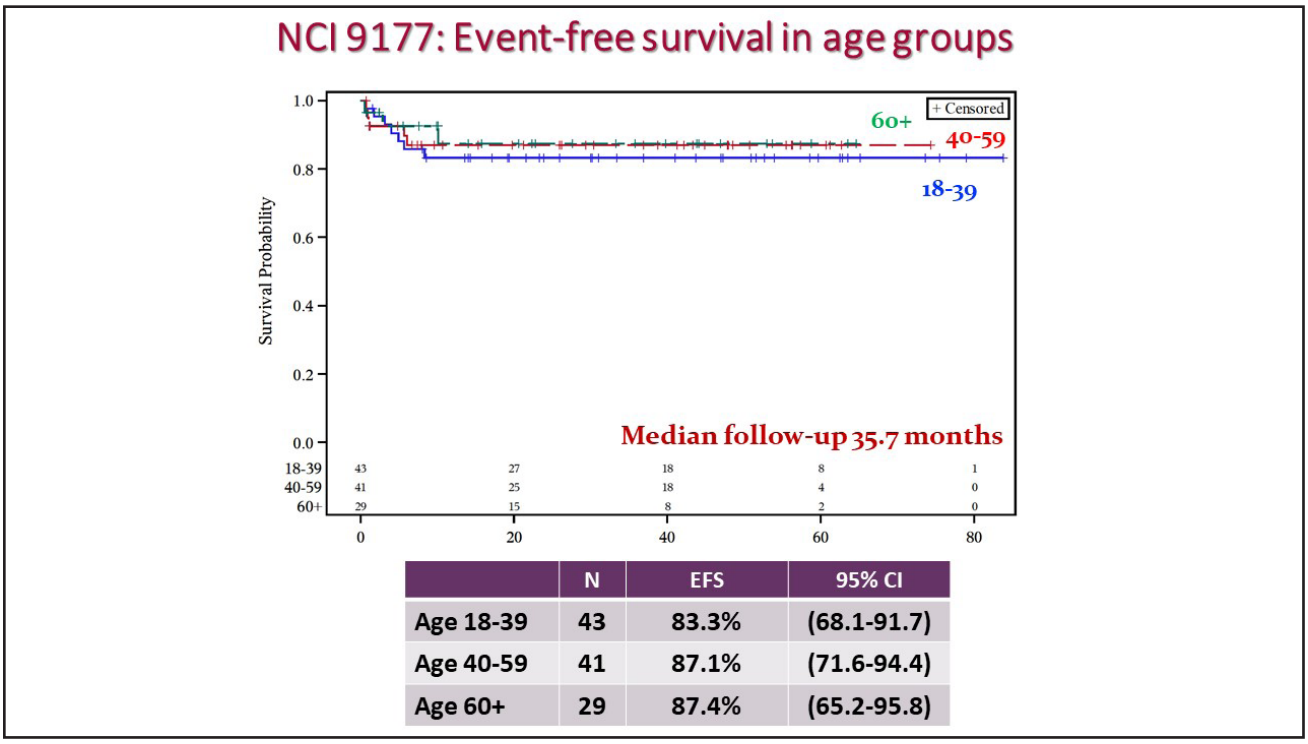
Slide 30: NCI 9177: Treatment schema

Patients with low-risk Burkitt lymphoma were treated with 2 cycles of dose-adjusted EPOCH-R, double doses of rituximab, and then a PET scan. If that PET scan was negative, they only got 1 more cycle of therapy, so 3 cycles in total. And, they didn't require any prophylaxis for disease in the brain. Whereas, patients that were high risk got a more standard regimen of 6 cycles of dose-adjusted EPOCH-R and got intrathecal methotrexate to prevent CNS relapse.



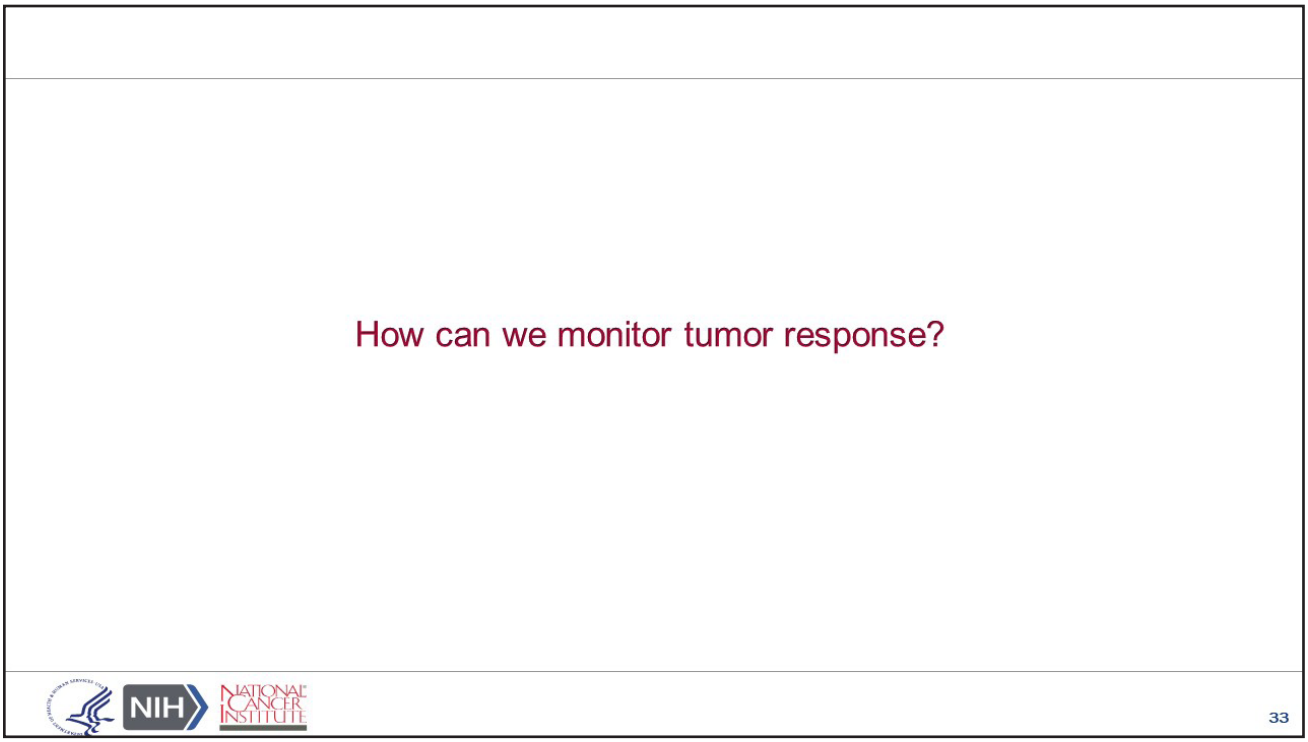
Slide 31: NCI 9177: Event-free survival

And, these results have been presented at ASH (The American Society of Hematology) this last year. What we saw was that the median event-free survival after 3 years of follow-up was about 85%. So, in 113 patients, some low risk and some high risk, we're curing probably around 80% to 85% of those patients with dose-adjusted EPOCH-R.



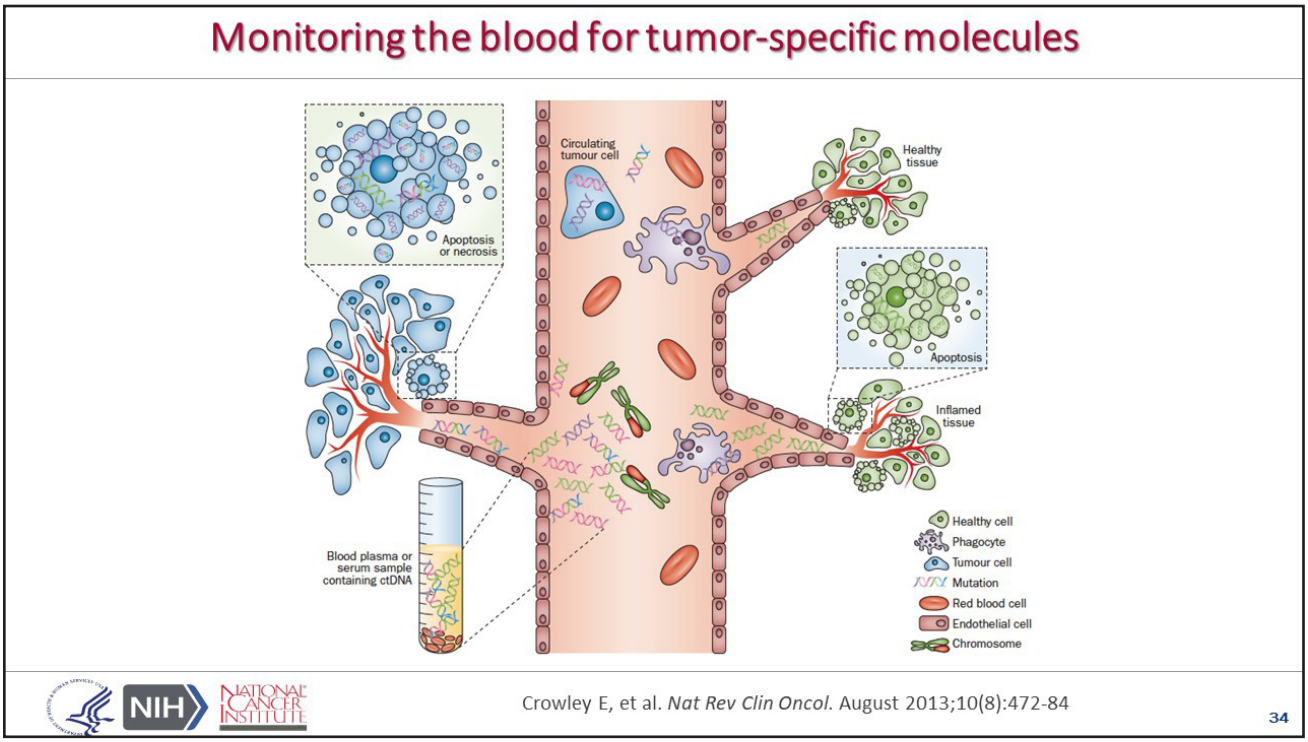
Slide 32: NCI 9177: Event-free survival in age groups

And, it didn't matter how old the patient was, which is a very important finding. So even patients over 40 or even over 60, which represented more than half the patients, had very similar results.



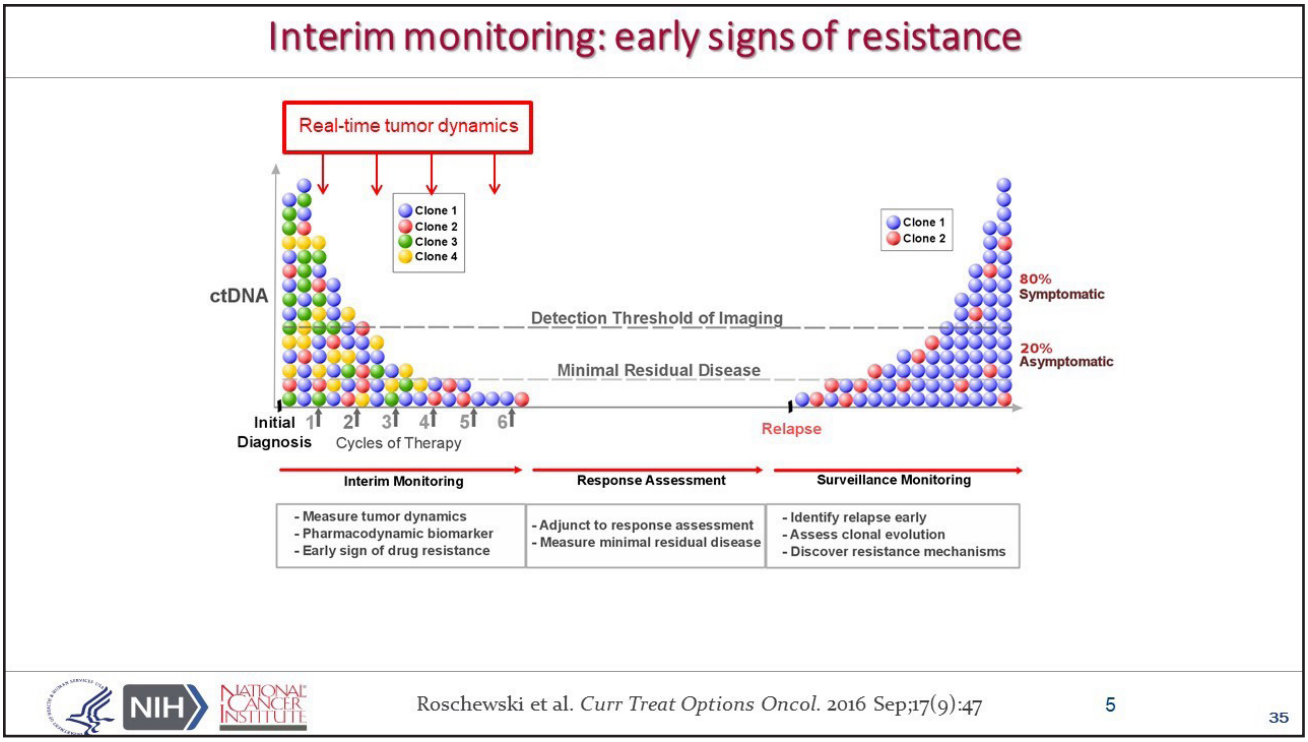
Slide 33: How can we monitor tumor response?

The last thing I wanted to touch on was whether or not there's improved ways that we can actually monitor our response. And, in so doing, as we monitor our response, can we find out how deep our remissions are and can we find out information about the tumor. This is something that should be considered research and something that is ongoing. We've been studying it here at our institution and this is not something that's part of routine clinical care, but it is something that is part of precision medicine as we approach lymphoma patients and it's something that I think we could see more studies and more blossoming of the use of this technology as we move forward.



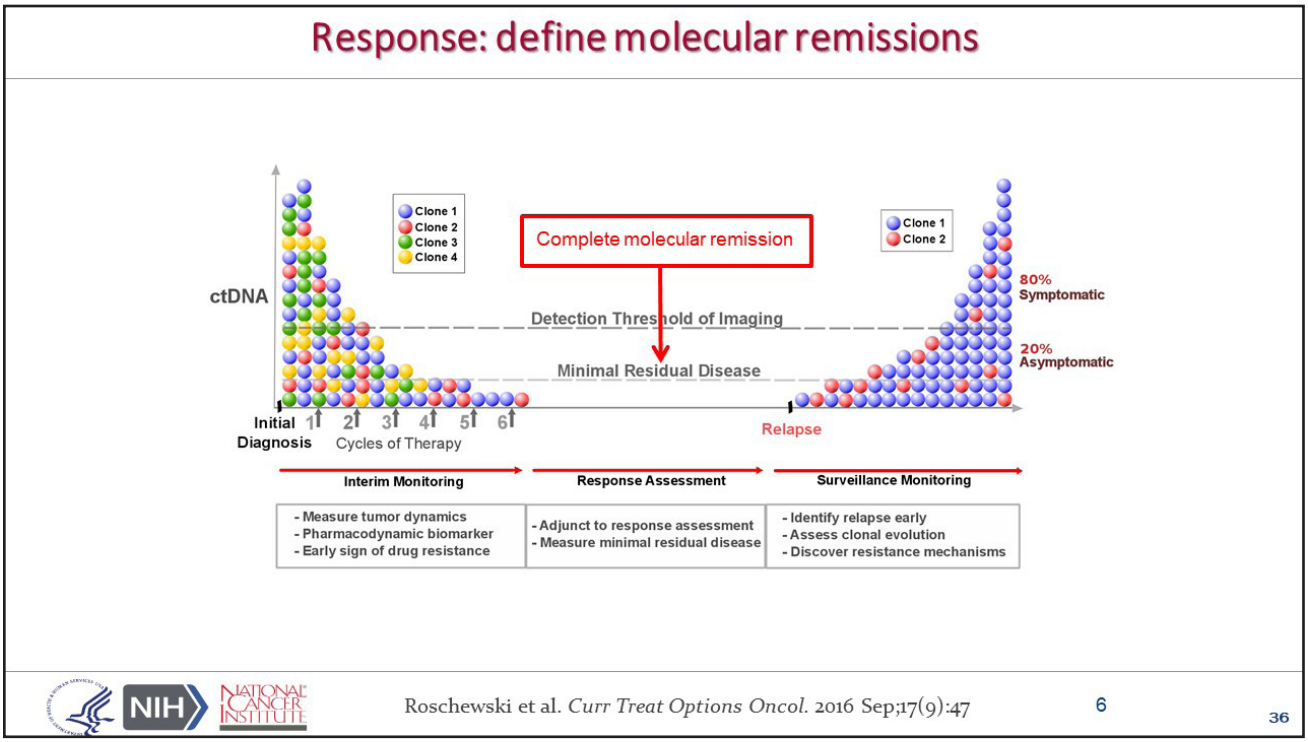
Slide 34: Monitoring the blood for tumor-specific molecules

So, what are we talking about? Well, what we are talking about is the ability to monitor the bloodstream or look for molecules within the peripheral blood that actually are coming from the tumor, and in so doing of monitoring these, can we rationally decide when we've cured patients or look for evidence of relapse. And so, there's various different molecules that could be picked up in the blood, so it's not true that there's only red cells in there. What we're talking about here in most cases is, as you can see the bottom left, is evidence of DNA from the patient's tumor. And, this is completely outside of cells, just floating in the bloodstream. Something known as cell-free DNA.



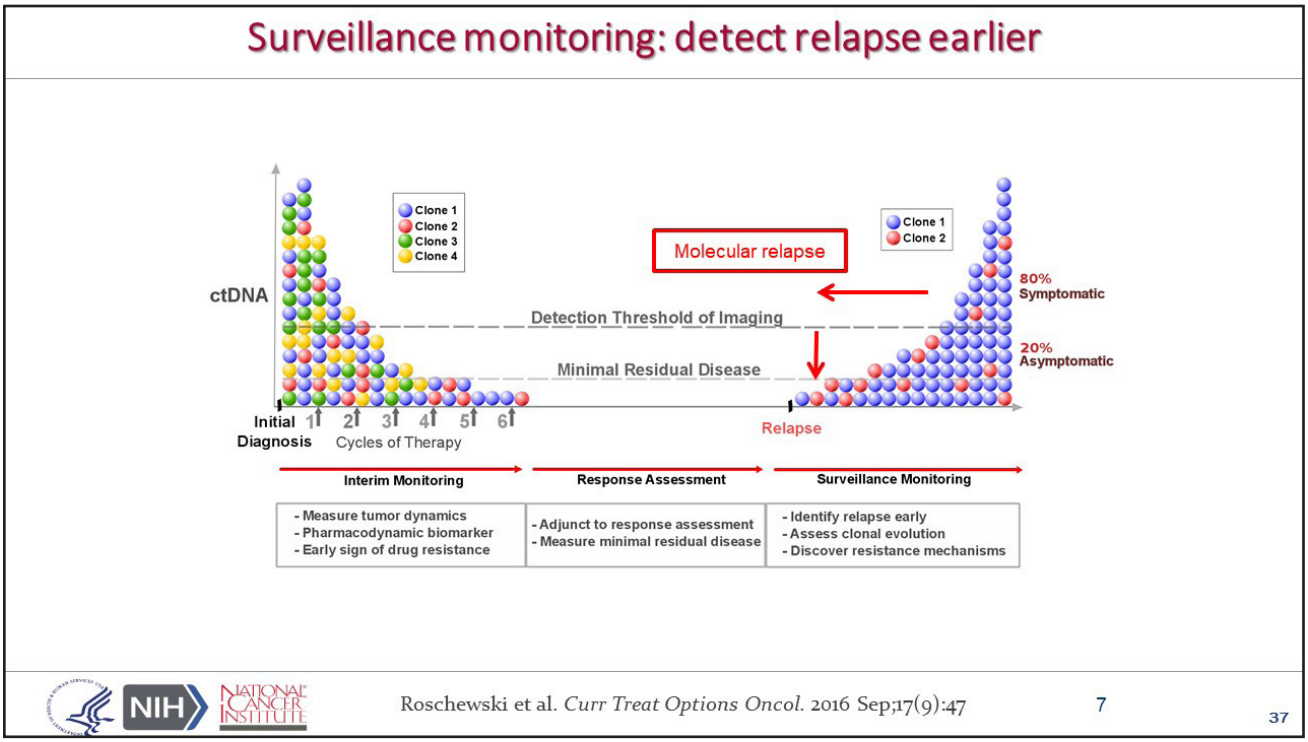
Slide 35: Interim monitoring: early signs of resistance

What can this do for us? Well, one of the things that happens is if we think about the molecular biology of cancer, in this case lymphoma, and all the differences that are present at the beginning, we give chemotherapy, but we don't actually have a way to effectively monitor how well the treatment is working in the middle of therapy. We do, do interim imaging scans, but they don't always tell us who gets the deepest responses. The use of cell-free DNA can show us not only that patients are getting deep remissions, but also that look for early signs of drug resistance, so we could stop therapy that wasn't currently working.



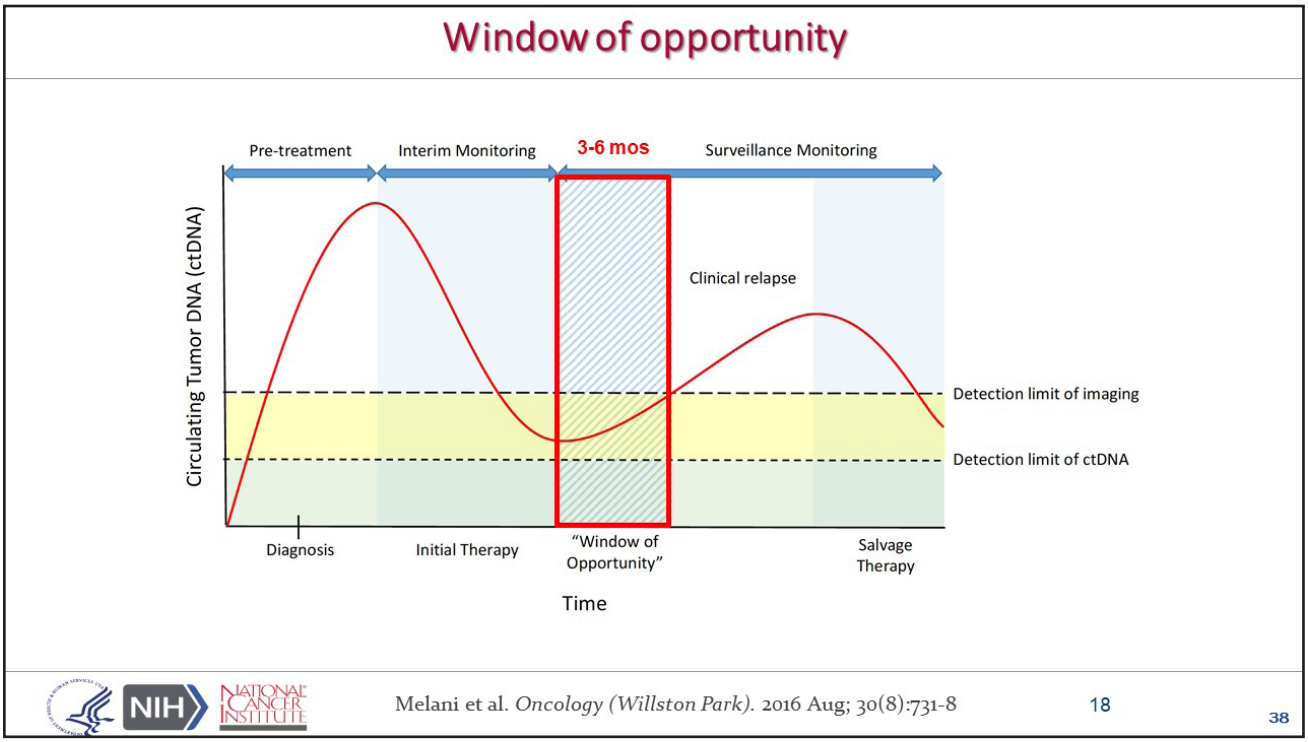
Slide 36: Response: define molecular remissions

It also affords us the ability to define the depth of remission in a way that we haven't done thus far in aggressive lymphomas. And, that is to say, we do scans after treatment, but we know that in many cases, that at least up to 10% to 15% of cases, patients that don't have any disease on their PET scan or CT scan, actually have evidence of disease if you look close enough. And so, these assays that can look for much lower depth and look for evidence of disease at the molecular level, can then define something known as minimal residual disease (MRD), and if there's absence of minimal residual disease after treatment, we might conceive of that as something known as a complete molecular remission, something we currently don't use in the vernacular of treating patients with aggressive lymphoma.



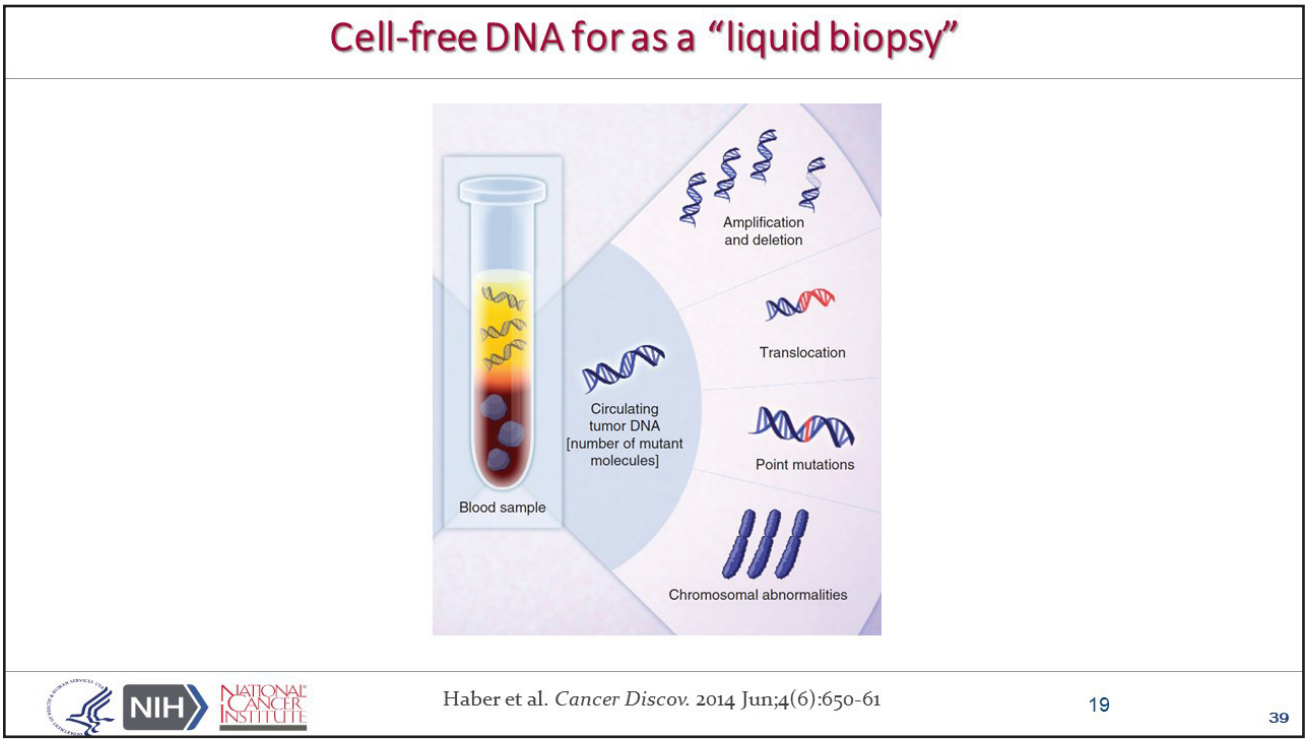
Slide 37: Surveillance monitoring: detect relapse earlier

Another thing it offers us is the ability to detect relapse early. Now, it's important to point out that it has never been shown that identification of relapsed aggressive lymphomas earlier affords us the ability to cure patients earlier, but it is theoretically of benefit. And, one of the things that is offered here with cell-free DNA is not only that one could detect disease earlier, but also at a lower level. And, if you detect disease at a lower level, at least hypothetically, you can do so at a time when it has less genomic complexity and perhaps then your interventions have a better chance of working. These are all things that need to be tested, but currently the way we follow patients after treatment is we wait for them to have symptoms. And, in most cases, at least 80% of the time, they develop symptoms before we ever detect disease. And so, this is an area that we're highly enthusiastic about trying to improve.



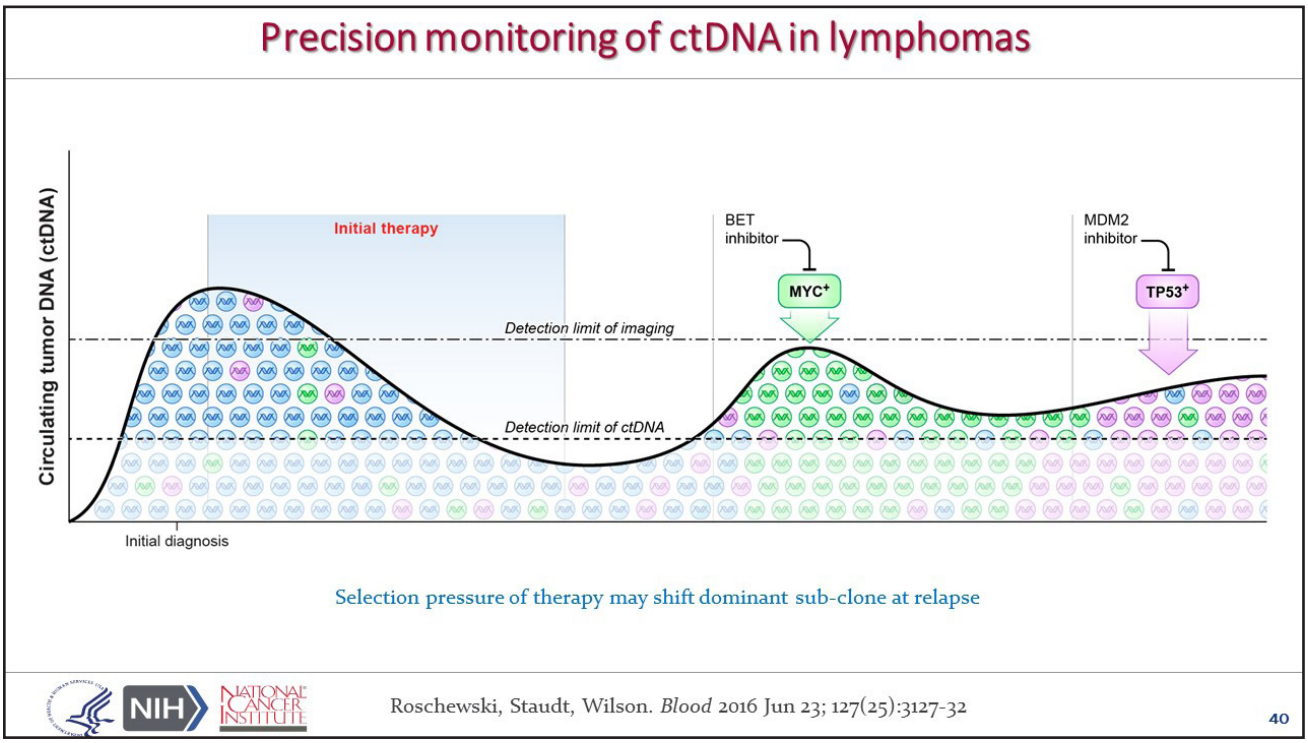
Slide 38: Window of opportunity

And, how would this look for an individual patient? Well, if there is a period of time by which you can identify the disease prior to when you would otherwise have identified it, something we might describe as a window of opportunity, then it offers you the potential opportunity to treat earlier, and in a study that we did at the NCI, we noticed that these assays routinely pick it up 3 to 6 months before a CT scan. And, this then becomes a window of opportunity of which is a testable hypothesis. That is to say, could earlier treatment of effective salvage therapy actually improve the number of patients that can be cured if they weren't already cured the first time they got chemotherapy?



Slide 39: Cell-free DNA for as a "liquid biopsy"

But, there's other uses of this technology and we will continue to see an explosion of research in this area. And, that's because the peripheral blood is imminently accessible and there are more things in the blood than just cell-free DNA. There are other things that are specific to lymphoma, such as translocations and actually abnormalities at the chromosomal level. All of these can be accessed in the peripheral blood and sets us up for an ability to finally use rational designs to test how well our therapy's working and potentially even select therapy in the future.



Slide 40: Precision monitoring of ctDNA in lymphomas

And, I leave you with this slide. This is, if you will, the Holy Grail of where we could get if we effectively move forward with precision medicine. And, this is showing us precision monitoring. So, we're trying to cure patients with aggressive lymphomas. We know that their disease is similar, but it's not all the same. And, what you're seeing is different sub-clones here represented in different colors. After treatment, you can see that disease drops below a level and then when it comes back we think of it as the patient has a relapse or a recurrence of their original disease. But, from a biological perspective, it's probably very different disease. And, right now, we don't typically use that information to select different therapies. But, if we have the right tools and technology, it is certainly possible that that could help us decide, based on the molecular features of the disease, what type of treatment, what the timing of treatment could be, and again the whole goal is to try to improve the number of patients that actually achieve cure with these terrible and aggressive diseases.

Slide 41: National Cancer Institute

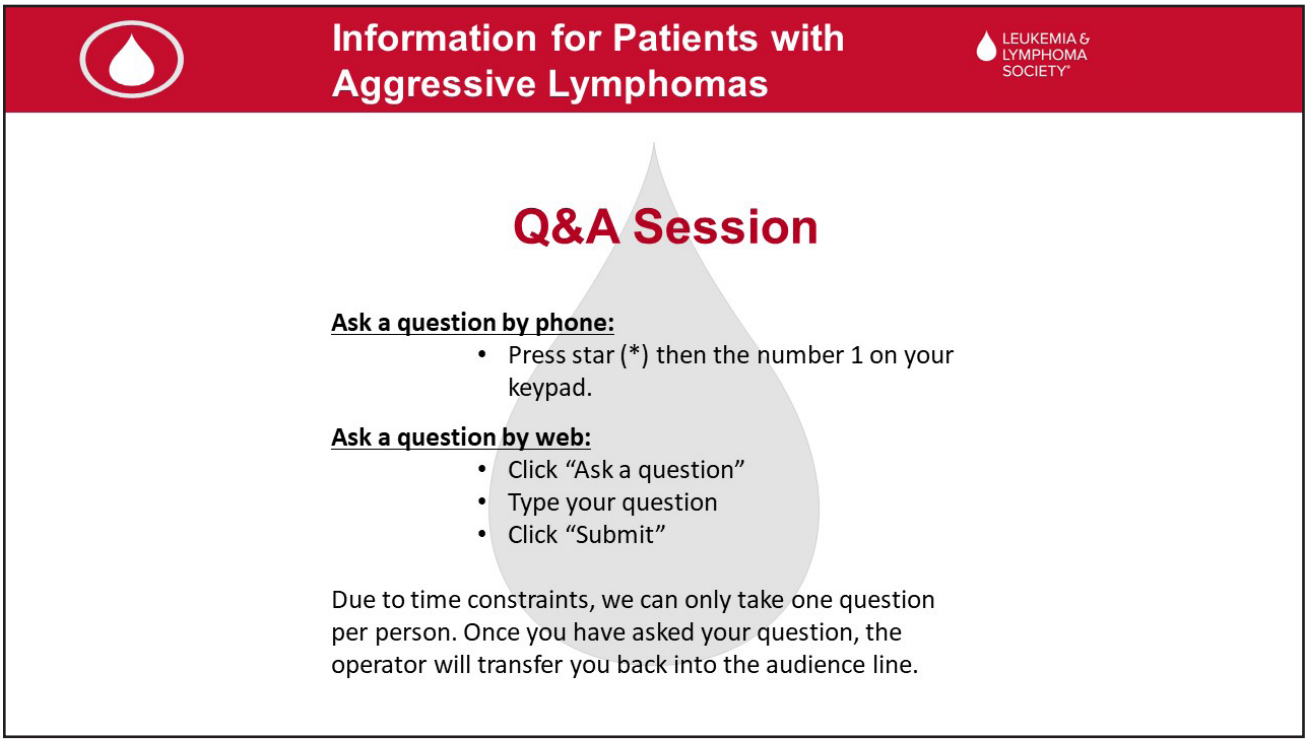
Lizette Figueroa-Rivera:
Dr. Roschewski, it sounds like there's a lot of studies for more personalized care. Did you want to speak about that for NIH? I know that NIH does a lot of studies specifically for personalized care.

Dr. Mark Roschewski:
Sure. No, I think that's an appropriate topic. We use these terms and I think sometimes it makes sense to us what they mean, but other times it can be confusing.

So, when I think of personalized care I think we already do personalized medicine. And, that is to say, when we're selecting the right treatment for a patient there are a number of things that go into that. We consider the biology of the disease, we consider the age of the patient, we consider how advanced the disease is, the wishes of the patient, all of these things are ways that doctors personalize their medicine. But, that's not the goal. The goal is to be more precise. And so, what we think of is that because this biology is different across different patients, if we were to develop the right tools to actually select who should get the individualized treatment, that could then be used to move forward.

Now, right now, most of the studies that have looked at this have been done in the relapse setting. And, at least with diffuse large B cell lymphoma it has been true that what's been done is we've given patients medicine and then went back and looked to see who actually responds. What the next wave of studies are going to be is to define the molecular biology ahead of time and then based on the molecular biology, then siphon those individual groups of patients off to individual therapies and see if that's a better way to actually marry up the precision of the biology and the treatment.

Lizette Figueroa-Rivera:
That's great. We're very interested in that and we're very happy at this time that so much is being done for this type of precision medicine.



Slide 42: Q&A Session

Lizette Figueroa-Rivera:
It is now time for our question and answer portion of our program.

We'll take the first question from our web audience. Amanda asks, if a patient is just told that they have diffuse large B cell lymphoma, but not ABC or GCB, what should they say to their doctor, what test needs to be run?

Dr. Mark Roschewski:
So, that's a very important question. Thank you for asking. One of the challenges that we have is those distinctions are made by a test called gene expression profiling. And that, at least the first iteration of that technology, required fresh frozen tissue samples. And so, mostly that was a research test and not available to us clinically. Since that time, however, actually fixed specimens, which is what most patients will have as a tumor biopsy that was actually fixed in paraffin, now there's a test known as a Nanostring assay that can actually distinguish between the 2. That is not available to all patients, but it is available to some, and it helps clarify if patients have GCB or ABC diffuse large B-cell lymphoma.

Keep in mind, or maybe I should tell you, there are cases that are actually unclassified, around 15%, and so there's still some more work to be done to breaking them down further.

Now, you can ask your doctor to try to estimate what the cell of origin is. That's something called immunohistochemistry. So, they will stain the outside of the cells and look for the presence or absence of individual markers known as CD10 and MUM1 and BCL6. And, these are ways to try to estimate whether it's GCB or non-GCB. And, they're about 85% to 90% accurate, so they're not perfect. But, you do have to ask your doctor. They don't always offer that because, at least outside of a clinical trial, most patients are not treated with these targeted agents, at least not now.

Lizette Figueroa-Rivera:
Thank you. And, we'll take the next question from our telephone audience, please.

Operator:
Excellent. And, our first question comes from Julie from Indiana. Please state your question.

Julie:
Hi. I'm diagnosed with cutaneous T cell lymphoma of the skin. And, I'm wondering if there is any for sure treatments that have been helpful to patients. I've had no success with treatment that I have had and it's just progressively getting worse.

Dr. Mark Roschewski:
Right. So, I'm sorry to hear that. It is true that there's other types of lymphomas that we didn't cover here. We actually didn't talk at all about T cell lymphomas, in part that's because they're less common. Now, when they do exist in the current patients, they can involve a number of different areas. They can involve lymph node change similar to diffuse large B-cell lymphoma, but they can also frequently involve the skin. And, that's what we heard the caller describe here.

Skin-based T cell lymphomas have a variety of different treatment options and because they usually behave in a more indolent fashion, most patients, at least at the beginning, don't require chemotherapy and combinations of chemotherapy. But, of course, sometimes those treatments don't work, and patients may look for secondary treatments or third treatments, and that's when it becomes appropriate to discuss with your doctor whether or not you're a good candidate for some of these newer medicines, some of these newer targeted therapies.

We have seen a number of new targeted therapies that do show some impressive activity in what we call cutaneous T cell lymphomas, and I would encourage patients, when they're not getting the results from standard therapy, to look for clinical trials because I would say that this is an area of great promise.

Lizette Figueroa-Rivera:
Thank you. And, we'll take the next question from our web audience. Judith is asking how effective is CAR-T cell treatment in treating diffuse large B-cell lymphoma?

Dr. Mark Roschewski:
So, that's an excellent question and I didn't talk about that. In part, just because that hasn't been our research efforts, but what we have seen with immunotherapy in general is that there certainly are a group of patients that tend to respond quite nicely to various forms of immunotherapy, and that is actually really a transformative finding. So, we here at the NCI, actually developed some of the first CAR-T therapies for patients with B-cell lymphomas and the target that's now been approved for diffuse large B-cell lymphoma is a CAR-T construct that goes after a protein on the outside of the cells known as CD19. So, there've been a number of different studies that have tested different CAR products. If we look at all the data in summary, what we see is that even patients in which chemotherapy has completely stopped working, something we call chemotherapy refractory disease, those patients can not only get responses, they can actually get complete responses and oftentimes those complete responses will last for longer than 6 months.

Now, we don't yet know if that cures those patients, but we think that some of those patients are cured. And so, if we look at how many patients actually get to 6 months and remain in remission, it's around 40%. So, best guess is, we might be curing up to 30% or 40% of patients even with refractory disease. That's a highly relevant finding and one that's being moved forward in various options to try to get more patients to this treatment. There are some barriers to getting the therapy, but for patients that can get on a trial or even standard treatment, this is a very exciting time to be trying to treat with CAR-T therapy.

Lizette Figueroa-Rivera:
Thank you. I'll take the next question from our telephone audience, please.

Operator:
Excellent. And, that comes from Peggy from Illinois. Please state your question, Peggy.

Peggy:
Hi. I was diagnosed with, well, I have follicular non-Hodgkin's lymphoma 12 years ago. Last January, I was diagnosed with aggressive lymphoma and it was, she told me it was treated aggressively, although I don't know with what. But, I had 6 chemo's and then had a PET scan and it showed that there was a different lymphoma, smaller cell, now they're finding something else in my stomach that they're thinking it might be the aggressive lymphoma again. Is that, once you've had it, does it come back again and again?

Dr. Mark Roschewski:
So, thank you for that question. I'm sorry to hear of your troubles. I think Peggy's story is informative on a number of different levels. First of all, it highlights the biology of these tumors and how it can change over time. And, one of the things she described was a diagnosis over 10 years ago that then when the disease comes back looks very differently underneath the microscope, and that is something that's been very well described, it's something we call histologic transformation. And, it's true that the treatment is different if the disease looks like diffuse large B-cell lymphoma or looks like follicular lymphoma. And, that is kind of the essence of precision medicine, where we're saying we want to approach these treatment options based on not only what it looks like under the microscope, but what it looks like with the underlying molecular biology.

So specifically, her question is can things change over time and the answer is yes. And, one of the things we know is that treatment itself, particularly chemotherapy, if it does not cure the patient of the disease, can in and of itself change the biology of the tumor. And so, all patients that have had treatment previously with chemotherapy and radiation therapy, when their disease comes back, it is almost always fundamentally different than it was prior to the first treatment. And so, that's partly what we think of when we try to select therapies for patients of all types of different aggressive lymphomas and indolent lymphomas at various time points in their disease course.

Lizette Figueroa-Rivera:
Thank you. And, the next question from the web is from Martine, Martine asks how do you select the right clinical trial in the myriad of choices we have, what criteria should we use?

Dr. Mark Roschewski:
Now, that is a fabulous question that I don't hear asked very often and the short answer is, we struggle with that. So, you're correct, there are a number of different agents that are available to patients and sometimes the message sent is you should select a clinical trial, but I can say from doing this for over a decade now, not all clinical trials are the same, not all of them offer the same amount of benefit. I think that's something where, if I were a patient I would make sure that I counseled with a lymphoma expert in that case if you're considering clinical trials. I think it's incumbent upon us to help make the right recommendation. In some cases, we are making recommendations based on what we think or hypothesize is the best for a patient, but quite honestly in many situations it does turn out to be a little bit of trial and error, meaning we don't have good biomarkers to actually select what trial a patient should go on. This is an important component of trials, to help us make these selections, but it is fair to say this is another area that's completely not up to snuff with where we need to be for helping patients make these decisions.

It is a little bit different if it's aggressive, if it's indolent. When we look to our patients and try to make these decisions, we do focus as much as we possibly can on the molecular biology and look for clues. But, at the end of the day, these are still clues and we still don't have the right way to direct patients.

Lizette Figueroa-Rivera:
Thank you Doctor and thank you Martine for that question. Doctor, Matthew's asking about clinical trials. He does have a mother-in-law that has refractory Burkitt's lymphoma and is trying to find options for clinical trials for her, but she does live in Argentina, and he is asking if there are ways for foreign nationals to participate in American clinical trial programs.

Dr. Mark Roschewski:
To address the second part of the question first, there absolutely is ways to participate in trials in the United States. We do that at our institution and it's just a matter of logistics and depending on the individual disease.

With respect to relapses of Burkitt lymphoma, that's a troublesome area because in most cases the patients get cured the first time with treatment and it grows quite quickly. So, what that means is there aren't many clinical trials that focus specifically on Burkitt lymphoma. In fact, there's no published prospective trial that's tested any agent in Burkitt lymphoma because of that reason. So, in situations like that, we tend to make our best guess for what the right treatment is for the patient and it depends on a variety of different things. I would say that things like CAR-T therapy, which was already discussed, would be something I would personally be looking into.

Lizette Figueroa-Rivera:
Thank you. And, we'll take the next question from the telephone audience, please.

Operator:
Excellent. The next question comes from Christine from New York. Please state your question.

Christine:
Hi, good afternoon. I was diagnosed with ABC diffuse large B-cell lymphoma 3 years ago and I did a modified regimen of dose dense R-CHOP followed by R-ICE. And so far, so good. I'm just looking at the future in case I do relapse, I was just wondering like I want to try to avoid something like a stem cell transplant if possible because I know that's a pretty rough regimen, and I was wondering if you could explain changes in the landscape of treatment with respect to that versus some of these newer agents.

Dr. Mark Roschewski:
So, that's a good question. Sometimes we see patients that we know has a disease that we think has more chemotherapy resistance than others as you described, and we are sometimes faced with the decision of whether or not we should proceed with a more standard approach, such as autologous stem cell transplant or try one of the targeted agents. There's a number of ways to try to make that decision. In general, the first remission a patient experiences, how long that is, is highly informative. So, in a case like what you described, where a patient has a relatively long remission, those patients still can be cured with an autologous stem cell transplant, provided they remain chemotherapy-sensitive. And so, that's probably what most lymphoma doctors would recommend.

On the other hand, if a patient was not a candidate for that or if the remission was short, that is to say within 6 months of the original remission, we know that that's a marker of chemotherapy resistance and in those situations it's my feeling that autologous stem cell transplant does not offer a high likelihood of cure. And, we typically move those patients more quickly to novel targeted therapies. And, then the decision, which was sort of already discussed, is which clinical trial would you try. We start focusing on okay, is there a targeted therapy that makes sense or a combination of targeted therapies that make sense specifically for this disease, or should we be looking at CAR-T therapy and these kinds of things. And, that's kind of where we move with that.

So, I think to kind of globally answer your question, the amount of time before you actually end up with a relapse does play into that decision, importantly.

Lizette Figueroa-Rivera:
Thank you. And, we'll take the next question from the web. John is asking, are bone marrow transplants still part of an effective therapy course of treatment.

Dr. Mark Roschewski:
So, I think one thing we have to do is describe bone marrow transplant. So, that term can mean different things to different patients. Typically, what we're talking about is a stem cell transplant, which is, you know, the use of the stem cells either from one patient to another or one person to another patient, or an autologous stem cell transplant, where the benefit is high doses of chemotherapy. If we're talking about, you know, a stem cell transplant that comes from another person, that's an allogeneic transplant, then there definitely is a role for that, particularly if chemotherapy stops working and there's no available clinical trial, and/or there's no CAR-T option. It becomes more complex when there are CAR-T options and most of us, or many of us, I should say, have now come to the conclusion that CAR-T probably offers more of a benefit to a patient because the amount of time by which they have to actually have risks of toxicity is shorter. But, that's not to say that allogeneic transplant doesn't have an important role. It certainly does. It's the most time-tested modality for curing patients with refractory lymphomas and we shouldn't forget about that, particularly in situations where it can be done quickly and safely at a transplant center. So, these become very complex discussions that we have with our patients, it's not always clear out of the gate, there are other factors that play into that, some of them are logistics such as, you know, identifying the right donor, but all of these things should be put on the table if a patient is faced with relapsed and refractory disease.

Lizette Figueroa-Rivera:
Thank you. And, we'll take the next question from our phone audience, please.

Operator:
Excellent, thank you, and that comes from James from Kentucky. Please state your question.

James:
How many years should a patient continue to have full-body CT scans after treatment with the RCVP and then Rituxan for the follicular non-Hodgkin's lymphoma that is in remission?

Dr. Mark Roschewski:
So, that's a very good question. One of the things that comes up is exactly that, how long should I be scanning. If we're talking about a patient that's been treated with follicular lymphoma, then what we're saying is we expect that disease to come back. So, over time it's more likely that the disease will come back. If we're talking about a patient with aggressive lymphomas, then we are hoping that we've cured that patient. So, over time it's less likely that their disease will come back. So, it does create some level of challenge about how often are we going to scan a patient.

My approach in patients with follicular lymphoma is to limit the number of CT scans that I do and in part that's because I'm not excited or interested in treating a patient too early with follicular lymphoma relapse because I know that the strategy is different. So, what I do is follow patients with symptoms only, and then I do, though, have a discussion with them about whether or not we should get annual CT scans. My rationale there is, if the disease is going to come back in 2 or 3 or 7 years, I would like to at least have some sense for what the pace of the relapse was, because there is a difference in, you know, managing a patient who has no evidence of disease and it comes back very quickly, versus a patient who has had evidence of disease for time and you just see it slowly marching up. I think there's different choices to be made. So, that's how I approach it. But, it's fair to say many doctors will do this very differently. I would say that there can be some harm of doing too many scans. But, information can be power, and I don't think it's wrong to periodically do a scan, just to get a sense for where things are.

Lizette Figueroa-Rivera:
Thank you. And, I have 3 questions on double-hit lymphoma. So, Robert, Joan, and Kristin are all asking about double-hit lymphoma, treatment results, length of time remission lasts?

Dr. Mark Roschewski:
Yeah, so this is a common question. What we're talking about here, I'll broaden it a little bit. What we know is that, there are clearly subsets of diffuse large B-cell lymphoma that do very poorly with standard therapy and at least with published data, R-CHOP does not cure enough of those patients. Oftentimes, we focus on double-hit lymphoma. I think potentially that's an over-simplification. I think there are other subsets that are genomically complex that we could tease out that require more aggressive chemotherapy and probably even targeted therapies as the first treatment. We aren't there yet because this is an entity that's only been described within the last, you know, 10 years or so, and there hasn't yet been a prospective study that's been done in this group. Now, we actually completed a multicenter study of dose-adjusted EPOCH-R in patients that have a MYC rearrangement. And, around 60% of those patients also had a BCL2 rearrangement. And, what we were able to show, and this is in multiple centers, is that we're curing a little bit over 60% of those patients. And so, I think it's true that if you get good therapy and you go into remission, that you could easily be cured with that treatment, and you don't necessarily need consolidation on top of that.

It becomes much more challenging if the patient doesn't go into remission or if a patient has a relapse of this disease. So, it's currently an unmet clinical need. Our approach when we're asked is to always recommend dose-adjusted EPOCH-R as the chemotherapy backbone. We also recommend that patients get treatment relatively aggressively with therapies inside the CNS to try to prevent CNS relapse, either in the form of intrathecal methotrexate or high-dose methotrexate and that they be monitored very closely after treatment. That's been our standard approach. But, I think this is an area where we'll learn more over time, this is just what we know at this point.

Lizette Figueroa-Rivera:
Thank you Doctor. And, we'll take the next question from the phone audience, please.

Operator:
Excellent, thank you, and our next caller is George from New Jersey. George, please state your question.

George:
Doctor, can you tell me, if anything you've been discussing is relevant to mantle cell lymphoma.

Dr. Mark Roschewski:
So that's a good question. The answer is yes. Certainly, many of the chemotherapy drugs are the same. Mantle cell lymphoma is an example of a lymphoma that can behave quite differently across patients. So, it's difficult to classify it as either indolent or aggressive and that's because some patients have a very indolent course, where it behaves very benign, meaning it doesn't proliferate very quickly, and other patients it grows very, very quickly. So, I think, you know, depending on those features, helps us understand how those patients should be treated. So, from that standpoint, taking the fact that these diseases are often different across patients, really limits our ability to use these sort of like one size fits all approaches.

Now, the other thing about mantle cell lymphoma is that it's an example of one that has had at least 3 new targeted agents that have actually been approved. And so, what's happening now in mantle cell lymphoma is those targeted medicines, some of them target BTK, which I highlighted, ibrutinib. There's a second generation BTK known as acalabrutinib, which may have some advantages. All of these are now being tested in the relapse setting and they're trying to be moved upfront so patients can get them earlier.

It's also true that we still need to learn a little bit about how CAR-T effectively works in these patients. So, there is an ongoing trial of testing CAR19 in patients with relapsed and refractory mantle cell lymphoma. That's a very important trial because most of us feel that it's highly likely to work in this group of patients. There should not be a reason why they're more resistant than other patients. And so, that's another, I guess you might say drug, that's being developed for these patients.

So, those are all the uniqueness and the similarities. Mantle cell is different because it's one of our newest lymphomas. It was only described in the early 1990s that it had its own biological entity. So, it hasn't been around long enough for us to develop newer therapies, but that seems to be changing over time.

The other problem with mantle cell lymphoma is that patients tend to be older. So, whereas diffuse large B-cell lymphoma and follicular lymphoma can commonly affect patients, you know, that are of all ages, even very young, even their 20s, even young adults, mantle cell lymphoma tends to be concentrated in men over the age of 60 and 65. And so, that limits sometimes our treatment options, but if a patient is able to tolerate therapies, there's many different therapies available to them.

Lizette Figueroa-Rivera:
Thank you. Our next question comes from the web from Christie. Christie is asking can curcumin, green tea, a plant-based diet, or other holistic remedies help keep the cancer in check?

Dr. Mark Roschewski:
So, you know, I don't know the answer to that. I think that there are clearly things that we do, and that we ingest, that have an effect on our immune system. And, we know that our immune system has a role in controlling disease. That's as much as we know. The best scientific evidence we have doesn't support that, but that doesn't mean there's not some benefit to that. I don't tell my patients that I can point to any data that helps me know that this dose or that dose of any natural substance will actually prevent growth of cancer. But, I also tell them that I don't know that it doesn't. What I typically do when we're giving medicines to people is I try to ask them not to take anything that I don't know about because of the concern of drug-drug interactions. So, these are important questions, you know, whether or not there's other medicines, I'm not sure that there's major advantages to things that are described as natural, considering many of our treatments do come from natural products. But, it's certainly important that we kind of explore all different areas that might work to help treat patients with cancer, because we just have to keep an open mind about what actually it is that actually affects the patient's cancer cells.

Lizette Figueroa-Rivera:
Thank you Doctor. And, Jeffrey is asking about the obstacles patients must hurdle when diagnosed. Often doctors speak in medical jargon that can overwhelm patients and with aggressive lymphomas there's a sense of urgency to get treatment underway, yet it's essential for patients to get a second or third opinion. What are the best ways for patients to navigate priorities and options for treatment?

Dr. Mark Roschewski:
Yeah, this is a real problem. I agree with him. I agree with that comment that it tends to be a bit of a fire drill at the beginning of a diagnosis, it's overwhelming, it's a challenge for patients and doctors to effectively communicate and try to actually get the information that's needed. I think that many times there's a, you know, discussion about whether or not one should get a second opinion. I think those are always worthwhile. When we, if they're feasible, when we talk to our patients we're always willing to support them at getting a second opinion because we know what happens at the beginning and how challenging it is to come to a decision. There does have to be some trust with the physician about, you know, is it safe to get a second opinion. In our experience in most situations with diffuse large B-cell lymphoma there is time, meaning a week or 2, and it will not change the outcome. It's a little bit different than other cancers in that the stage or the, you know, how advanced the disease is doesn't change the outcome, it boils down to chemotherapy resistance. So, unless there's an organ that is actually being threatened at the time, there is an option to get a second opinion.

But, I think you kind of have to just ask questions. I think this is a role for the LLS and other things like that to help patients get information. But, you're right, it's a real challenge and, actually boiling things down and saying them in a way that a patient understands is, is more art than science.

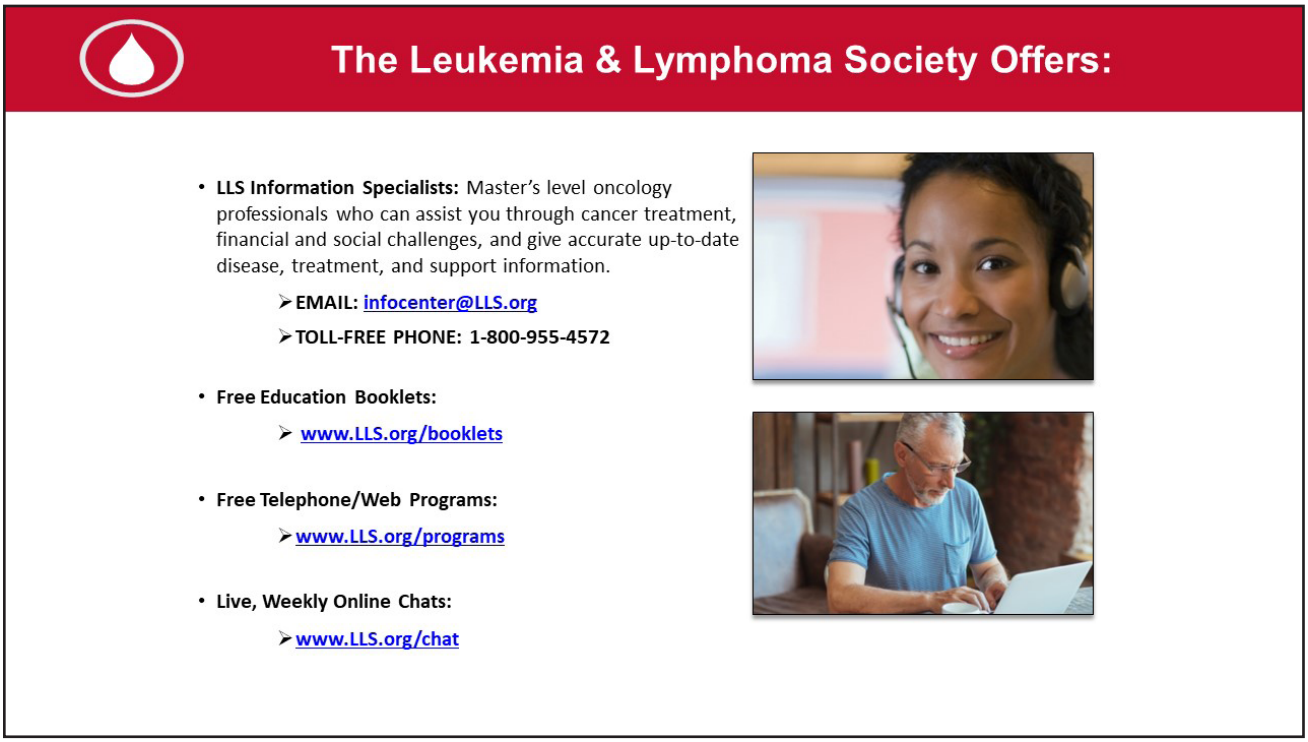
Lizette Figueroa-Rivera:
Thank you Doctor, and yes, we could definitely help with questions for your doctor, so you can definitely have a shared ability to come up with your treatment plan. And our last question today Doctor, David is asking is anyone doing studies on long-term survival, studies for late-term effects, and where to find these resources?

Dr. Mark Roschewski:
Well, so that's a very good question. You know, we'd like to have that problem in most lymphomas, we don't have it, unfortunately in many of them because we aren't curing enough patients. The best data to my knowledge of these things is in Hodgkin lymphoma and some of the pediatric literature is pretty good about that because they cure a high enough percentage of patients, they can then follow them over time. These are things that become very expensive and so that's one of the at least listed reasons why long-term toxicity studies aren't done as often.

Now, we here at the NCI can get around that barrier. We tend to do long-term follow-up of our patients. Some of the data I showed you in diffuse large B-cell lymphoma, of course we report 5 year outcomes, but we follow these patients for 10, 15, 20, and we can see whether or not there is long-term toxicity. This becomes important for things like how many patients are able to have children after they're cured, how many patients, you know, have neurotoxicity that actually goes away, and how many of them get secondary malignancies and so on and so forth.

I wouldn't say that there's a wealth of data on this. There are some repositories in other countries, such as Sweden and others that have much better sort of centralized reporting of this kind of thing and they tend to publish on this. But, you know, it is difficult to get that information and have any kind of sense for what the long-term effects are, particularly with these targeted therapies. Like, we have to always admit to ourselves as researchers that we want to believe that these newer medicines are good and they're better, but we don't know until we've done it, what happens to patient's long term. And, we constantly remind ourselves of that as researchers that the toxicity a patient experiences doesn't stop, you know, after the first go around, particularly if they're on indefinite therapies

Lizette Figueroa-Rivera:
Well, thank you, David, for your question, which was our final question today. And thank you so much Dr. Roschewski for your continued dedication to patients.



Slide 43: The Leukemia & Lymphoma Society Offers:

If we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by email at infocenter@LLS.org.

Slide 44: The Leukemia & Lymphoma Society Offers:

Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.

Again, The Leukemia & Lymphoma Society would like to thank Genentech & Biogen and Pharmacyclics, an AbbVie Company, & Janssen Biotech for support of this program.

Slide 45: THANK YOU FOR PARTICIPATING

Dr. Roschewski, thank you again for volunteering your time with us today and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.

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