Transcript Details
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Updates in CLL Treatment: 5 Year Follow-up Data from the CLL14 Trial

Announcer:

You're listening to Project Oncology on ReachMD, and this medical industry feature titled "Updates in CLL Treatment: 5 Year Follow-up Data from the CLL14 Trial" is developed and sponsored by AbbVie. This activity is intended for United States and Puerto Rico health care professionals only.

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Dr. Russell:

Research has shown that venetoclax in combination with obinutuzumab is an effective first-line treatment option for CLL, exhibiting responses after a fixed-duration regimen of one year with a well-studied safety profile.[1] But how durable are these treatment responses years after their last dose?

Before we dive further into our program, let's review the improved indication

Announcer:

Indication

Venetoclax is a BCL-2 inhibitor indicated for the treatment of adult patients with chronic lymphocytic leukemia (or CLL) or small lymphocytic lymphoma (or SLL).

Dr. Russell:

This is ReachMD and I'm Dr. John Russell. Joining me to discuss the primary analysis and five-year update to the CLL14 trial, studying fixed duration venetoclax-obinutuzumab in treating CLL, is Dr. Joanna Rhodes.

Dr. Rhodes is the Director of Lymphoma at Rutgers Cancer Institute of New Jersey in New Brunswick, New Jersey.Dr. Rhodes, welcome to the program.

Dr. Rhodes:

Thanks Dr. Russell for having me here today.

Dr. Russell:

So to start us off, Dr. Rhodes, can you give us some background on the CLL14 study and its primary analysis?

Dr. Rhodes:

Sure. CLL14 was an open-label, multicenter, randomized, active controlled phase 3 trial, studying the efficacy and safety of the B-cell lymphoma-2 inhibitor, venetoclax plus obinutuzumab, as a first-line treatment for CLL.

The study looked at a one year fixed duration regimen of venetoclax plus obinutuzumab, compared to chemotherapy chlorambucil plus obinutuzumab, in previously untreated CLL patients with coexisting medical conditions, which was defined as a cumulative illness rating scale score greater than six or a creatinine clearance less than 70 milliliters per minute.

The median age of the patients was 72. By design, the study population, by age and comorbidity, was representative of the general target population of CLL patients, who tend to be older and frailer when initiating treatment.

In the original analysis for CLL14, a key endpoint was progression-free survival, or PFS for short, as assessed by an independent review committee. The trial met its primary endpoint, demonstrating a 67 percent reduction in risk of progression or death in the venetoclax-obinutuzumab arm versus the chlorambucil-obinutuzumab treatment arm.[1]

A key secondary endpoint included the achievement of undetectable minimal residual disease – also known as uMRD – in peripheral blood and bone marrow.

The rates of achieving uMRD in peripheral blood or bone marrow in the venetoclax arm were significantly higher than in the chlorambucil treatment arm, including in patients with complete remission. By the end of treatment, approximately 76 percent of patients in the venetoclax-obinutuzumab arm achieved uMRD in the peripheral blood.[1]

And looking at the response rate, patients in the venetoclax-obinutuzumab group had a higher percentage achieving a complete response, at 50 percent versus 23 percent, of patients in the chlorambucil-obinutuzumab group. The overall response to treatment was also higher in the venetoclax group, at 85 percent compared to 71 percent in the chlorambucil arm.[1]

Dr. Russell:

Now I'd like to turn to the safety profile of venetoclax. Can you tell us more about the data from the primary analysis?

Dr. Rhodes:

In the primary analysis, the safety profile of the venetoclax-obinutuzumab arm was consistent with the known safety profile of venetoclax, with similar rates of Grade 3/4 AEs between treatment arms. The most common adverse reactions, greater than or equal to 20 percent, of any grade were neutropenia, diarrhea, and fatigue.[1]

The most common Grade 3/4 adverse event was neutropenia.[1] Grade 3/4 febrile neutropenia were reported in 5.2 percent of the venetoclax arm and 3.7 percent of the chlorambucil arm.[1]And Grade 3/4 infections were seen in 17.5 percent of patients of the venetoclax arm and 15.0 percent of the chlorambucil arm.[1] Now, I'd like to take a moment to focus on tumor lysis syndrome, or TLS for short. In the primary analysis, TLS occurred in three patients, or 1.4 percent, of the venetoclax-obinutuzumab arm and five patients, or 2.3 percent, in the chlorambucil-obinutuzumab arm. None of these patients met the Howard criteria for clinical TLS. And all of the TLS events in the venetoclax arm occurred before the first dose of venetoclax.[1]

Now, the results of the primary analysis also showed that rates of Grade 3 /4 adverse events decreased after the combination treatment period.[3] For example, the most common adverse event, neutropenia, had an incidence of 46 percent during the combination therapy period and decreased to 23 percent during the venetoclax monotherapy period.[4] More importantly, the combination treatment period had an incidence rate of four percent for febrile neutropenia whereas no events were reported during the venetoclax single agent treatment period.[4]

But looking at grade five adverse events, the number of fatal adverse events was 16 or 7.5 percent in the venetoclax–obinutuzumab group; and 8 or 3.7 percent in the chlorambucil–obinutuzumab group.[1]

Dr. Russell:

For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. John Russell, and with me today is Dr. Joanna Rhodes, who is discussing the five-year follow-up data to the CLL trial on fixed treatment duration venetoclax-obinutuzumab.

In 2022, the results for the five-year follow-up of the CLL14 were presented at a scientific conference. Could you take us through those findings?

Dr. Rhodes:

I'd be happy to. First, we see that PFS is sustained after the fixed-duration treatment has ended, with a median follow-up of 65.4 months after randomization.The estimated PFS at five years was approximately 63% in the venetoclax arm, compared to 27% in the chlorambucil-treated patients. Four years after completion of treatment, about 18% of patients treated with venetoclax had sustained

UMRD versus 1.9% of patients with chlorambucil.

Another finding was time-to-next-treatment results. 72.1 percent of patients in the venetoclax-obinutuzumab arm didn't need to start another line of CLL treatment four years after having completed one year of treatment, versus 42.8 percent of patients in the chlorambucil-obinutuzumab arm. This demonstrates that patients treated with fixed-duration venetoclax-obinutuzumab were often able to have a prolonged treatment-free period.[5] Five years after randomization, median overall survival had not been reached in either treatment arm.[6] There were 40 deaths in the venetoclax-obinutuzumab arm, with eight being related to progressive disease. And in the chlorambucil-obinutuzumab arm, 57 deaths were reported, with 23 being related to progressive disease.[5] And finally, the five-year follow-up data didn't identify any new safety signals over these longer periods.[5,7]

Dr. Russell:

I'd like to take a step back and look at this data as a whole. So could you tell us how the overall data of the original primary analysis and the five-year follow-up have impacted clinical practice?

Dr. Rhodes

Clinically, CLL14 made an impact as venetoclax-obinutuzumab is an approved first-line treatment for CLL and is part of a paradigm shift away from chemoimmunotherapy to targeted treatments.[1] Uniquely, venetoclax-obinutuzumab is the only chemotherapy-free treatment that's of fixed-duration that allows time off treatment rather than therapies such as BTK inhibitors, which we continue until progression or an adverse event that requires discontinuation.[1]

Now, we do see that venetoclax can induce both uMRD and a complete remission.[1,5] Even though treatment is just 12 cycles, we're seeing that a majority of patients who respond do sustain these responses at least four years after treatment completion. This can be of great benefit to patients as they aren't on active treatment during this time while maintaining clinical remissions.[5]

And so, further long-term follow-up is giving us a better understanding of the long-term toxicities and efficacy, as well as durability of the remissions after completing a fixed-duration treatment regimen of venetoclax-obinutuzumab.

Dr. Russell:

That's a great place to round out our discussion today, and I look forward to seeing the six-year results as well. I wanna thank my guest, Dr. Joanna Rhodes, for her insights into the CLL14 trial primary analysis, and five-year data. Dr. Rhodes, it was great speaking with you today.

Dr. Rhodes:

Thank you so much for having me today!

Dr. Russell:

I'm Dr. John Russell. Before we close, please stay tuned to hear some important safety information.

Announcer:

Contraindications

Strong CYP3A Inhibitors: Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL and SLL is contraindicated.

Warnings and Precautions

TLS: Tumor lysis syndrome (or TLS), including fatal events and renal failure requiring dialysis, has occurred in patients treated with venetoclax. Anticipate TLS; assess risk in all patients. Premedicate with anti-hyperuricemics and ensure adequate hydration. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk increases.

Neutropenia: Monitor blood counts. Interrupt dosing and resume at same or reduced dose. Consider supportive care measures.

Infections: Fatal and serious infections such as pneumonia and sepsis have occurred in patients treated with venetoclax. Monitor patients for signs and symptoms of infection and treat promptly. Withhold venetoclax for Grade 3 and 4 infection until resolution and resume at same or reduced dose.

Immunization: Do not administer live attenuated vaccines prior to, during, or after venetoclax treatment until b-cell recovery.

Announcer:

Embryo-Fetal Toxicity: May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

Increased mortality in patients with multiple myeloma (or MM) when venetoclax is added to bortezomib and dexamethasone: In a randomized trial in patients with relapsed or refractory MM, the addition of venetoclax to bortezomib plus dexamethasone, a use for which venetoclax is not indicated, resulted in increased mortality. Treatment of patients with MM with venetoclax in combination with bortezomib plus dexamethasone is not recommended outside of controlled clinical trials.

Adverse Reactions

In CLL and SLL, the most common adverse reactions (≥20%) for venetoclax when given in combination with obinutuzumab or rituximab or as monotherapy were neutropenia, thrombocytopenia, anemia, diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, and edema.

Review full prescribing information for additional information at www.rxabbvie.com or contact AbbVie Medical Information at 1-800-633-9110 or go to abbviemedinfo.com.

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