PNH Highlights at ASH 2021 – Transcripts

Hello. I am Carlos De Castro. I am from Duke University in Durham, North Carolina. Today, we are going to be talking about the PNH highlights that were shown at the 2021 ASH Annual Meeting.

To start out with, let's just briefly describe what is PNH. Paroxysmal nocturnal hemoglobinuria, or PNH, is a rare and acquired blood disease characterized by hemolytic anemia, bone marrow failure, thrombosis, and fatigue. It is caused by two things and they can occur in either order.

There has to be a sporadic mutation of the TGA gene which affects one or more hematopoietic stem cells, and these are called defective PNH stem cells. Then there's a process that leads to the multiplication and expansion of these defective stem cells. Currently, there are three FDA approved treatments for PNH and this includes pegcetacoplan, eculizumab, and ravulizumab. Additional treatments, for example, iptacopan and pozelimab are currently in development. And there's others that are also in development.

Since it's a rare condition data presented at large medical conferences, like Ash 2021, can get overlooked. The Ash meeting is the American Society of Hematology. It's held every December and this year it was held in December 11th through 14th, 2021 in Atlanta, Georgia. And it was both live and virtual. It's the largest gathering of clinical research on hematological disorders and hematological cancers. And the abstracts are published in the journal, Blood.

We'll take a few of these abstracts that were focused on clinical aspects of PNH. The first one we'll look at is the drug called, pegcetacoplan. Pegcetacoplan is a C3 inhibitor and the abstract presented was on the phase three PRINCE study, which is evaluating the efficacy and safety of pegcetacoplan compared to standard of care in patients who are complement-inhibitor naive.

Fifty-three patients were in the study. They were randomized two to one to receive either pegcetacoplan or standard of care. And the co-primary endpoints of the study were hemoglobin stabilization and change in baseline LDH levels. In this study, what was demonstrated was that pegcetacoplan was superior to standard of care in both co-primary endpoints.

Hemoglobin stabilization occurred in 85.7% of the PEG treated patients compared to zero of the standard of care patients through week 26. In addition, pegcetacoplan patients showed superior reductions in mean LDH levels from baseline to week 26, compared to the standard of care patients. Patients with PNH that are naive to complement inhibitor treatment demonstrated meaningful hematological clinical improvements following 26 weeks of PEG treatment.

What this study suggests is this drug, which is FDA approved now is effective and safe for PNH patients who have not received any complement-inhibitor treatment.

The next abstract we will look at as a summary of a post-hoc analysis of the PADDOCK, PALOMINO, and PEGASUS trials using pegcetacoplan, and this was not restricted to naive or complement-inhibitor treated patients. They had to have low hemoglobin levels, but they could also have base near normal baseline hemoglobin levels. And all of these were the hope would

result in further clinical improvements in relevant PNH parameters. And what was seen is a substantial proportion of patients achieved and maintain good, major, or complete hematological responses to pegcetacoplan suggesting that pegcetacoplan can lead to very sustained improvements in hematologic parameters.

PEGASUS data also demonstrate a correlation of improved hematologic response category with meaningful improvements in quality of life as measured by the FACIT-F or FACIT-Fatigue score. And we'll look at that FACIT-Fatigue score later in this talk. So these post-hoc analysis further established the safety and efficacy of pegcetacoplan as a treatment for PNH.

Finally, there was an abstract that looked at the pegcetacoplan extension study. So with all these studies that were going on, once they hit their endpoint date, patients were allowed to roll over and get the pegcetacoplan no matter what arm they were on. So now 160 adult patients who have completed the previous PEG trials, which included PADDOCK, PHAROAH, PALOMINO, and PEGASUS, and now the PRINCE trial were put on this. The aim is to determine the long term safety and efficacy of PEG for PNH treatments, as well as to evaluate treatment regimen to address acute hemolytic events in these patients.

This study will continue to monitor safety outcomes such as the current and the severity of these events within a two year timeframe from baseline. And we're hoping we're going to have results of this in 2022. The next abstract we'll look at is the long term survival benefit of eculizumab. Eculizumab is a monoclonal antibody that targets C5, and it was the first FDA approved drug for treating PNH, which occurred in 2007.

In this study, they looked at the international PNH registry and compared the baseline characteristics and overall survival of a large international cohort of patients who were either treated with eculizumab or those who were never treated with eculizumab. Compared to the never treated patients who had been treated with eculizumab usually had an LDH which was greater than 1.5, the upper of normal and fewer of these patients had clone size less than 10% in their granular sites or history of bone marrow failure. Using statistics and a univariate Cox proportional hazard ratio for mortality, what was shown was that those that got treatment with eculizumab versus the never treatment had a hazard ratio of 0.48, which indicates a 52% increase in survival in the treated group.

This is a additional evidence along with two previous publications that eculizumab improved survival compared to no treatment in PNH. From the same study, this is, again, looking at the patients who had a high degree of disease activity at baseline. And you see compared to those who had a high degree, and those who didn't have a high degree, you got the same survival benefit, and it was actually bigger in those that had a high degree of disease activity from the start. But either way, there was still a survival benefit, whether you had a high degree of activity or you didn't have a high degree of activity at baseline.

Another study looking at patients with PNH showed that LDH reductions with treatment are strongly associated with improvements in fatigue and quality of life. So they were looking at the relationship between clinical outcomes with fatigue and quality of life. And this was measured again by the FACIT-F, or FACIT-Fatigue score, and the EORTC Quality of Life Questionnaire.

And these are patients who are all receiving C5 inhibitor therapy.

What the data showed was that reduced levels of LDH at day 183 were clearly associated with improvements in FACIT-F in both treatment groups, but there was no such association with improvements in hemoglobin level. So the FACIT-F level shows that fatigue gets better as your LDH goes down, indicating that as you control hemolysis your fatigue will get better, but that doesn't correlate necessarily with a hemoglobin level.

When multiple clinical variables were considered, the reductions in LDH were one of the strongest predictors of improvements in fatigue and quality of life. Patients who had an increase in hemoglobin levels from baseline were only predictive of a improvement in the fatigue score if their LDH levels were less than up 1.5 times, the upper limit normal at day 183.

Again, this just points that you have to control the homolysis in patients with PNH. And these results suggest that hemoglobin alone is not a very good predictor of improvements to fatigue and quality of life in this disease setting.

We're going to move on now to some drugs that are in development, including iptacopan. This abstract looked at the 12 month interim data of a phase two trial of iptacopan, which is a factor B inhibitor, which works on the proximal portion of the complement pathway. This phase two trial had been previously published last year in Lancet Hematology, but this is now looking at 12 months of data.

Patients in this study were randomized to receive twice daily iptacopan in one of two dose sequences, either 25 milligrams for four weeks, followed by a hundred milligrams for up to two years, which was cohort one. Or cohort two, which received 50 milligrams for four weeks followed by 200 milligrams for up to two years. And the key objectives of this pilot study were to study and assess the effect of iptacopan on markers of both intravascular and vascular hemolysis.

So I mentioned enrollment has been completed, and the study was initially published, but now we're looking at updated 12 month data. Amongst 12 evaluable patients, all of whom were C5 inhibitor naive patients, all reached the primary endpoint of lowering the LDH by at least 60% within the first 12 weeks. LDH response was rapid and durable with all patients treated with greater than 50 milligrams of BID dosing reaching the threshold after only one week of treatment.

All ongoing patients, except one, maintained this threshold for at least 52 weeks. Equivalent improvements in markers of both intervascular and extravascular hemolysis were seen even at the 52 week mark. Similarly, hemoglobin levels improved significantly and durably in most patients, and all except one, of the ongoing patients have remained transfusion free since the start of iptacopan treatment. There have been no thromboembolic events occurring during the study and the FACIT-Fatigue score improved significantly in most patients.

So in summary, iptacopan is a new and very well tolerated oral complement alternative pathway inhibitor that's going to block both intravascular and extravascular hemolysis in adult PNH

patients with hemolytic PNH. And the hopes is that this will be a new treatment on the horizon that will be administered orally.

Another drug presented at ASH is the drug called pozelimab, which is an anti-C5 monoclonal antibody. This was a phase two open label single arm study. The treatment was a single IV loading dose, 30 milligrams/ kilogram followed thereafter by weekly subcutaneous dose of 800 milligrams of the pozelimab.

Treatment with this drug, again, led to rapid and sustain reductions in LDH throughout study week 26. All 17 patients achieved LDH reductions to below the clinically significant threshold of less than 1.5, the upper limited normal of LDH levels. All but one patient achieved control of intravascular hemolysis at week two and all, but one patient, achieved normalization of LDH by week four.

Importantly, one patient who was a carrier of a C5 polymorphism variant, which we know leads to resistance to eculizumab and ravulizumab had a rapid and sustained response to this drug with normalization of the LDH.

There were no adverse events or serious adverse events in this study that led to any treatment discontinuation. Over all it was a administered sub-q once weekly and did very well leading to blockage of intravascular hemolysis in patients with active PNH and was well tolerated. Pozelimab is going to be another option in our treatment armamentarium in the future. It is well tolerated and efficacious, and obviously leads to control of disease.

It is now being studied in combination with a drug called, cemdisiran, which is a small interfering RNA that blocks production of C5. So the hope is both by blocking it at the production level and by the monoclonal antibody, you'll get even better improvement in disease control.

So in summary, we've reviewed some of the abstracts that were presented at the ASH meeting, PNH is still a rare and acquired blood disease characterized by hemolytic anemia, bone marrow failure, and thrombosis. And these patients are quite symptomatic. The ASH 2021 meeting provide some nice abstracts about treatments of these diseases. These were published in the journal, Blood.

There are three FDA approved drugs now for PNH. These include pegcetacoplan, eculizumab, and ravulizumab, and they all continue to show clinically meaningful benefits for PNH patients. Two treatments in development were presented at the meeting including iptaclopan and pozelimab and both have been shown to be safe and efficacious in PNH patients and studies are ongoing with both of these agents.

And with that, I thank you for your attention.