Transcript Details
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Updates in CLL Treatment: 5-Year Off-Treatment Analyses of the CLL14 and Murano Trials

Announcer:
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Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. In the summer of 2023, researchers presented the long-term data updates of two trials studying a fixed-duration venetoclax regimen in treating chronic lymphocytic leukemia, or CLL for short. Joining me to examine the 6-year update from the CLL14 trial and 7-year final analysis of the MURANO study is Dr. Joanna Rhodes. Dr. Rhodes is the Director of Lymphoma at Rutgers Cancer Institute of New Jersey in New Brunswick, New Jersey.

Now, before we dive further into our program, let's review the approved 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. Caudle
And now, Dr. Rhodes, welcome to the program.

Dr. Rhodes:
Thanks for having me.

Dr. Caudle:
Let's begin with the CLL14 study. Dr. Rhodes, can you give us some background on the original primary analysis of the CLL14 study?

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.[1]

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. This was defined as a Cumulative Illness Rating Scale score greater than 6 or creatinine clearance less than 70 mL per minute.[1] The primary endpoint in the original analysis for CLL14 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]

And the safety profile of the venetoclax/obinutuzumab arm of the CLL14 primary analysis was consistent with the known safety profile of venetoclax. The most common adverse reactions greater than or equal to 20 percent of any grade were neutropenia, diarrhea, and fatigue.[1] Similar rates of grade 3/4 adverse events between treatment arms were observed, with neutropenia being the most commonly reported grade 3/4 adverse event.[1] And tumor lysis syndrome, or TLS for short, occurred in 3 patients, or 1.4 percent, of the venetoclax/obinutuzumab arm and 5 patients, or 2.3 percent, in the chlorambucil/obinutuzumab arm. All 3 events of TLS in the venetoclax/obinutuzumab arm resolved and did not lead to withdrawal from the study.[1]

Dr. Caudle:
Thank you for taking us through the CLL14 trial's primary analysis, which brings us to the recent update presented at this summer's congress with the 6-year data from CLL14. Can you share some of the findings with us?

Dr. Rhodes:
I'd be happy to. The CLL14 6-year data cut shows 5 years off treatment and has a median follow-up time of 76.4 months after randomization. The estimated 6-year PFS was 53.1 percent in the venetoclax arm compared to 21.7 percent in the chlorambucil-treated patients.[2] The median PFS in the venetoclax/obinutuzumab treatment arm was reached at 76.2 months versus 36.4 months in the chlorambucil/obinutuzumab arm.[2] Additionally, with 5 years off treatment at the 6-year follow-up analysis, the overall survival rate for the venetoclax-treated patients was 78.7 percent versus 69.2 percent in the chlorambucil group.[2]

Another finding was time to next treatment results. 65.2 percent of the patients in the venetoclax/obinutuzumab arm didn't need to start another line of CLL treatment 5 years after having completed one year of treatment versus 37.1 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.[2]

Dr. Caudle:
Now, Dr. Rhodes, I'd like to turn to the safety profile for venetoclax. Could you tell us a little bit more about those findings in the recent update?

Dr. Rhodes:
Yes. Consistent with the previous analyses, no new safety signals have been identified in the 6-year follow-up data, and the most common grade 3 and above adverse events was neutropenia. The grade 3/4 adverse events observed decreased over time.[2]

Dr. Caudle:
For those just tuning in, you're listening *to Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and with me today is Dr. Joanna Rhodes, who is reviewing the recently updated long-term data from both the CLL14 and MURANO trials, which are designed using a fixed-duration treatment regimen with venetoclax in CLL.

We've gone through the recent 6-year follow-up data released from the CLL14 trial, but now, Dr. Rhodes, let's turn to the MURANO trial. Before we get to the recent update, can you give us some background on this study of fixed-duration venetoclax/rituximab in the relapse or refractory population?

Dr. Rhodes:
So, MURANO is a multicenter, open-label, phase 3 randomized study of venetoclax plus rituximab versus bendamustine plus rituximab in patients with relapsed or refractory CLL.[3] 389 patients were randomized 1 to 1 to receive either bendamustine/rituximab for 6 cycles or venetoclax plus rituximab for 6 cycles followed by single-agent venetoclax until progression of disease, unacceptable toxicity, or the 2-year maximum duration.[3] The primary endpoint was independent review committee-assessed PFS.[3]

The original protocol didn't allow crossover treatment with venetoclax after disease progression, but a later protocol amendment allowed patients from either arm who progressed to receive venetoclax/rituximab as either a crossover treatment or retreatment.[3]

Dr. Caudle:
And what were the findings from the primary analysis of the MURANO study?

Dr. Rhodes
With a median follow-up of 23.4 months, patients in the venetoclax plus rituximab arm demonstrated an 81 percent reduction in risk of disease progression or death compared to those in the bendamustine arm. The median PFS wasn't reached in the venetoclax group versus being 18.1 months in the bendamustine plus rituximab group.[3] The safety findings from the primary analysis of the MURANO

study were consistent with the known safety profile of venetoclax. The most common adverse reactions of any grade reported in at least 10 percent of patients were upper respiratory tract infection, diarrhea and neutropenia. The most common grade 3/4 adverse events reported was neutropenia.[3]

The incidence of TLS was 3 percent in the venetoclax/rituximab arm, and after the study protocol was amended to incorporate a more gradual ramp-up period to reach the target dose, no clinical TLS was observed in patients who followed the amended ramp-up schedule along with TLS prophylaxis monitoring measures.[3]

Dr. Caudle:
Thank you for that. Now, knowing the design and primary analysis results of the MURANO study, could you take us through the recent 7-year findings?

Dr. Rhodes:
Sure. Now, this 7-year follow-up, also showing 5 years off treatment, is the final analysis for MURANO. The median follow-up was 85.7 months.[4] 23 percent of venetoclax/rituximab patients remain progression-free at 7 years, while all patients treated with bendamustine/rituximab had disease progression at this time point.[4] And the median PFS was 54.7 months in the venetoclax/rituximab arm compared to 17 months in the bendamustine/rituximab arm.[4] Looking at overall survival, the 7-year overall survival rates were 69.6 percent with the venetoclax regimen and 51 percent with the bendamustine regimen.[4]

Turning over to the time to next treatment results. The median time to next treatment is 63 months in the venetoclax arm compared to 24 months in the bendamustine arm.[4] And finally, the 7-year safety findings reported trends seen in the primary analysis, with the most common grade 3/4 adverse reaction being neutropenia.[3,4]

Dr. Caudle:
Now, Dr. Rhodes, you mentioned a protocol amendment to the MURANO study that allowed retreatment and crossover with the fixed-duration venetoclax regimen. Can you give us an update on any findings here?

Dr. Rhodes:
The protocol was amended to allow for retreatment and crossover treatment with venetoclax/rituximab.[4] There are very small patient numbers – 25 reported patients in the venetoclax retreatment group and 9 in the bendamustine crossover arm. The data should be interpreted cautiously, as it may not be representative of a larger CLL treatment population due to small cohorts.[4]Let's review the results from the retreatment group.25 patients received 2-year fixed-duration venetoclax/rituximab and were retreated with the MURANO protocol of 2-year fixed-duration venetoclax/rituximab after disease progression.[4] The venetoclax retreatment subgroup had an overall response rate of 72 percent and a complete response rate of 24 percent.[4]and the median PFS for the venetoclax retreatment group was 23.3 months.

The overall safety profile for venetoclax in combination with rituximab in the retreatment and crossover substudy remained consistent with the safety profile of the main MURANO study, with the most common adverse event being neutropenia.[4]

Announcer:
In summary, for CLL14, the primary analysis showed that venetoclax/obinutuzumab reduced the risk of progression or death by 67 percent versus chlorambucil/obinutuzumab as assessed by independent review committee, but median PFS was not yet reached in either arm. And in the five-year off treatment analysis, the median PFS was 76.2 months and 36.4 months for the venetoclax group and the chlorambucil group, respectively. Five years after completing treatment, we see that an estimated 65 percent of patients in the venetoclax/obinutuzumab arm had not yet received a subsequent treatment versus 37 percent for chlorambucil/obinutuzumab. In terms of safety, the most common adverse events of any grade for venetoclax/obinutuzumab were neutropenia, diarrhea, and fatigue, while the most frequent adverse event of grade three or higher was neutropenia. Of note, the incidence of select grade three to four adverse events in the CLL14 study decreased over time from the venetoclax/obinutuzumab combination period to the venetoclax single-agent treatment period, and no new safety signals were identified at the five-year off treatment analysis.

Moving on to MURANO, at the primary analysis, venetoclax/rituximab reduced the risk of progression or death by 81 percent versus bendamustine/rituximab, as assessed by independent review committee. In this study, the median PFS wasn't reached for venetoclax/rituximab and was 18.1 months for bendamustine/rituximab. Now, at the five-year off treatment analysis, investigator-assessed median PFS was 54.7 months for the venetoclax arm versus 17.0 months for the bendamustine arm. With venetoclax/rituximab, the estimated seven-year overall survival rate was 69.6 percent at the five-year off treatment analysis compared to 51 percent for bendamustine/rituximab. Also, the median time-to-next-treatment for venetoclax/rituximab was 63 months versus 24

months for bendamustine/rituximab at the five-year off treatment analysis. Turning to safety data, the most common adverse events of any grade for venetoclax/rituximab were neutropenia, diarrhea, nausea , upper respiratory tract infection, and fatigue. And the most frequent adverse event of grade three or higher was neutropenia. In MURANO, we also note that the incidence of select grade three to four adverse events decreased over time from the venetoclax/rituximab combination period to the venetoclax single-agent treatment period. And no new safety signals were identified at the five-year off treatment analysis. And finally, in the venetoclax/rituximab retreatment substudy, the best overall response rate was 72 percent.

Dr. Caudle:
That's a great place to round out our discussion today. I'd like to thank my guest, Dr. Joanna Rhodes, for her insights into the updated CLL14 and MURANO trial data. Before we close, please stay tuned to hear some important safety information.

Announcer:
Important Safety Information

Contraindications

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

Warnings and Precautions

- **TLS:** Tumor lysis syndrome (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, 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.

Warnings and Precautions continued

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

Dr. Caudle:
And with that important safety information, we've come to the end of our program. Dr. Rhodes, it was great speaking with you today.

Dr. Rhodes:
Thank you for having me.

Announcer:
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