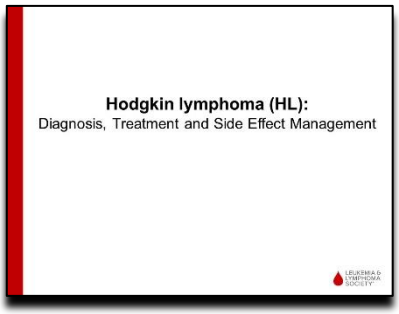
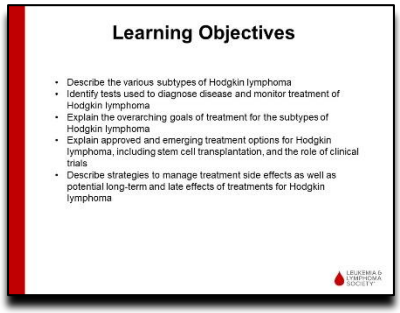


Slide 1: Hodgkin lymphoma (NHL): Diagnosis, Treatment and Side Effect Management

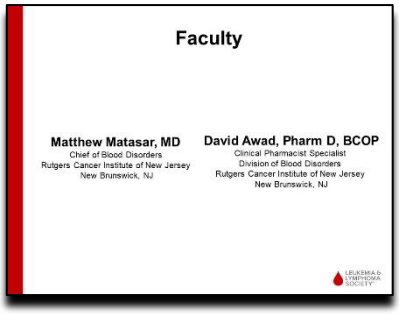
Lauren Berger: Hello everyone. On behalf of The Leukemia & Lymphoma Society, thank you for sharing your time w/us for this continuing education program on Hodgkin Lymphoma: Diagnosis, Treatment, and Side Effect Management.



Slide 2: Learning Objectives

The learning objectives for this program are listed on this slide.

- Describe the various subtypes of Hodgkin lymphoma
- Identify tests used to diagnose disease and monitor treatment of Hodgkin lymphoma
- Explain the overarching goals of treatment for the subtypes of Hodgkin lymphoma
- Explain approved and emerging treatment options for Hodgkin lymphoma, including stem cell transplantation, and the role of clinical trials
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for Hodgkin lymphoma
- Describe the roles of the pharmacist, the nurse, and the social worker in treating patients classical HL

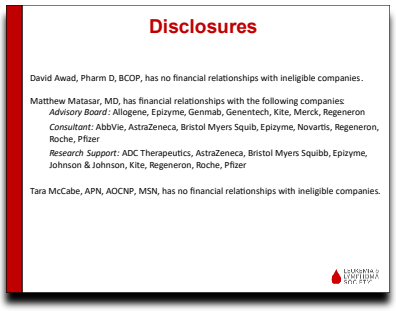


Slide 3: Faculty

We're fortunate to have as our presenters, Dr. Matthew Matasar, a leading expert in Hodgkin lymphoma, and his colleague, Dr. David Awad, a clinical pharmacy specialist. We appreciate their dedication and their commitment to caring for patients living with blood cancers.

Dr. Matthew Matasar is Chief of Blood Disorders at Rutgers Cancer Institute of New Jersey in New Brunswick, NJ. Dr. David Awad, is Clinical Pharmacist Specialist in the Division of Blood Disorders at Rutgers Cancer Institute of New Jersey in New Brunswick, NJ

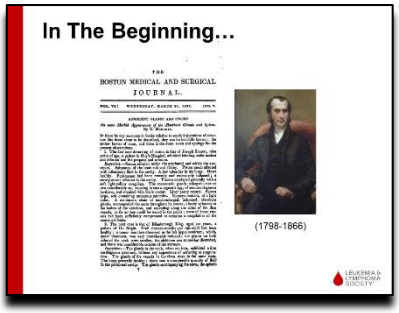
Dr. Matasar & Dr. Awad, I am now privileged to turn the program over to you.



Slide 4: Disclosures

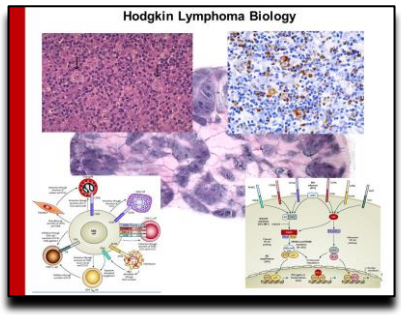
Slide 5: Roadmap

Matthew Matasar, MD: Thank you so much for those introductions. And why don't we go ahead and get started. So shown here is a roadmap for what we're going to try to cover together, David and I, as we walk through Hodgkin lymphoma with you. So, we're going to start just with our overview of Hodgkin lymphoma before we dive into the therapeutic approaches.



Slide 6: In The Beginning

So, obviously, Hodgkin lymphoma has been recognized for a long time as an illness, although it used to be Hodgkin's disease. Why Hodgkin's disease? Because it was found by this dude Hodgkin, right? But it was first recognized as an illness, not even as a form of cancer. And it wasn't until more recently that we even understood that this was a form of lymphoma. And on the next slide, you'll see why.

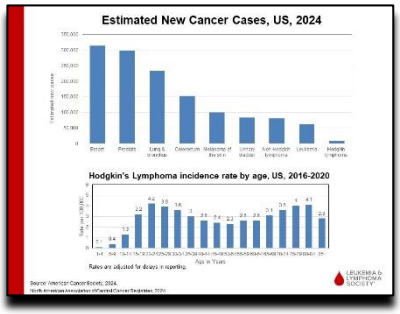


Slide 7: Hodgkin Lymphoma Biology

And, he was a pathologist; and when he took out involved lymph nodes from patients with this illness, he found this bizarre appearance of the tissue. First naming it, and not even understanding that it was necessarily a malignancy. He thought it was perhaps an infectious illness given the bizarre appearance of the immunophenotype below. And we now understand that this is indeed a form of lymphoma.

You see these very bizarre appearing cells in the upper left. These Reed-Sternberg-like cells and their variants, these owl's eye nuclei. But with modern technology and understanding the immunohistochemistry, we see that these are indeed abnormal lymphocytes expressing some form of B-cell program, the stand upper right of CD30, which is a very stereotypical protein to see on the surface of Hodgkin lymphoma cells and as you'll hear later in the presentation, a target of modern therapeutics.

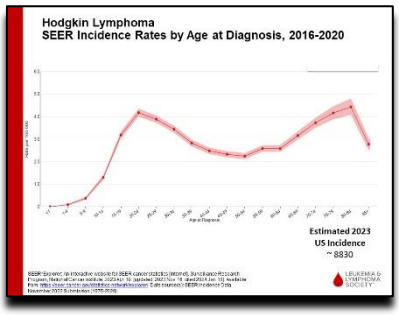
We also now understand the underlying disease biology with greater clarity, understanding that there's key intracellular signaling pathways that drive lymphocyte survival proliferation among these Reed-Sternberg cells and their variants, as well as an understanding that these cells exist in a very complex immune microenvironment that promotes their survival and proliferation.



Slide 8: Estimated New Cancer Cases, US, 2024

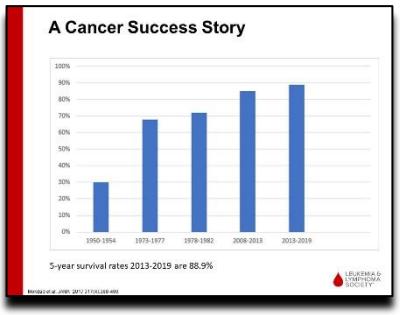
Hodgkin lymphoma is not a very common type of lymphoma. As you see here, certainly dwarfed in its numerical impact by some of these more common solid tumors – breast cancer, prostate cancer, lung cancer, colon, and others. It's an uncommon illness, but it has this very unusual biphasic incidence pattern where you see that there's younger person Hodgkin lymphoma where it peaks in our 20s, then incidence goes down during middle age, and then there's a second hump during our advanced age where then, again, incidence goes up during our 70s and 80s.

Turns out that early-person Hodgkin lymphoma and elderly-person Hodgkin lymphoma do have some clinical as well as biological differences making them somewhat distinct, both in terms of our diagnostic considerations, as well as therapeutic approaches, as we'll talk about.



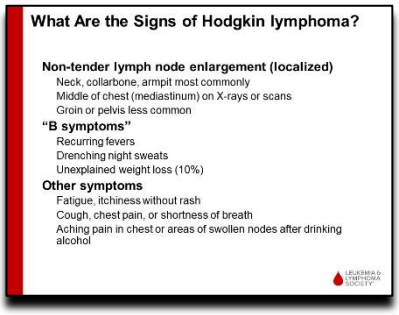
Slide 9: Hodgkin Lymphoma SEER Incidence Rates by Age at Diagnosis, 2016-2020

When you look at the translation of that pattern into incidence rates by diagnosis, you see that it is actually quite common in terms of, the rarity of childhood illness writ large and it's one of the more common forms of cancer in general and, certainly, of lymphoma for adolescent and young adult populations. And, again, you see that second peak during advanced stage represented by the data out of the SEER dataset.



Slide 10: A Cancer Success Story

Certainly, it's a less common form of lymphoma, but it's had an outsized impact in terms of the story that we tell ourselves as oncologists in terms of our ability to cure cancer. And it really is a paradigmatic success story within medical oncology where we've seen five-year survival rates historically were very, very poor. But during the modern era, we see that, indeed, the overwhelming majority of patients will obtain five-year survival despite being diagnosed with an aggressive and potentially life-threatening illness.



Slide 11: What Are the Signs of Hodgkin lymphoma?

So, first, just to talk about some of the clinical presentation of Hodgkin lymphoma, so what are the signs and symptoms of Hodgkin's? So, the most typical presentation of Hodgkin lymphoma is a patient presenting to their healthcare provider with painless adenopathy, nontender lymph node enlargement, typically showing up in one or a few sites that the patient notices these. Most typically, it'll be either in the neck overlying the collarbone or in the armpits. Less common would be presentation in the groin. Typically, this will ultimately lead to body imaging with a CAT scan or other diagnostic modalities, and you will very often find that there is mediastinal or central just swelling either on plain film x-rays or on body scans.

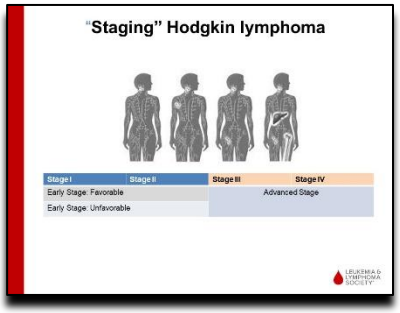
Hodgkin's does tend to follow sort of an orderly progression where it typically will start either in the armpit or the neck, spread into the central chest, and then it can go below the diaphragm into upper abdominal lymph nodes and ultimately into the pelvis. The inverse order where it starts in the groin and then moves north can be seen but is less common, particularly in Western countries and in Caucasian patients.

The other sort of consideration in terms of presenting symptoms of Hodgkin lymphoma are the so-called B symptoms, those being recurring and unexplained fevers, drenching night sweats, or significant unexplained weight loss. Most patients with Hodgkin lymphoma will not have these B symptoms, but when you see these symptoms in an undiagnosed patient, certainly invokes the possibility of either Hodgkin lymphoma or other aggressive lymphomas.

There certainly can be other symptoms that are associated with Hodgkin lymphoma, including progressive and profound fatigue, pruritus, or itchiness, that often can be quite debilitating and body wide, typically without a rash. So, itch without rash is paradigmatic.

Chest involvement either in the mediastinum or the lungs can lead to cough or chest pain, shortness of breath.

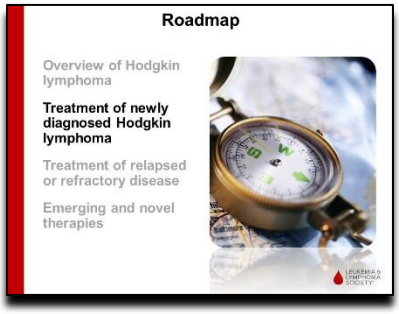
There is this phenomenon of patients experiencing an aching pain either in their chest in the context of mediastinal adenopathy or in other areas of swollen lymph nodes, immediately after drinking alcohol, either beer, wine, or spirits. And it is said that this alcohol-induced nodal pain is almost diagnostic of Hodgkin lymphoma. Indeed, I've only had one patient in my career who had that symptom and didn't have Hodgkin lymphoma and they had a lymphoma that was biologically related to Hodgkin's called Gray zone lymphoma.



Slide 12: "Staging" Hodgkin lymphoma

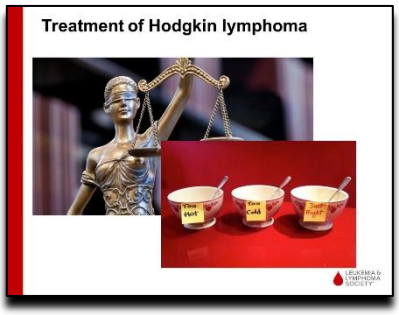
After you've made a diagnosis of Hodgkin lymphoma on a biopsy, we often talk about, the stage of the illness, and staging of Hodgkin lymphoma is important to understand because it has treatment implications. Certainly, it also helps in terms of prognostication.

We divide the four stages, Stage I being a single lymph node chain, Stage II being multiple lymph node chains on the same side of the diaphragm, either all above or all below, and then Stage III is lymph nodes both above and below the diaphragm, Stage IV being lymph nodes and sites outside of lymph nodes, other organs. But we divide those into these different categories for prognostic and therapeutic planning of early stage favorable and early stage unfavorable based upon the number of lymph node chains that are involved as well as blood tests and other characteristics. And then advanced stage, both Stage III and Stage IV is generally approached as a single clinical entity.



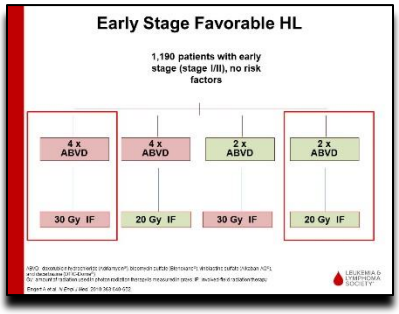
Slide 13: Roadmap

But let's move out of this overview phase and really talk about what we're here today to talk about, which is a practical understanding of how we approach the treatment of Hodgkin lymphoma, starting with patients that are newly diagnosed.



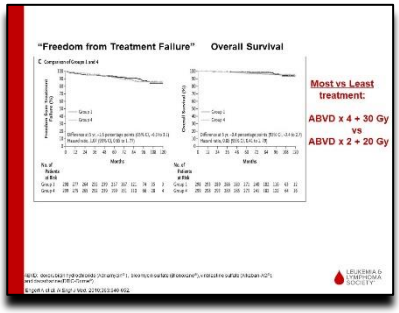
Slide 14: Treatment of Hodgkin Lymphoma

When we think about the therapeutic approach to patients with Hodgkin lymphoma, we really are trying to conduct this balancing act of wanting our treatments to be no more toxic than is necessary to achieve cure, but not wanting to undertreat patients and put them at an unnecessary and elevated risk of recurrence. Sometimes we talk about this with our patients as the Goldilocks phenomenon, right, of not wanting the porridge to be either too hot or too cold but searching for that just right approach to an individual patient's diagnosis with Hodgkin's.



Slide 15: Early Stage Favorable HL

I've already told you that we divide patients into these different risk categories. And from that, we will often derive optimal therapies looking at the category of early stage favorable, the lowest risk patients, these patients that have early-stage disease and don't have additional risk factors either clinically or on the basis of blood testing. And there was an important study that looked at the optimal treatment of these patients using what we call combined modality therapy, meaning both chemotherapy and radiation therapy, and compared the sort of less and more intense approaches of two cycles of chemotherapy with a traditional treatment of doxorubicin (Adriamycin®), bleomycin (Blenoxane®), vinblastine (Velban®), and dacarbazine (DTIC-Dome®), or ABVD, combined with different dosages of radiation therapy, as you see here.

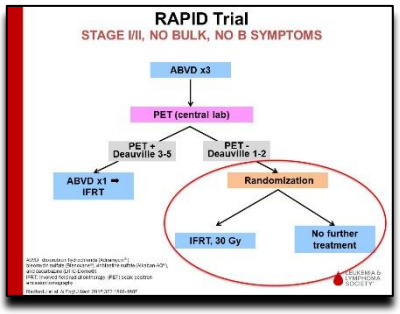


Slide 16: "Freedom from Treatment Failure" Overall Survival

And, when you look at the treatment of early-stage disease, trying to compare, again, less versus more chemotherapy and less versus more radiation therapy, it really gets to the heart of the matter.

So, when you compare the most and the least treatment from this important study, those that received four cycles of chemotherapy and 30 Gy, or a higher dose radiation treatment, versus those that received the least, only two cycles of chemotherapy and less radiation therapy, we see that there was no detectable difference in terms of outcomes. There was no increased risk of relapse, there was no difference in overall survival teaching us that in this context, the less-is-more approach is really just right. And the two cycles of chemotherapy and 20 Gy

lower-dose radiation therapy emerged as the standard combined modality approach on the basis of these findings.

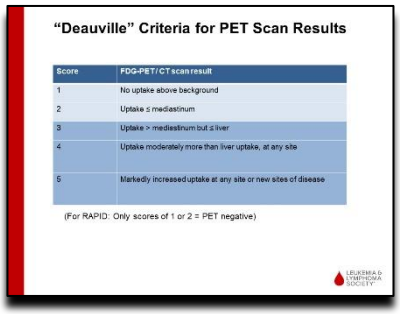


Slide 17: RAPID Trial

Obviously, radiation therapy comes with its own risk, both in terms of short-term toxicities, but perhaps even more importantly, long-term toxicities. And we recognize that radiation therapy can lead to a number of adverse late effects, including, depending upon the site irradiated, risks of heart disease or secondary malignancies or other damage.

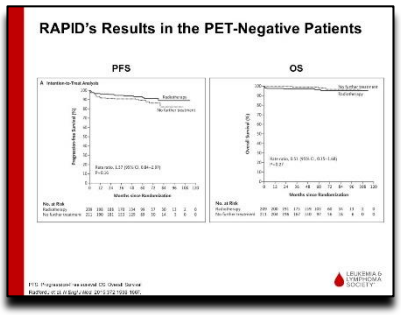
Efforts have continued to try to develop chemotherapy-only treatment approaches for early-stage Hodgkin lymphoma, including the important RAPID trial, which took patients who had low-risk disease and administered three cycles of chemotherapy with ABVD to those patients, and then performed a PET scan after those three cycles. For those that achieved a complete response by PET criteria, strict criteria using only scores of 1 or 2 out of 5 on, on the end-of-treatment PET scan. Such patients were randomized in the RAPID trial to receive additional radiation treatment or no radiation at all.

And this is the important part of the RAPID trial that we focus on in terms of its guidance of clinical management. Patients who had persistent PET positivity after induction ABVD went on to receive from that modality as would be appropriate.



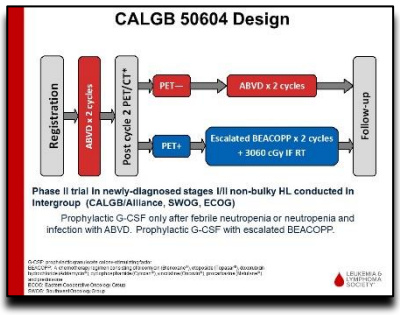
Slide 18: "Deauville" Criteria for PET Scan Results

I talked about the stringent criteria there for the RAPID trial, meaning the Deauville scores of 1 or 2. A Deauville score of 1 is completely normalized PET scan. A Deauville 2 is normalized even below the background of mediastinal uptake. Deauville 3 is included in the PET negative category in many studies where uptake is maybe slightly higher than mediastinal blood pool but still less than the liver mean. And then Deauville 4 and 5 are considered positive in all studies.



Slide 19: RAPID's Results in the PET-Negative Patients

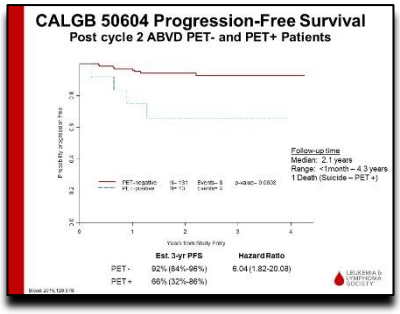
So with this stringent result of defining PET negativity as only a Deauville 1 or 2, when you look at the outcomes for those that received radiation therapy or no further treatment, there was no statistically significant difference in either progression-free or overall survival, most importantly, teaching us that, indeed, after three cycles of chemotherapy with ABVD, if a Deauville 1 or 2 complete response has been achieved, such patients can be successfully followed without consolidated radiation treatment.



Slide 20: CALGB 50604 Design

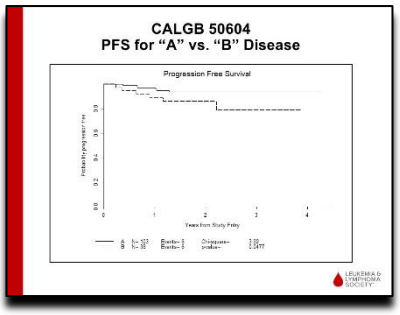
Perhaps more relevant to us in routine practice is the CALGB 50604 study, which took a slightly different approach of giving at first two cycles, performing a PET scan after two cycles, defining that more broadly negative as a Deauville 1, 2, or 3, so if patient is going to receive two more cycles for a total of four rounds of chemotherapy, and subsequently were followed.

For those that were PET positive after those two cycles, they went on to receive treatment intensification.



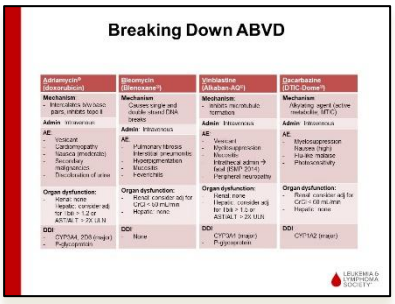
Slide 21: CALGB 50604 Progression-Free Survival

And what we see is that the PET negative patients in 50604, those that had a Deauville 1, 2, or 3 after only two cycles went on to get a total of four cycles, enjoyed excellent outcomes even for many years after treatment suggesting that such patients really can be successfully managed with four cycles of chemotherapy. Importantly, very few patients were PET positive with Deauville 4 or 5 after those two cycles, telling us that we really can very significantly reduce our administration of intensified treatment or our reliance upon radiation therapy by defining PET negative more broadly in this context.



Slide 22: CALGB 50604 PFS for "A" vs. "B" Disease

Of note, and it's worth recognizing that in this study, those patients that had those B symptoms that I mentioned at first – unexplained fever, drenching night sweats, significant weight loss more than 10% of body weight – did seem to have a little bit worse outcomes than patients who did not have B symptoms with this approach, and this leads us to sometimes favor consolidative strategies or more intense strategies for patients who present with those B symptoms initially.



Slide 23: Breaking Down ABVD

David, it'll be helpful for us to move away from these data and actually talk in a little bit more detail about the ABVD program.

David Awad, PharmD: Yeah. Thank you, Matt. So we've been talking about how to treat using ABVD, but let's specifically go into what each of these drugs are. So ABVD stands for Adriamycin®, which is the brand name for doxorubicin, bleomycin, vinblastine, and dacarbazine. So going through each drug, Adriamycin® or doxorubicin is a topoisomerase II inhibitor, and it also intercalates between base pairs in DNA. This will eventually stop DNA synthesis and cause the malignant cell to die. Doxorubicin is given by intravenous route as is all of these drugs ~~in,~~ in these cases. And important side effects to think about with doxorubicin when we're looking at our patients is doxorubicin is a vesicant, meaning that it will cause tissue necrosis if it's administered outside of a vein. So, it's really important that these patients have very good intravenous access.

Typically, they'll have a chest port or they'll have some sort of central line since they'll be getting these treatments every two weeks. If they don't have a central line, it's important to be administering this agent slowly, via a peripheral line, and it has to be a very good peripheral line with ensuring that the nurse is very comfortable giving it through that line. And, typically, we'll give it as an IV push making sure that there's blood return between each push. So, we call this a push-and-pull method where you'll pull for blood return and then you'll push a little drug. Pull makes sure you have drug return and then push to make sure that you're getting drug into the vein.

We also think about cardiomyopathies, and this is typically going to be dose dependent with doxorubicin, so the more doxorubicin that you give, the more cardiac toxicity we expect with the drug. It doesn't mean that you can't get cardiac toxicity with lesser doses,

and it also does not mean that you will definitely see cardiac toxicities with higher doses, but this is something that we will monitor for with a baseline ejection fraction for the patient and then monitor throughout therapy if indicated.

Doxorubicin's also moderately emetogenic, so we will give prophylactic antiemetics with these drugs. There's also a risk of secondary malignancies down the line due to the effect of the DNA in, with the drug mechanism. And it's also common to see discoloration of urine and discoloration of bodily fluids such as sweat. Doxorubicin is red as it goes in, so it's red as it comes out so it can make urine orange. It could also be confused as blood.

Typically for doxorubicin, we don't need to dose adjust for any renal toxicity if the patient has baseline renal dysfunction. However, it is metabolized hepatically so patients who do have baseline hepatic dysfunction we should evaluate and consider dose adjusting if the bilirubin is greater than 1.2 or if the transaminases are greater than two times the upper limit of normal.

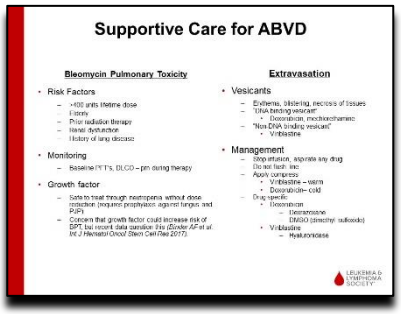
Important drug interaction to think about include, CYP3A4 and CYP2D6, which is a major substrate of CYP2D6 and P-glycoprotein. With all of these cases, it is important to evaluate drug interactions and look at the risk-benefit of holding or dose reducing the chemo versus changing the offending agent that's implicating the drug interaction.

Next, looking at bleomycin, bleomycin causes single and double strand DNA breaks in DNA. It is given intravenously. And really, the main thing that we think about with bleomycin is going to be pulmonary toxicity. So, bleomycin pulmonary toxicity is dose dependent, and we'll talk about it more actually on the next slide since it really does deserve its own slide for that. Other side effects that we can see include hyperpigmentation, can cause mucositis, and can cause fever and chills. Bleomycin does require a dose reduction for patients who have a creatinine clearance less than 50 mLs per minute, however, does not require any hepatic dose adjustments and does not require any drug interaction monitoring.

Vinblastine is our next drug. Vinblastine is a microtubule inhibitor. It'll inhibit the microtubule formation. It is given intravenously. Vinblastine is also a vesicant just like doxorubicin and important side effects to think about include myelosuppression, mucositis, and peripheral neuropathy. Just as a side note, vinblastine, in addition to all vinca alkaloids, should never be given via syringe since it is fatal if it is given intrathecally. So typically, we'll give this in a small mini bag in 25 mLs to ensure that it is never given via a syringe and mistaken for an intrathecal injection. Does not require any renal dose adjustments. However, we should consider dose adjusting for patients with hepatic dysfunction, typically a bilirubin over 1.5 or if transaminase is over the two times the upper limit of normal.

Vinblastine is a major subset of CYP3A4, and we do see high concentrations when CYP3A4 is inhibited, which puts the patient at risk for more drug toxicity. So, if a patient is on a CYP3 or A4 inhibitor, typically it's going to be an antifungal. Then we should consider just dose reducing the vinblastine.

And then, finally, dacarbazine, which is our last drug part of this regimen, dacarbazine is an alkylating agent. This is a noncell cycle-specific agent. It is given intravenously. Common side effects of dacarbazine include myelosuppression. It is highly emetogenic, and it is not uncommon for patients to have flu-like malaise. And it can cause photosensitivity reaction so patients should be counseled to avoid direct sunlight and wear sunscreen when they're going outside. Dacarbazine should be considered to be dose reduced for patients with a creatinine clearance less than 60. And it is a CYP1A2 substrate so, again, drug interactions should be screened at the start of therapy to ensure that we're not causing toxicity for these patients.



Slide 24: Supportive Care for ABVD

So, like I said before, bleomycin pulmonary toxicity is a really important side effect that we have to think about. Typically, the risk factors are going to be patients who receive greater than 400 units in their lifetime dose. We'll try to avoid getting anywhere near that, but if patients have already received that much, we won't use bleomycin in most cases.

Elderly patients at baseline are going to be at risk. Patients who received prior radiation therapy, specifically to their lungs, will be at risk. Patients who are also receiving concurrent radiation therapy into their lungs can be at higher risk. However, that's not definitive. Renal dysfunction as well as it'll cause bleomycin to linger around. And then patients who have just prior history of lung diseases, can be history of pneumonitis or interstitial lung disease, will put them at higher risk ~~of,~~ of developing pulmonary toxicity.

To help avoid these, we'll typically start with a baseline pulmonary function test and look at their DLCO and then if they have any deficiencies or if they're seeing any signs of pulmonary toxicity, then we'll repeat them throughout their therapy as needed.
There is also a question if growth factor can cause or exacerbate pulmonary toxicity with bleomycin. Typically, it is safe to treat through neutropenia without dose reducing their therapy so we can avoid using growth factor until there is febrile neutropenia. And this is really because we want to avoid causing this pulmonary toxicity. However, recent data does question this as you can see. So, we really aren't sure, but, Dr. Matasar, do you find that you and your patients are typically using growth factor to get them through their ABVD?

Matthew Matasar: It's a good question. And, the answer for me, David is almost never. We have very good data that the infectious risks of treating through neutropenia are very low as long as you're using appropriate and broad antimicrobial prophylaxis. So, I really restrict my use of growth factor when I'm using ABVD as my therapeutic platform to only those patients who are at increased risk of febrile neutropenia due to underlying comorbidities.

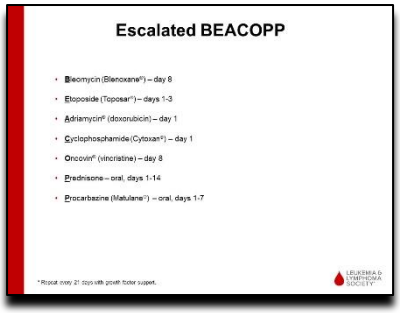
So, for instance, for patients who have an impaired GI Lumen due to active inflammatory bowel disease, those are patients that I may be reluctant to treat through neutropenia and may instead prefer to use growth factor. When I do use growth factor with ABVD, I often will try to use filgrastim as opposed to pegylated formulations and give a few days between the exposure to bleomycin and introduction of the GCSF out of concerns regarding this theoretical risk of increased pulmonary toxicity due to the inflammatory state that may be promoted by GCSF.

David Awad: Thank you for that insight, Dr. Matasar. So, let's now move on to extravasation. So, we mentioned that two drugs are at risk of extravasation in this regimen, including doxorubicin and vinblastine. And chemotherapeutics, in general, that are at risk of causing extravasation are going to be our vesicants, and these are going to be the ones that will cause tissue necrosis if they do leave the blood vessel.
This is typically going to look like erythema at first and then can progress to blistering and then even necrosis of the tissue as it progresses. We have two different types of vesicants. We call them DNA binding vesicants, which will include doxorubicin and mechlorethamine (Valchlor®). And then we also have non-DNA binding vesicants, which will include vinblastine and our other vinca alkaloids.

It's important whenever we identify a patient who might be having an extravasation to stop the infusion if this is going to be in an infusional drug and then start to go back and aspirate any drug as much as possible. Don't flush the line since that'll just push. You've already compromised essentially the access into the body so just by flushing the line, you'll push it more into the tissue. So that's why we want to aspirate any drug, if possible. And then depending on the drug, there'll be different guidelines as to whether we use a warm or a cold compress. So, in this case, vinblastine will use a warm compress and then doxorubicin we will use a cold compress.

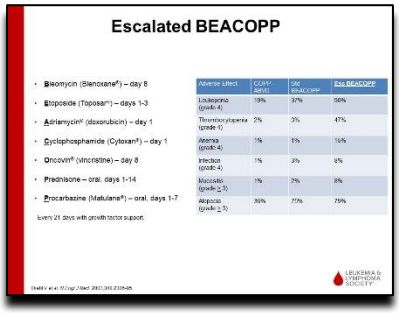
For drugs specifically, we have different antidotes that we can use. So, doxorubicin we can use dexrazoxane and, essentially, we'll be using any of these drugs by infiltrating the tissue with many different needle sticks and then slowly injecting that drug into that area to make sure that we try to bind as much of that drug as possible before it has a chance to act on the tissue. We can also use DMSO in many cases, which is dimethyl sulfoxide. For vinblastine, we can use hyaluronidase (Vitrase®) and will administer it in a very similar

fashion as dexrazoxane (Totect®) where we're slowly injecting it into multiple parts of the invaded tissue. It's going to be very important to monitor that patient as the necrosis can happen and can progress very quickly over time.



Slide 25: Escalated BEACOPP

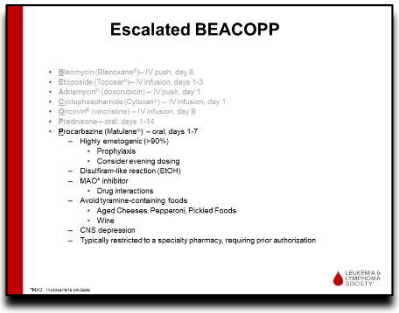
And we briefly talked about the escalated BEACOPP regimen. So, this is going to be very similar drugs to ABVD, but we're going to add a few drugs. So, it's going to consist of bleomycin on day 8. We're going to add etoposide (VePesid®) on days 1, 2, and 3. We're going to have doxorubicin on day 1.



Slide 26: Escalated BEACOPP

We're going to add cyclophosphamide (Cytoxan®) on day 1, and then vincristine (Marqibo®) on day 8, and the patient will take oral prednisone daily for two weeks from days 1 to 14 and then oral procarbazine (Matulane®) on days 1 to 7.

So, the escalated BEACOPP regimen, if we compare it to ABVD, is a very toxic regimen, as you could see. And one main difference between escalated BEACOPP and ABVD is we are definitely going to use growth factor as primary prophylaxis in these patients.



Slide 27: Escalated BEACOPP

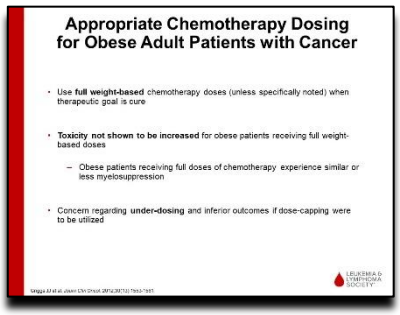
And, as you could see, just by looking at escalated BEACOPP, we have leukopenia of 90% and infection rate of 8%. And this is going to be attributed to the higher doses of drug that we're using and the multiple drugs that we are using.

And just to highlight one of the nontraditional drugs that we don't use in many regimens but is an effective drug, which is procarbazine. Procarbazine is an oral drug, and this is actually, it's going to be common for your community pharmacist or your specialty pharmacist to see this being dispensed because it is an oral oncolytic.

Procarbazine is an alkylating agent. So, think of it very similar to dacarbazine, a close cousin and oral analog of dacarbazine so we're going to see similar side effects to dacarbazine. And that's going to be, it's a highly emetogenic drug. When we're

dispensing oral medications that are highly emetogenic, it's very important to also ask for or also dispense an antiemetic as prophylaxis. So, this can be ondansetron (Zofran®) 8 milligrams right before the dose of procarbazine that day. Also giving the dose at night tends to help calm nausea, but every patient will be a little different.
Procarbazine can cause a disulfiram-like reaction when patients drink alcohol at the same time. This is a common reaction that we see similar to metronidazole (Flagyl®) with alcohol. And kind of unique to procarbazine, it is an MAOI or a monoamine oxidase inhibitor. This means that we have to look out for drug interaction specifically, and we have to also counsel our patients to avoid tyramine-containing foods. These include aged cheeses, pepperonis, pickled foods, and wine.

Procarbazine can cause CNS depression so patients should be counseled on that. And most of the cases, because of all of this monitoring and all of these counseling points, it will be restricted to a specialty pharmacy and require prior authorization to make sure that patients are receiving this in a controlled manner and are counseled on the side effects. So many specialty pharmacists will see this as part of their dispensing log.

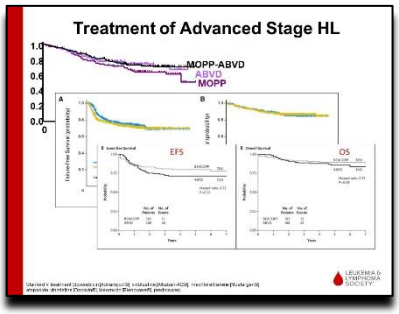


Slide 28: Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer

Another consideration for patients who are receiving chemotherapy is those who may be obese. And there's always a question of what dose should be used for patients who are obese.

And the general consensus is that full weight-based chemotherapy doses should be used whenever we're thinking about cure. So in these cases, we're going to be thinking of curing our patients, so we don't want to cheat anyone on the amount of chemotherapy that we're giving. And this is typically because a lot of the chemotherapy will be invading into the tissue and some of it can get lost in patients who are obese.

Most of the studies show that toxicities are not shown to be increased or any worse in patients who are obese when they do receive their full weight-based doses. And they show that patients who are obese receiving full dose chemo will experience similar or less myelosuppression. There is concern regarding underdosing and inferior outcomes if dose capping were to be utilized, so we try to avoid dose capping these patients so that we don't underdose them and we can really get them to that curative intent.



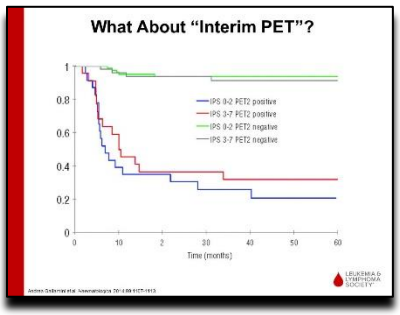
Slide 29: Treatment of Advanced Stage HL

And I'll now pass it on back to Dr. Matasar, who will speak about advanced stage Hodgkin lymphoma.

Matthew Matasar: Awesome, thanks for that incredible overview of these agents and their profiles. Why don't we pivot from talking about early-stage disease where ABVD and sometimes intensification to escalate BEACOPP have continued to really dominate our therapeutic decision-making to advanced stage Hodgkin lymphoma

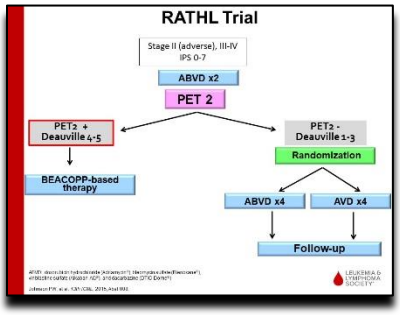
And here, you know, originally ABVD had been the standard of care for quite some time. Not because it was necessarily superior to either the older MOPP regimen or the MOPP/ABVD hybrid that came after it, but really on the basis of an improved toxicity profile compared to those older regimens.

There was an additional competitive regimen called Stanford V which was a combined modality approach leveraging a more abbreviated but intensified chemotherapy program that incorporated radiation therapy as part of the platform, and it too was unable to surpass the quality results that we got with ABVD with advanced stage disease.



Slide 30: What About "Interim PET"?

We did see some improvement in event-free survival with the intensified and more toxic BEACOPP program that David explained for you here today, but there was no difference in overall survival that was detected with this intensified program, essentially leaving us to believe that you're trading toxicity for an improvement in relapse-free survival that wasn't necessarily the patients' best interests.



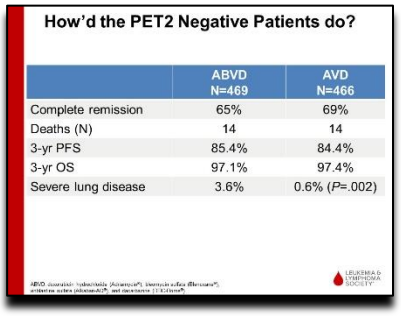
Slide 31: RATHL Trial

There was some question, and, indeed, we learned that an interim PET scan can be very prognostically powerful when using any of these treatments. And we see that for patients who achieve an interim PET negative status, meaning that their PET scan has become normalized to Deauville score of 1, 2, or 3 after two cycles of chemotherapy, is very powerfully prognostic regardless of initial risk of disease. The International Prognostic Scoring System is a risk stratification program that we use for Hodgkin lymphoma advanced stage disease, and it pales in the

comparison to the functional response as measured by interim PET scan in terms of prognostication.

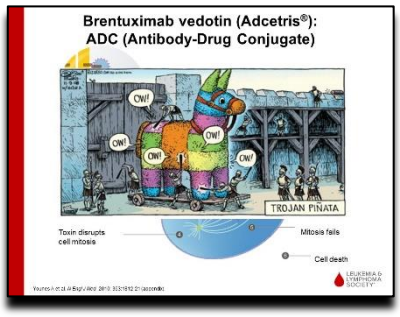
And what we learned from that is that we can try to leverage that response-adapted strategy to not just escalate therapy as we saw with early-stage patients who failed to achieve an early complete response, but to de-escalate therapy for patients who do achieve a good early response.

And that was highlighted in the important RATHL trial which took patients with either high-risk Stage II or mostly Stage III or IV disease, started everybody with ABVD chemotherapy, and then after two cycles got a PET scan. You'll see on the right, for those who achieved a PET-negative response, they were randomized to either continue the four-drug platform of ABVD or to withdraw the bleomycin at that point, given the key pulmonary toxicities that David explained to you, and instead treat them with AVD without bleomycin to see whether you could achieve similar outcomes with a reduced toxicity profile.



Slide 32: How'd the PET2 Negative Patients do?

And what we see is that this was, indeed, a successful approach in that for those patients who did achieve a PET2 complete response, patients who were de-escalated to the AVD without bleomycin enjoyed excellent outcomes and, of course, had much lower rates of severe lung injury. Due to bleomycin pulmonary toxicity.



Slide 33: Brentuximab vedotin (Adcetris®): ADC (Antibody-Drug Conjugate)

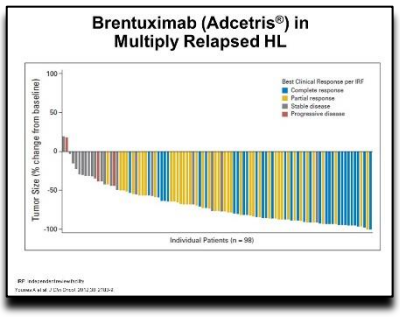
Certainly, the treatment of advanced stage Hodgkin lymphoma has moved on from ABVD and, really, that progress has been driven in part by an understanding of this important medicine, brentuximab vedotin (Adcetris®). Maybe David, if you could walk us through brentuximab or BV and talk to us a little bit about this drug and what it brings to the table.

Dr. Awad: Yeah, thank you. So brentuximab really changed the treatment of Hodgkin lymphoma for us; and by introducing a monoclonal antibody, but not only that, it is an antibody drug conjugate, which is the first in this disease state. And what that means is that we have a monoclonal antibody that binds to CD30, and CD30 is going to be found on the exterior of the Hodgkin lymphoma cells.

CD30 is just going to be the method to bring in this potent toxin that is bound to this CD30 monoclonal antibody or the brentuximab. Once CD30 makes connection with the monoclonal antibody brentuximab, that whole conjugated antibody is going to be taken up in a lysosome into the cell. That cell is going to start to break up that protein and start to reuse it and think that it is just a benign piece of trash. However, that's actually going to release that toxin that is bound to the antibody into the cell. And that toxin's going to be vedotin, which is a microtubule inhibitor.

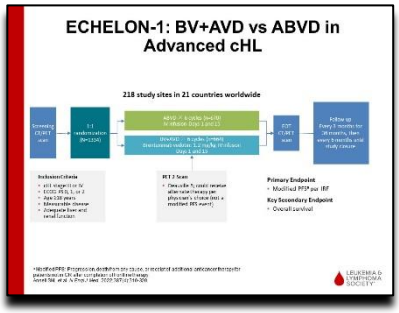
Vedotin will go in, and it will break down into, it'll break down further; and it'll disrupt the microtubules, and it'll disrupt mitosis in the cell. That will then cause that cell to fail and eventually die off. So, the way that I described it, we can think of it similar to a Trojan horse where you have a benign antibody just getting attached to the cell. And then once it gets inside the walls of the cell, it will then go in and release that toxic agent wreaking havoc and killing that cell ultimately.

Dr. Matasar: I love that visual of the Trojan piñata. You know, the idea that the cell's breaking that thing up and releasing MMA intracellularly leading to microtubule disruption is a very powerful mechanism and leads to very powerful results.



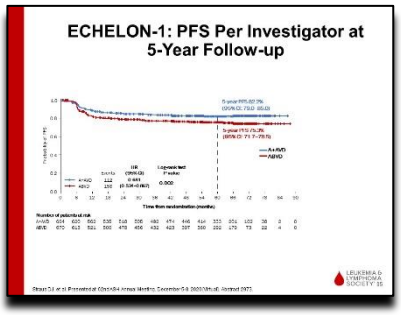
Slide 34: Brentuximab (Adcetris®) in Multiply Relapsed HL

And brentuximab was first developed as a treatment of relapsed Hodgkin lymphoma and even in patients who'd been failed by prior chemotherapy, stem cell transplants. It has very potent single-agent activity, as you see here with this waterfall plot, where the overwhelming majority of patients derive clinical benefit from receiving it as monotherapy.



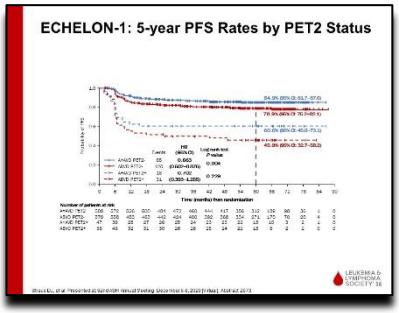
Slide 35: ECHELON-1: BV+AVD vs ABVD in Advanced cHL

So given that the potency of this medicine in relapsed or refractory Hodgkin lymphoma, we were eager to study it in patients with newly diagnosed Hodgkin's to see if including it in a treatment program could improve outcomes and, equally importantly, could enable us to eliminate the lung-toxic bleomycin from our treatment programs. And this study called ECHELON-1 was a globally conducted randomized trial to ask just that question of, can you treat people with brentuximab plus AVD instead of ABVD and achieve either equal or superior outcomes.



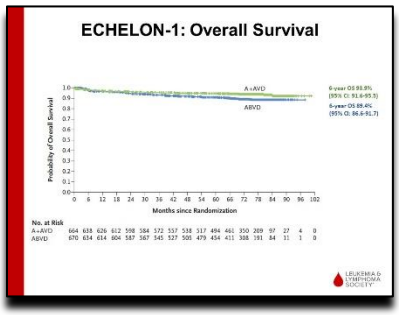
Slide 36: ECHELON-1: PFS Per Investigator at 5-Year Follow-up

What we learned early on with this study was that, indeed, there was an improvement in progression-free survival or PFS, meaning that fewer patients were relapsing at five years when they were treated with the brentuximab Canadian treatment program as opposed to traditional ABVD.



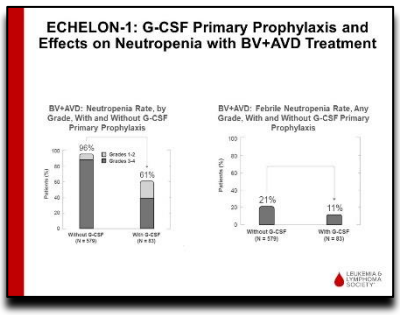
Slide 37: ECHELON-1: 5-year PFS Rates by PET2 Status

This was seen both in PET-positive as well as PET-negative patients. Importantly, ECHELON-1 did not build in any treatment escalation or de-escalation based upon the PET2 status; and while patients that were PET2-positive did have worse outcomes, as you'd expect compared to those that were PET2-negative, outcomes were better for both of those patient categories if they were being treated with brentuximab vedotin as part of the treatment.



Slide 38: ECHELON-1: Overall Survival

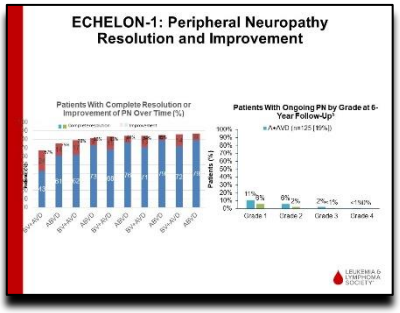
Importantly, it was more recently that we learned that not only was progression being delayed with inclusion of brentuximab, but indeed we were improving overall survival, which remains our gold standard for how we define standards of care in Hodgkin lymphoma. And with a detectable, statistically significant improvement in overall survival and concurrently giving a treatment that we know eliminates the risk of bleomycin pulmonary toxicity, this is the win-win that we were hoping for in writing and conducting the ECHELON-1 trial and really redefined brentuximab plus AVD as the standard of care for patients with advanced stage newly diagnosed classical Hodgkin lymphoma



Slide 39: ECHELON-1: G-CSF Primary Prophylaxis and Effects on Neutropenia with BV+AVD Treatment

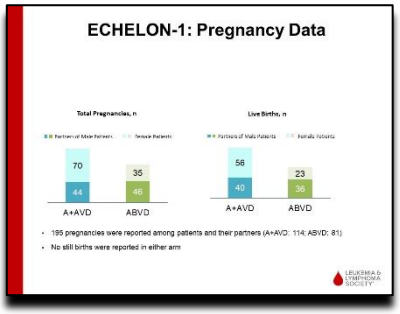
David mentioned before that we always use growth factor when we give escalated BEACOPP, given its increased myelosuppressive nature. We do also need to use growth factor prophylaxis when treating with the brentuximab plus AVD program because the DV is a little bit more myelosuppressive than bleomycin is. When we look at the

data from ECHELON-1, outcomes for those patients who were supposed to have received growth factor prophylaxis, but didn't, we saw that there was an increased risk of febrile neutropenia among those patients, really affirming our understanding that primary prophylaxis with growth factor is standard when administering the BV plus AVD treatment program.



Slide 40: ECHELON-1: Peripheral Neuropathy Resolution and Improvement

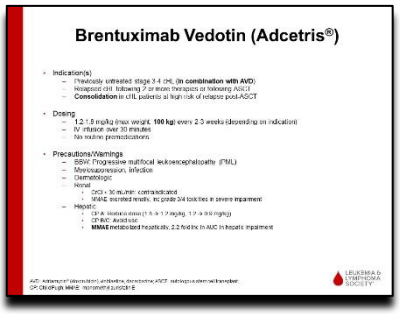
Brentuximab, as I've said, does have a little bit more myelosuppressive nature than bleo. It spares us the pulmonary toxicity of bleomycin, which is wonderful, but it does have its own toxicity profile; and as an antitubulin, as David showed you, it won't surprise you to hear that its chief toxicity is that of peripheral neuropathy. Fortunately, we learned from ECHELON-1 that that neuropathy tends to be mild, lower grade in severity, and tends to be reversible over time.



Slide 41: ECHELON-1: Pregnancy Data

We talked a lot about pregnancy and fertility considerations when we're administering treatments to Hodgkin lymphoma, you know, harkening back to those curves that I showed you at the outset only that it's a disease that can affect people during their fertile years.

When we changed treatments away from ABVD, we always want to requery this idea of are we jeopardizing fertility with these adjustments to the chemo 30 program? ECHELON-1 here offers reassurance in that we see that there was no difference detected in subsequent pregnancies or live births among those patients that were treated with brentuximab versus those receiving ABVD; and there were no differences in birth complications or birth defects in either treatment arm, thankfully.



Slide 42: Brentuximab Vedotin (Adcetris®)

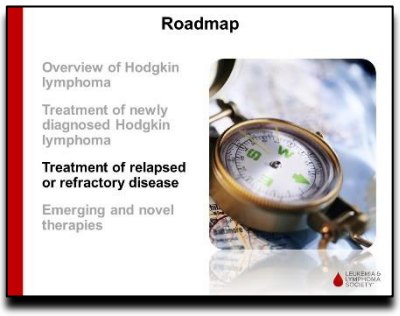
To talk a little bit more about BV in detail, why don't you help us here if you can, David?

Dr. Awad: Yeah, sure thing. So brentuximab vedotin has many different indications now, but specifically we'll focus on the classical Hodgkin's patients. So, in previously untreated Stage III and IV classical Hodgkin lymphoma, when in combination with AVD, as we already discussed,

also in relapsed classical Hodgkin's following two or more therapies or following autologous stem cell transplant, and then in consolidation in classical Hodgkin's patients at high risk of relapse post-transplant. Dosing is going to be 1.8 mgs/kg. You can go as low as 1.2 milligrams per kilogram. However, it's important that we cap the dose at 180 milligrams or at 100 kilograms to avoid further toxicity. And it will be given every two to three weeks, depending on the indication.

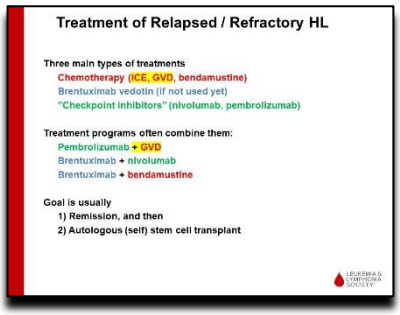
We give it as an IV infusion over 30 minutes, and there are no routine premedications. Generally, well tolerable infusion that is very uneventful. It does have some warnings that we have to think about including progressive multifocal leukoencephalopathy or PML. As we discussed, there is a higher risk of myelosuppression, which can cause infection. We do see sometimes some dermatologic toxicities as well. Does not need any renal dose adjustments, but rather it is contraindicated in patients who have a creatine clearance less than 30. And this is because that toxic metabolite, MMAE is excreted renally, and we do see more toxicities in patients who have more renal dysfunction since it'll accumulate.

Additionally, patients who have hepatic dysfunction who have Child-Pugh Class A, while we do have to dose reduce. If we're starting off at 1.8 milligrams per kilogram, we dose reduce to 1.2. And if we're starting off at 1.2 milligrams per kilogram, we're dropping it 0.9 milligrams per kilogram. And in general, we do have to avoid for Child-Pugh Class B and C. And that is because MMAE is metabolized hepatically, and we do see an increased AUC in patients who have hepatic impairment. So, we will expect more toxicities in those patients. So now I'll kick it back to Dr. Matt Matasar who will continue in our therapy for patients who have relapsed or refractory disease.



Slide 43: Roadmap

Dr. Matasar: Perfect. So and thank you for that. So we've summarized together here our treatment for early stage Hodgkin lymphoma and advanced stage Hodgkin lymphoma in the first-line setting. What about patients with relapsed or refractory disease?

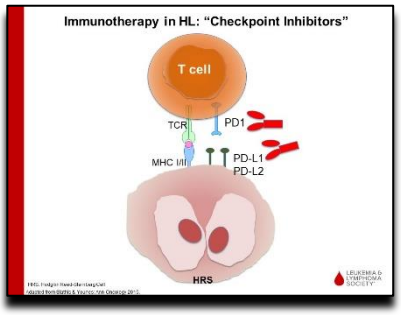


Slide 44: Treatment of Relapsed or Refractory Disease

And here there are a number of different approaches. The first thing to say, however, is to remember that the goal here is to achieve remission. And then for the majority of patients, as long as they're candidates for high-dose therapy, to then pursue cure with a consolidative autologous or from yourself, stem cell transplant. So, if you think of this as a multistep process, Step 1 is to get patients into remission again, or for the first time, if the first-line treatment failed, and then to consolidate a response to that to try to prevent it from ever recurring again.

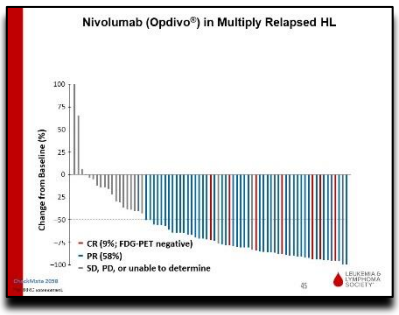
And you can populate different items into those different stages in the treatment program. We have chemotherapy programs that are noncross resistant with either ABVD or BV-AVD that we can use, such as ICE, which is ifosfamide (Ifex®), carboplatin (Paraplatin®), and etoposide; or the GVD program, which is gemcitabine (Gemzar®), vincristine, and dexamethasone (Decadron®) or bendamustine (Treanda®), which is a subtoxic chemotherapy as well. If patients didn't receive brentuximab vedotin as part of their first-line therapy, you can use BV either alone or in combination. And we have the family of medicines called checkpoint inhibitors, including both nivolumab (Opdivo®) and pembrolizumab (Keytruda®), both of which are very active in the treatment of patients with Hodgkin lymphoma. We often will use programs that combine these agents. We have data for the combination of pembrolizumab plus GVD.

We have data for brentuximab plus nivolumab. We have data for brentuximab plus bendamustine. And as is thematic across oncology, when you develop combination programs, you tend to add toxicity, but you also tend to augment activity.



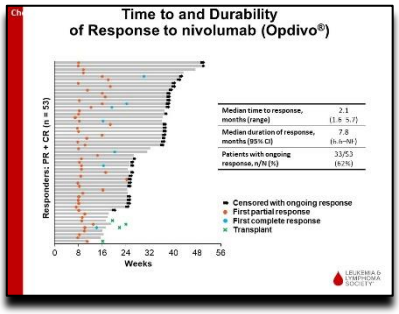
Slide 45: Immunotherapy in HL: "Checkpoint Inhibitors"

The importance of checkpoint inhibitors in Hodgkin lymphoma really can't be overemphasized, particularly in the relapsed/refractory setting. And we know that these drugs work by allowing innate immune recognition of malignant Hodgkin's Reed-Sternberg-like cells, and it can be either PD-1 or PD-L1-directed treatments, both of which are very active in the treatment of Hodgkin lymphoma



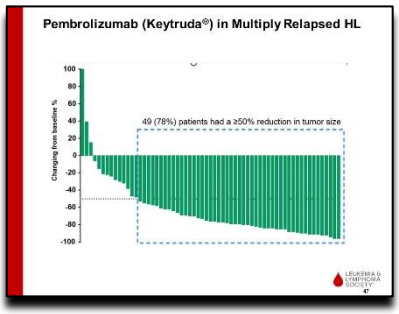
Slide 46: Nivolumab (Opdivo®) in Multiply Relapsed HL

Nivolumab was the first of these agents that was approved in relapsed/refractory Hodgkin lymphoma. And as you see with this waterfall plot, again, this is patients who have been failed by multiple prior treatments, including chemotherapy, brentuximab, many patients prior transplant. Again, overwhelming single-agent activity with the vast majority of patients deriving clinical benefit and more than half of patients actually achieving radiographic partial or complete response.



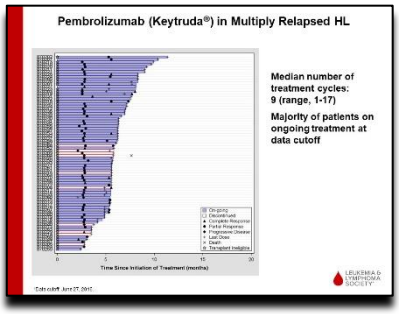
Slide 47: Time to and Durability of Response to nivolumab (Opdivo®)

Even more importantly than the response rates, radiographically, is the durability of disease control with nivolumab or other checkpoints. And we now understand full well that checkpoint monotherapy in this context can lead to very prolonged remissions that are either truly or functionally cures for many patients with relapsed Hodgkin lymphoma.



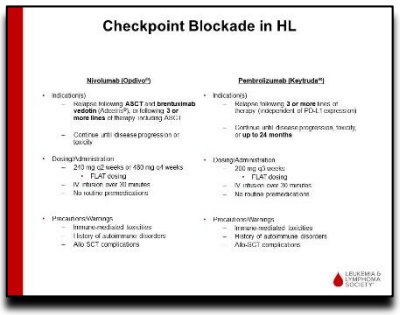
Slide 48: Pembrolizumab (Keytruda®) in Multiply Relapsed HL

Pembrolizumab is the other of these agents approved in Hodgkin lymphoma; and when you look at the waterfall plot for pembrolizumab monotherapy, it looks very similar to that which we saw with nivolumab, highlighting the similarity of these drugs in terms of their clinical activity.



Slide 49: Pembrolizumab (Keytruda®) in Multiply Relapsed HL

And similarly, when you look at the durability of response to pembro monotherapy, again, we see that this drug is capable of achieving extremely long durations of remission, even in very heavily pretreated patients.
Can you help us understand checkpoint blockade in a little bit more detail, David?



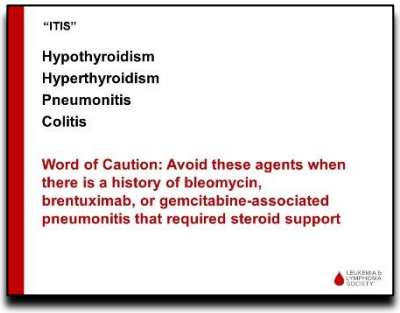
Slide 50: Checkpoint Blockade in HL

Dr. Awad: Yeah, of course. So, the two checkpoint inhibitors that we spoke about are nivolumab and pembrolizumab. And luckily, they're very similar from a toxicity perspective since they work on the same mechanism of action, which is PD-1 inhibitors. Nivolumab is currently indicated or FDA approved for relapse following autologous stem cell transplant and brentuximab or following three or more lines of therapy including transplant. And it's going to be continued until disease progression or toxicity. We give it as a 240 milligram infusion every two weeks. There's also now dosing for every four-week dosing where we just double the dose to 480 milligrams every four weeks.

It's important to note that in adults these are flat doses. So, no matter how big or small you are, you'll get either 240 every two weeks or four 80 milligrams every four weeks. It's given as a simple IV infusion over 30 minutes, and there's no routine premedications.

Generally going to be a well-tolerated infusion. Does have warnings and precautions including immune-mediated toxicities. There's caution in patients who have history of autoimmune disorders. And then there is some data that shows that patients who will go on to allogeneic stem cell transplant will have further complications. Likewise, pembrolizumab is FDA approved in relapsed setting following three or more lines of therapy, which is independent of their PD-L1 expression.

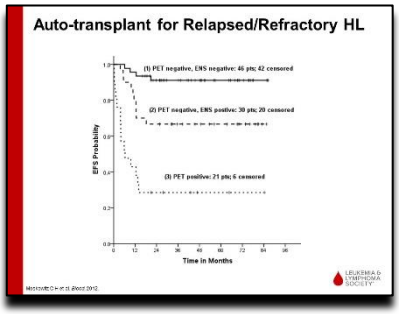
And we will continue until disease progression or toxicity or up to 24 months. Pembrolizumab is going to be administered as 200 milligrams every three weeks; and, again, this is flat dosing. It's given as an IV infusion over 30 minutes without any routine premedications. So like nivolumab, generally well-tolerated infusion without any reactions. And it does have the same warnings and precautions as nivolumab.



Slide 51: "ITIS"

So delving a little deeper into these immune-mediated reactions, we think of these as the -itises. So, hypothyroidism. Hyperthyroidism, pneumonitis, and colitis; and it can really be any immune-mediated reaction to any organ of the body. Typically, this will start off as simple as a skin toxicity or as GI toxicities, as colitis but then can, as therapy gets longer and longer, you'll see more diverse reactions to different types of patients. As a word of caution, avoid these agents when there's a history of bleomycin, brentuximab, or even

gemcitabine-associated pneumonitis that required steroid support since there's a high association with that patient developing later pneumonitis.

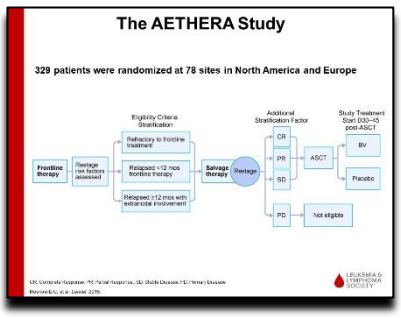


Slide 52: Auto-transplant for Relapsed/Refractory HL

So now taking it back, we can now talk about more of these, more data associated with relapsed/refractory Hodgkin lymphoma.

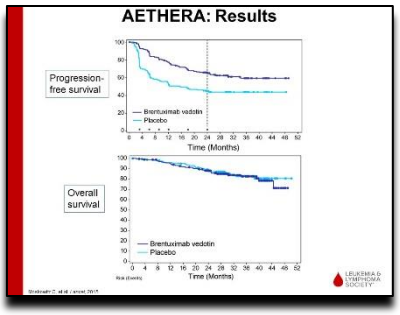
Dr. Matasar: Thanks, David. So, as I said, it's a multistep process for patients with relapsed/refractory disease. Step 1 is to get them into remission, and then Step 2 is to try to consolidate that response. And we typically do that with high-dose therapy or what's called an autologous stem cell transplant. And we know that an autotransplant can cure many patients with relapsed or refractory Hodgkin lymphoma. We know that the likelihood of cure is very strongly influenced by the quality of response to second-line therapy.

And you see here that patients who achieve a PET-negative response, most of those patients will be cured, even for those patients who had higher-risk disease at time of relapse. Whereas those patients who were still PET-positive going into an autotransplant are at much higher risk of subsequent relapse.



Slide 53: The AETHERA Study

The question of whether we can further enhance outcomes for patients undergoing consolidative auto transplant is an important one; and part of that answer is yes, that we now understand on the basis of the AETHERA trial that patients can receive post-transplant maintenance therapy with Brentuximab to improve the durability of response to second-line therapy. And patients in the AETHERA trial were randomized to either receive BV maintenance or not following a transplant.

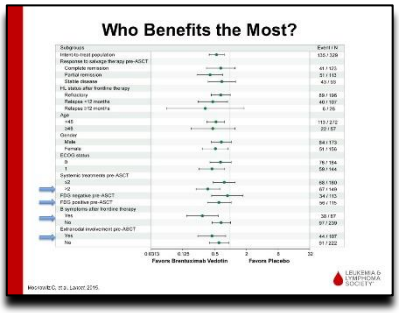


Slide 54: AETHERA: Results

And we looked at risk factors to try to understand which patients may derive incremental benefit from maintenance brentuximab vedotin.

And what we saw from the AETHERA trial is, indeed, progression-free survival is significantly improved by the administration of post-transplant brentuximab. Importantly, however, we continue to not see an improvement in overall survival for this treatment approach which is, perhaps, perplexing, but when taken into context may make more sense. We don't believe that brentuximab is likely to cure many patients in relapsed or refractory setting, but it is a very powerful treatment and further reducing the presence of residual disease.

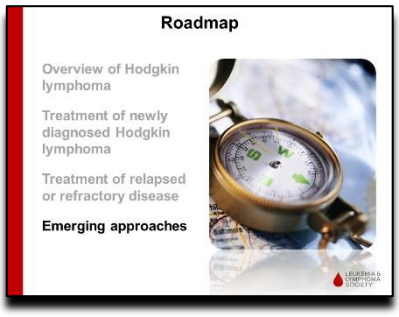
That disease will subsequently relapse at some point, so the overall survival outcomes were likely to be similar with or without maintenance therapy. But the administration maintenance allows us to successfully defer or delay that subsequent relapse for those patients in whom relapse occurs, trading some short-term immediate toxicity with BV for more sustained disease control.



Slide 55: Who Benefits the Most?

Understanding that there is toxicity from brentuximab, including the peripheral neuropathy most prominently, we want always to take that Goldilocks approach of wanting just right. So, can we identify patients who derive more benefit from maintenance brentuximab and thus may be worth the effort and the potential toxicities of maintenance therapy? The answer is yes. It appears that patients who have higher-risk disease going into their transplant derive more incremental benefit from maintenance BV. And when you look at the traditional risk factors of line of therapy, PET positivity going into a transplant, the presence of B symptoms at the time of relapse, the presence of extranodal disease prior to transplant, these recognized risk factors identify patients who derive greater benefit from BV maintenance.

And it's really those patients that we prioritize the use of brentuximab as maintenance treatment.

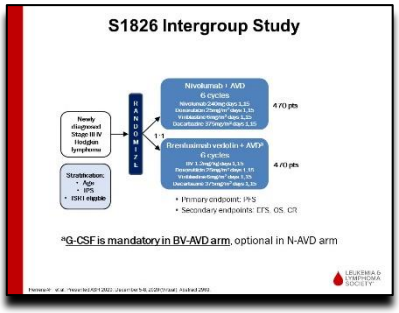


Slide 56: Roadmap

So that's, there's obviously a lot that we could talk about in the context of relapsed/refractory disease, but if we leave you with an understanding of the importance of brentuximab, the power of checkpoint inhibitors, and the ongoing clinical relevance of consolidative transplant with or without maintenance, then we're at a good point. I do want to end our time by focusing on emerging treatment approaches, particularly emerging strategies for patients with newly diagnosed disease in our ongoing efforts to cure more people with less toxicity the first go-round.

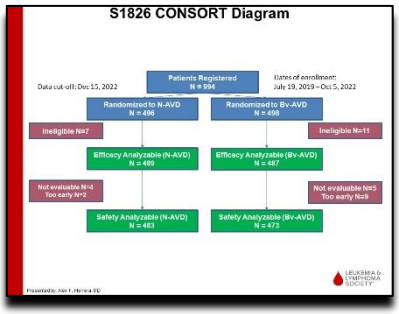
Slide 57: Moving Treatment of Newly Diagnosed HL Forward

So, you know, we've already shown you how powerful brentux-, the checkpoint inhibitors pembrolizumab and nivolumab are; and David detailed for you their relatively favorable toxicity profile. So given the activity I showed you of checkpoint inhibitors, pembrolizumab and nivolumab as monotherapy in the relapsed or refractory setting, and given the relatively favorable toxicity profile that David detailed for you, it should make sense to you that we're evaluating the incorporation of checkpoint inhibitors into first-line therapy for patients with newly diagnosed classical Hodgkin lymphoma



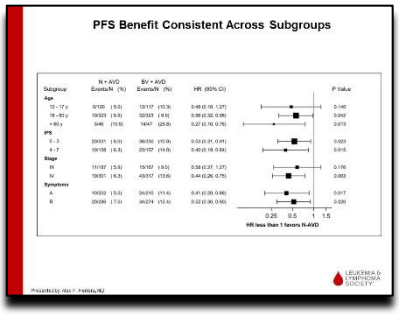
Slide 58: S1826 Intergroup Study

And I'm going to show you three studies attempting to answer this question of can we improve outcomes with incorporating checkpoint inhibitors into first-line therapy? The first is the Intergroup Study 1826 which takes patients with advanced stage Hodgkin lymphoma and randomizes them in a one-to-one fashion to receive either the ECHELON-1 program of brentuximab plus AVD or to replace brentuximab with nivolumab plus AVD for these six cycles.



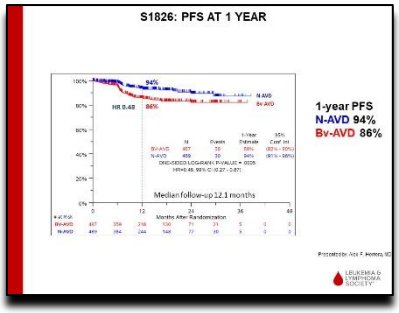
Slide 59: S1826 CONSORT Diagram

Here's the CONSORT diagram for this study, and we've had data cutoff already occur; and we're starting to get clinical readout of this study. You see that almost a thousand patients were enrolled in this important trial, most of whom ended up being evaluable both for efficacy as well as safety.



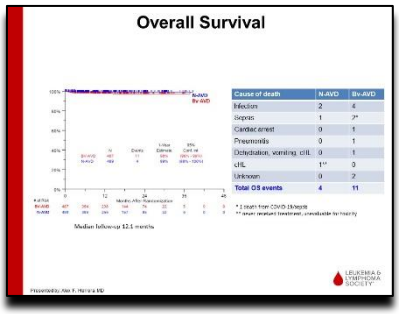
Slide 60: PFS Benefit Consistent Across Subgroups

The data are still relatively immature, but still provocative at this early point where we see that there is an improvement in progression free survival across risk categories and patient subsets. And that includes both younger and older patients. It includes patients with lower or higher risk disease via the IPS prognostic model and the presence or absence of B symptoms.



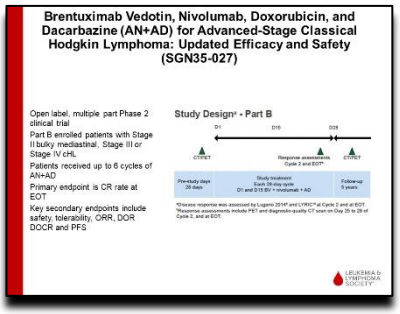
Slide 61: S1826: PFS at 1 year

Shown here are the Kaplan-Meier curves for, again, an early cut point progression-free survival, demonstrating an improvement that has already achieved statistical significance in progression-free survival at that early timepoint for the patients treated with nivolumab-based treatment as opposed to rituximab-based treatment.



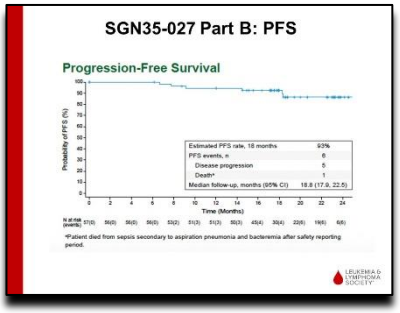
Slide 62: Overall Survival

We do not yet have any evidence that overall survival is improved in the patients treated with checkpoint inhibitor; and I've already told you that we use this as the gold standard to define preferred therapy. So, on the basis of this, we do not yet adopt nivo plus AVD as the active standard of care; but the data are very encouraging and quite provocative, even in this overall patient population presentation. It's worth pointing out that we now have data as well in the subset of older patients where it does appear that the outcomes are dramatically improved with the incorporation of nivolumab as opposed to brentuximab, suggesting that we may already have a new standard of care with checkpoint inhibitors as part of first-line therapy in older patients.



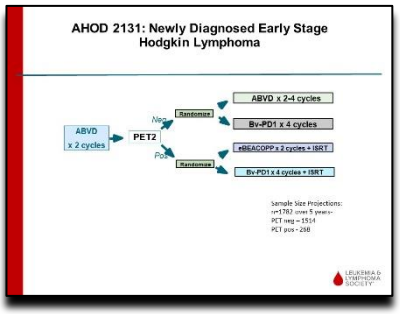
Slide 63: Brentuximab Vedotin, Nivolumab, Doxorubicin, and Dacarbazine (AN+AD) for Advanced-Stage Classical Hodgkin Lymphoma: Updated Efficacy and Safety (SGN35-027)

1826 shows you the strategy of nivo versus brentuximab as part of the treatment. What about having your cake and eating it too? What about trying to use brentuximab and nivolumab in combination with doxorubicin and dacarbazine in advanced stage disease? And this is the strategy being adopted by the trial SGN35-027. This is a single-arm Phase II study evaluating the safety and activity of that four-drug combination in patients with advanced stage or, Stage II bulky disease. I've shown you the study design here just to give you a sense for how this work is being conducted. This is research that is ongoing.



Slide 64: SGN35-027 Part B: PFS

We do have some earlier readout from this trial, however, and given that it is a single-arm Phase II study, we won't have the ability to compare it to standards of care. But at 18 months, an estimated progression-free survival rate of 93% has been reported with very few events of either disease progression or death, suggesting that this four-drug combination is, indeed, highly active in patients with newly diagnosed Hodgkin lymphoma.



Slide 65: AHOD 2131: Newly Diagnosed Early Stage Hodgkin Lymphoma

The third study, and this is a study that is currently open and accruing at our center and nationally being co-led by the adult cooperative groups as well as the pediatric cooperative groups taking patients with early-stage Hodgkin lymphoma and taking the strategy as follows. Everybody starts with two cycles of ABVD chemotherapy and a PET2 is performed, a PET scan after these first two cycles.

For those patients who are PET-negative at that point, which is the majority of patients, such patients are then randomized to complete ABVD chemotherapy, according to baseline risk. Or instead, to receive only brentuximab plus checkpoint inhibitor for four cycles with no additional chemotherapy. For patients who are PET2-positive, a Deauville score of 4 or 5, such patients are being randomized to receive intensified chemotherapy with escalated BEACOPP followed by radiation therapy or, instead again, to take a chemotherapy-free approach. Instead of using brentuximab plus checkpoint inhibitor for four additional

cycles, followed by involved site radiation therapy. This study will take a long time to achieve. It's intended to enroll almost 2,000 patients, likely taking approximately five years, but it's a very ambitious attempt to ask the question of whether we can leverage brentuximab, checkpoint inhibitors to limit therapeutic exposure to chemotherapy in the first-line setting and hopefully improve outcomes concurrently.

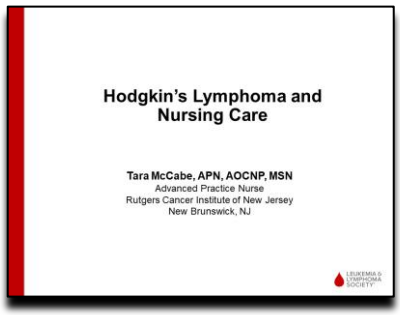
Slide 66: Things are Looking Up

So in summary, we've really come a long way with Hodgkin lymphoma. We led off by talking about this disease, understanding of its biology and its clinical characteristics. A recognition that it is a modern success story, even where we stand now, where the majority of patients will achieve long-term disease control or be cured. And yeah, we recognize that there are opportunities to drive progress further forward, both by improving and increasing our cure rate, as well as by limiting short- and long-term toxicities of our treatments.

An understanding of these drugs, their specific pharmacologic properties, their toxicities, and the benefits that can be accrued to patients with their safe and careful administration is critical to the shared care of patients with Hodgkin lymphoma. And hopefully you've heard from and David today, the critical importance of partnership between medical oncologists and our partners in pharmacy in a shared care delivery model to optimize results and outcomes for our patients with Hodgkin lymphoma.

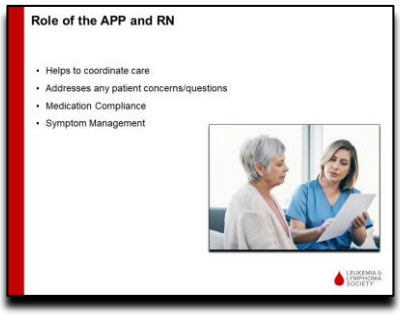
Slide 67: Thank You

Thank you Dr. Matasar and Dr. Awad for your very clear & informative presentations.



Slide 68: Hodgkin's Lymphoma and Nursing Care

Lauren Berger: I am now pleased to introduced Nurse Practitioner Tara McCabe to talk about the nurse's role in caring for patients with Multiple Myeloma. Ms. McCabe is an Advanced Practice Nurse at The Rutgers Cancer Institute of New Jersey in New Brunswick, NJ, Nurse McCabe. Nurse Practitioner McCabe.



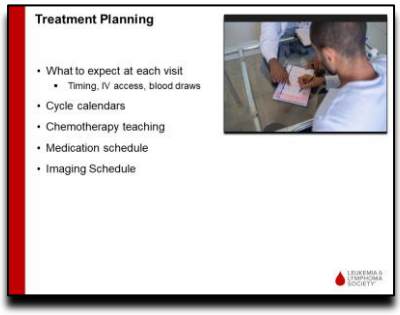
Slide 69: Role of the APP and RN

So, to discuss the role of the nurse practitioner and the registered nurse in the treatment of Hodgkin lymphoma, they help to coordinate care. This includes setting up patients for appointments, scans, follow-up visits, bloodwork, and scheduling the actual chemotherapy. They're here to address any patient questions and concerns. They're here to help patients with medication compliance and symptom management.

Slide 70: Initial Diagnosis

At the initial diagnosis or the consult visit, the nurse or the nurse practitioner will review the diagnosis with the patient. We'll ask them if they have any questions regarding their diagnosis. We ask if they understand what the physician or the provider has explained to them. We will then help with the treatment plan discussion after the physician has said what the plan is going to be. We will help them to understand what medications they're getting, how often they're going to be getting them. We'll address again any questions that they may have regarding their diagnosis. At these initial visits, they can be somewhat overwhelming for patients and family members, so we want to make sure that we really take the time to address their needs and make sure that they are understanding everything appropriately.

We'll do a brief overview of the review of medications and side effect profiles, depending on the treatment that is chosen; and one of the biggest things that we will address at these visits is we will make sure that they have financial and social support. We want to address their social system, make sure that they have good support systems that are going to be able to bring them to their treatments, help them when they are at home. We want to make sure that they have the financial resources that come along with treatment to pick up medications that may be prescribed for treatment, the resources to be able to get to and from treatments. We will, at this visit, loop in our social workers and our financial counselors to make sure that everything is set on that end.

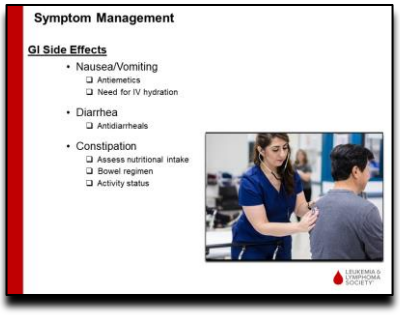


Slide 71: Treatment Planning

Nurses and nurse practitioners are also instrumental in the treatment planning. We will go over with patients what to expect at each visit. This may include how long they'll be here for their treatment. We will assess their IV access points, making sure that their veins are good enough for chemotherapy and/or immunotherapy. We may have to talk to them about getting a central line if appropriate. We'll talk to them about blood draws, what tests we're doing before each treatment, what tests we may be doing in between each treatment. We will also provide patients with calendars of their cycles, so they know when they're going to be at the treatment center, how often they're going to be at the treatment center, and what drugs are going to be administered during the cycles.

We will do an in-depth chemotherapy teaching. This will include the most important side effects and the most common side effects that patients will experience while they're receiving treatment. We'll discuss hair loss with them, and any type of support they may need such as cranial prosthesis or wigs. We will go over what to expect with each chemotherapy drug and what each drug is being used to target. We'll talk to them about the medication schedule, whether it be the chemotherapy or immunotherapy itself. We will also talk about any supportive medications that patients will be getting throughout their treatment.

We'll also be going over their imaging schedule and how often they will be getting PET scans, CAT scans. Sometimes patients will also get echocardiograms in between treatments. We'll talk about the importance of each of those tests and what we're looking for when we do those tests.



Slide 72: Symptom Management

One of the biggest roles of nurses in symptom management is GI side effects. These are commonly the most experienced side effects while patients are undergoing treatment. We want to make sure that we discuss nausea and vomiting and what the role is for antiemetics or otherwise known as antinausea medications. We will usually commonly send at least one prescription medication to a patient's pharmacy. We will discuss the role of anticipatory nausea.

This, this can happen when patients know they're coming in for treatment, so we will discuss with them taking an antiemetic before they come for treatment. We want to

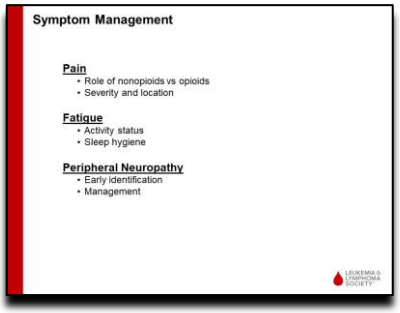
assess, if they are having nausea and vomiting, how much they're having, and also the need for IV hydration if they are not eating because of the nausea. If they are having active vomiting, we'll talk to them about when they need to come in to have their electrolytes checked and if they do need some IV hydration.

This is one of the biggest concerns about, that patients have when they are starting treatment is, "Am I going to be nauseous? Am I going to be vomiting?" We want to make sure that they understand that we give premedications before their treatment, and we will also give them something at home to reduce this risk.

Diarrhea is also a common side effect. We will talk to them about staying well-hydrated. The role of antidiarrheals, whether prescription or nonprescription. We usually like to start with over-the-counter, but if we do need to send a prescription, we will.

We will also talk to them about constipation. Usually, patients will experience constipation due to the antinausea medications that are prescribed to go along with treatment. We want to make sure that we're telling them to increase their oral intake of water. We want to assess their nutritional intake to make sure they're getting enough fiber. We do want to talk to patients about starting a bowel regimen before treatment. Some examples would be to use over-the-counter laxatives and stool softeners, just to make sure they are not getting constipated, and we prevent it from happening.

We also want to address their activity status. We want to make sure they're as mobile as possible and walking around just to make sure that the bowels stay active and don't slow down.



Slide 73: Symptom Management

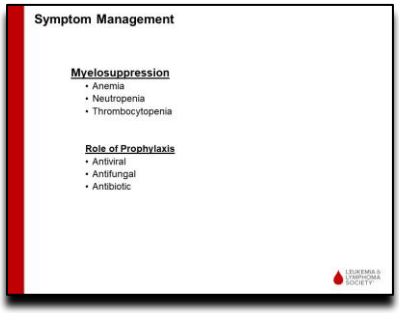
We want to talk to them about pain that they may experience. Hodgkin lymphoma can be a very bulky disease. There can be some pressure points and pain that they experience upon diagnosis. We'll talk about the severity and the location of the pain, what their triggering factors are, what makes things worse or better. We'll talk about the role of nonopioids and opioids when they're appropriate. We try to have patients start off with nonopioid therapy first, over-the-counter medications, physical therapy, warm packs, cold packs. But if the pain is unrelieved, then we'll counsel them on safe use of opioids.

We want to assess their activity status again because fatigue is a very common side effect of all chemotherapy and immunotherapy. We want to make sure that they are remaining as active as possible. We want to talk to them about good sleep hygiene, making sure

they're getting enough sleep. If they're not sleeping well at night, we want to make sure that they're resting throughout the day.

And one of the biggest things that we like to discuss in terms of symptom management is peripheral neuropathy. Peripheral neuropathy is experienced by some patients that are receiving some of the regimens for Hodgkin lymphoma. Early identification is key. We want to identify those patients that may be predisposed to peripheral neuropathy, such as patients that are smokers, patients that are diabetics, patients that have peripheral vascular disease. Those are the patients that we want to keep a close eye on. And when we manage peripheral neuropathy, we want to encourage patients to be honest with us. We want to assess at each visit to make sure that it's not getting any worse because then we will talk about dose reduction in some of the chemotherapy that they're getting to help alleviate the symptoms that they're feeling.

The peripheral neuropathy, we want to have patients tell us, are they having any numbness and tingling in their hands and feet? Are they having any weakness in their legs? Usually, we'll have a patient sign their name in front of us or pick up an object such as a penny or a paperclip. We will also have the nurse assess the patient unbuttoning their shirt when they go to access their port just to make sure that they are not experiencing any weakness or any loss of sensation. We sometimes will get our pain and palliative team involved to manage severe peripheral neuropathy to make sure that their pain is well-controlled so that we can finish their treatment on time and not have to take any breaks in their therapy.



Slide 74: Symptom Management

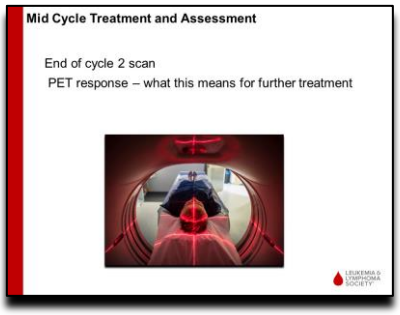
Very important when it comes to symptom management is the role of myelosuppression. We want to make sure our patients understand that they may experience low blood counts; and what that means is anemia, which is a low red blood cell count and what comes along with that. We want to make sure that patients understand they may be more tired more frequently while on chemotherapy or immunotherapy because of the anemia. Their red blood cells will drop, causing them to have some more fatigue. They may experience side effects such as heart racing or heart palpitations. We want to make sure they understand that this is normal and expected.

One of the very important things that we also have to discuss with patients is neutropenia, which is a low white blood cell count. This is when they are prone to infections and susceptible to getting sick. We want to make sure they understand that when their white count is at a certain level, the precautions that they do have to take, whether it's masking,

avoiding crowds, following an antimicrobial diet, meaning that they are not eating raw or undercooked food. We want to make sure that their fruits and vegetables are washed very good, and avoid anything that can introduce bacteria.

Thrombocytopenia, which is a low platelet count, platelets are the component of the blood that help prevent patients from bleeding. Your platelets may also drop while on treatment, so we want to make sure they understand thrombocytopenic precautions such as using a soft toothbrush, using an electric razor, avoiding flossing of the teeth, making sure that they understand they may bruise a little easier, so not to be alarmed if they see a lot of bruising.
We want to make sure they're looking out for any signs of petechiae, which are small little dots on the skin, that can alert us that the platelets are low.

We will have patients come in for blood checks, sometimes between cycles. Depending on what their blood counts look like, they may have them twice a week, they may have them once a week, or they may not need to come in at all, but it is something that we monitor very closely. We will discuss with them the role of the prophylactic regimen. This may include antivirals which will help prevent them against viral infections, most importantly the shingles infection. We may talk to them about starting an antifungal, and we may talk to them about starting an antibiotic. The antiviral, the antifungal, and the antibiotic are all used in combination to help prevent patients from getting opportunistic infections such as pneumonia, viral infections, and bacterial infections.

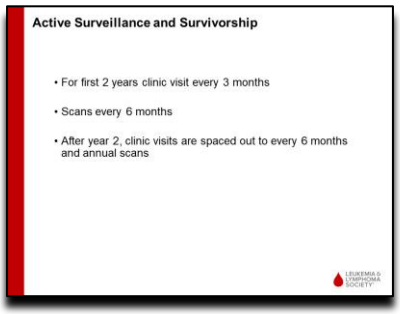


Slide 75: Mid Cycle Treatment and Assessment

Nurse will also play an instrumental role in the midcycle assessment. At the end of Cycle 2, depending on what treatment regimen the patient is getting, whether they're on standard of care or a clinical trial, most often they will get a PET or a CAT scan at the end of the second cycle. Depending on that scan response, this will help us determine what it means for their further treatment. We want patients to understand what the physician or the provider is explaining to them. We want to make sure they understand what their results mean for the future of their treatment.

Slide 76: End of Treatment Planning and Assessment

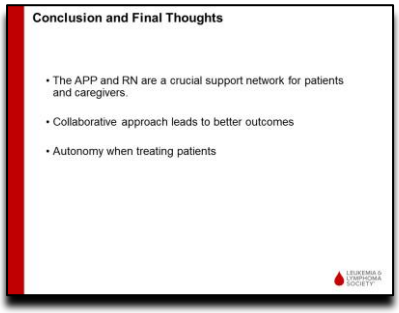
We are also, as nurses, very important in the end-of-treatment planning and assessment. At the end of their treatment, they will get another PET or CAT scan. We will help the patients understand what this means for their future. We'll talk about, if the patient has a central line, when they would get that central line removed. Usually, if patients are going to relapse, it's within the first year; so, we would like the patient to understand that we want to keep that central line in for at least a year. We'll talk about what it means to maintain that central line and how often they will have to come in to have it flushed and maintained. We'll also start the conversation at the end of treatment about the role of active surveillance and survivorship.



Slide 77: Active Surveillance and Survivorship

What does active surveillance and survivorship look like from a nursing perspective? We'll have the patient understand that for the first two years they will come to the clinic every three months. We will make sure they understand that they know they're going to be getting scans every six months for the first two years.

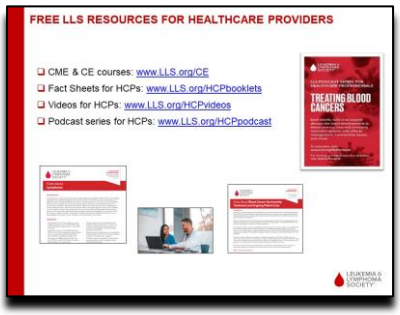
After year two, clinic visits are then spaced out to every six months with annual scans unless clinically warranted. We will also talk to them about routine health maintenance. We want to make sure that they understand that they should be following with their primary care physician, maintaining a good vaccine status. For females, making sure that they're attending their GYN appointments, getting annual PAP smears, mammograms. For males, making sure that they are following with their PCP, getting PSAs if they need them, and also regular health maintenance.



Slide 78: Conclusion and Final Thoughts

So, just in conclusion and some final thoughts, the advanced practice provider, such as nurse practitioners and registered nurses, are a crucial support network for patients and caregivers. We are the ones that provide support to the physicians and practice collaboratively with them to ensure that the patient has a positive and compassionate experience. It has been shown that collaborative approaches and teamwork leads to better outcomes for patients, and we have some autonomy when treating these patients to make sure that they are receiving the best possible care.

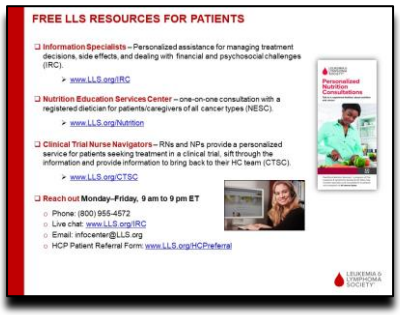
Thank you so much for allowing me to go through this with you. And, Lauren, I will turn it over to you.



Slide 79: Free LLS Resources for Healthcare Providers

Lauren Berger: Thank you, Nurse Practitioner McCabe, and again thank you to Drs Matasar and Awad.

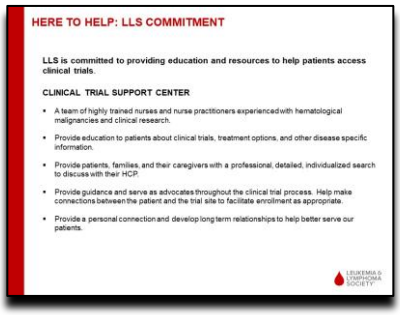
I am now pleased to share free resources for You & Your patients. The Leukemia & Lymphoma Society offers free CE & CME online and in-person regional programs, as well as a podcast channel for Healthcare Professionals, where you can listen to discussions on treatment, side-effect management & more. New & interesting topics are added every few wks. Access these as well as Videos & Fact Sheets for HCPs @ www.LLS.org/CE



Slide 80: Free LLS Resources for Patients

LLS Information Specialists are highly trained Oncology Social Workers & Nurses who provide accurate, up-to-date disease, treatment & support information, including financial. Patients can Contact them Directly, or you can complete a Referral Form. Information Specialists can also help you order Free Copies of booklets to Give to your patients and we also offer Free 1 on 1 Nutrition Consultation with our Registered Dietitians by phone - for patients of All Cancer Types & ages. Our Clinical Trial Support Center Nurse Navigators are RNs and NPs w/expertise in blood cancers.

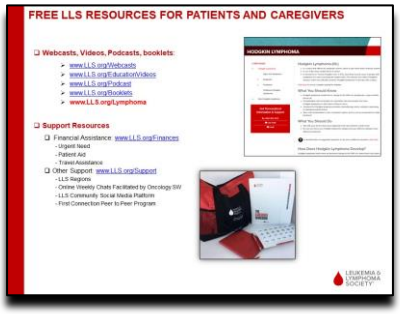
CTSC Nurse Navigators work 1 on 1 with patients, via telephone, to provide user friendly information, help find appropriate clinical trials, personally assist them throughout the clinical trial process and provide information for the patient to bring back to their Healthcare Professional. They also work with Healthcare Professionals. This is a unique service from LLS. I hope you will consider all of these Specialists an extension of your team.



Slide 81: Here to Help: LLS Commitment

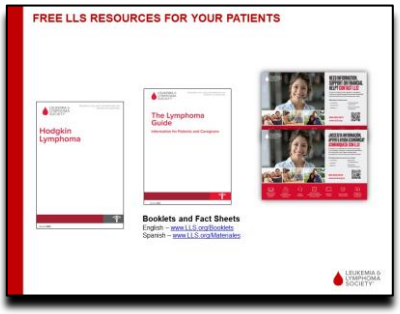
Here is a brief overview of the CTSC Process for Supporting Patients.

The Goal is not to enroll every patient into a trial, rather to increase opportunities for participation by facilitating informed decision making & minimizing logistical barriers for the patient. They work in collaboration with the patient's healthcare team to decide if a clinical trial is right for them. Ultimately, they educate, support, and empower patients to be active participants in and have control over their treatment decisions.



Slide 82: Free LLS Resources for Patients and Caregivers

LLS offers blood cancer disease specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts and booklets. I encourage you and your colleagues to stay up to date on the availability of LLS' Financial Assistance programs, and other resources, using links in these slides.



Slide 83: Free LLS Resources for Your Patients

Through targeted and culturally appropriate programs and services, we are committed to addressing needs of minoritized communities impacted by a blood cancer and those facing barriers to optimal care. We are increasing resources that provide education on health equity and/or are designed to support groups that experience health disparities and access – as well as resources for healthcare providers who serve groups that experience health disparities. Our materials are available in English & Spanish and our Information Specialists and other Specialists, consult with patients in additional languages.

Slide 84: Thank You

I hope this information will be helpful as you care for your patients. If you would like more information for yourself or support for your patients, please contact an Info Specialist at LLS at 800.955.4572 www.LLS.org/support.