REGULAR ARTICLE

blood advances

Acalabrutinib plus venetoclax and rituximab in treatment-naive mantle cell lymphoma: 2-year safety and efficacy analysis

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Key Points

- Acalabrutinib plus venetoclax and rituximab resulted in high clinical and molecular response rates in patients with TN MCL.
- This chemotherapy-free, targeted triple combination was well tolerated, with no unexpected safety concerns reported.

This phase 1b study evaluated safety and efficacy of acalabrutinib, venetoclax, and rituximab (AVR) in treatment-naive mantle cell lymphoma (TN MCL). Patients received acalabrutinib from cycle 1 until progressive disease (PD) or undue toxicity, rituximab for 6 cycles with maintenance every other cycle through cycle 24 or until PD, and venetoclax, beginning at cycle 2, for 24 cycles. Twenty-one patients were enrolled; 95.2% completed induction (6 AVR cycles) and 47.6% continued acalabrutinib maintenance. Thirteen (61.9%) patients had grade 3-4 adverse events (AEs), most commonly neutropenia (33.3%). Seven (33.3%) patients had COVID-19 infection (6 [28.6%] serious AEs and 5 [23.8%] deaths, all among unvaccinated patients). There was no grade ≥3 atrial fibrillation, ventricular tachyarrhythmias, major hemorrhages, or tumor lysis syndrome. Overall response rate (ORR) was 100% (95% CI, 83.9-100.0) with 71.4% complete response. With median follow-up of 27.8 months, median progression-free survival (PFS) and overall survival (OS) were not reached. PFS rates at 1 and 2 years were 90.5% (95% CI, 67.0-97.5) and 63.2% (95% CI, 34.7-82.0), respectively; both were 95% after censoring COVID-19 deaths. OS rates at 1 and 2 years were 95.2% (95% CI, 70.7-99.3) and 75.2% (95% CI, 50.3-88.9), respectively; both were 100% after censoring COVID-19 deaths. Overall, 87.5% of patients with available minimal residual disease (MRD) data achieved MRD negativity (10^{-6}; next-generation sequencing) during treatment. AVR represents a chemotherapy-free regimen for TN MCL and resulted in high ORR and high rates of MRD negativity. The trial was registered at www.ClinicalTrials.gov as #NCT02717624.

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Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page outlining further details is also available at https://vivli.org/ourmember/astrazeneca/.

The full-text version of this article contains a data supplement.

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Introduction

Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) that comprises 5% to 10% of NHL.[1] The disease has a heterogeneous clinical course, and despite improved response and survival rates achieved by recent advances in treatment, the vast majority of patients relapse and chemotherapy-refractory patients fare poorly.[1]

Currently, there are a number of frontline therapy options for MCL, including a high-dose cytarabine-containing chemoimmunotherapy regimen followed by autologous stem cell transplantation (ASCT), with or without rituximab maintenance, for young, fit patients, and combination chemoimmunotherapy, with or without rituximab maintenance, for older or unfit patients.[1-3] Bendamustine- and rituximab-based induction therapy is a widely preferred regimen because of its good tolerability and high response rates.[1,4] However, aggressive chemoimmunotherapy is associated with significant hematologic and nonhematologic toxicities, including an increased risk of second malignancies in other B-cell malignancies.[5]

Acalabrutinib is a potent, highly selective, second-generation, covalent Bruton tyrosine kinase (BTK) inhibitor approved for the treatment of patients with relapsed or refractory (R/R) MCL and patients with chronic lymphocytic leukemia or small lymphocytic lymphoma.[6,7] One of the mechanisms of BTK inhibition in MCL is to mobilize tumor cells from lymph nodes to the peripheral blood, where they are most vulnerable to the action of venetoclax, a B-cell lymphoma 2 (BCL-2) inhibitor approved for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, and newly diagnosed acute myeloid leukemia.[8-11] Preclinical mechanistic models have demonstrated a strong synergistic effect between BTK inhibitors and BCL-2 inhibitors in MCL cell lines, which leads to increased inhibition of B-cell proliferation and enhanced apoptosis.[12]

These mechanistic observations support the rationale to further explore this combination in clinical trials.[13] In a phase 2 historically controlled study, mostly in patients with R/R MCL, the combination of ibrutinib plus venetoclax treatment yielded high response rates and high rates of minimal residual disease (MRD) negativity.[14] In the phase 3 SYMPATICO study, patients with R/R MCL treated with ibrutinib plus venetoclax achieved high response rates and the combination demonstrated a tolerable safety profile.[15,16]

The clinical benefit of using BTK inhibitors in the frontline MCL setting was explored in the randomized TRIANGLE trial of ibrutinib with or without ASCT, which demonstrated strong efficacy with acceptable safety in patients with treatment-naive MCL (TN MCL).[17] Furthermore, preclinical studies have demonstrated that the addition of an anti-CD20 monoclonal antibody, such as rituximab or obinutuzumab, further decreases BCL-2 signaling by downregulating BCL-X_L and sensitizes MCL cells to venetoclax.[18] A triplet combination of ibrutinib, venetoclax, and obinutuzumab demonstrated high response rates and was well tolerated in a phase 1/2 trial of patients with MCL, including a small cohort of patients with TN MCL that achieved deep, MRD-negative responses.[19] Although these data support triplet therapy, including an anti-CD20 monoclonal antibody, safety concerns related to ibrutinib warrant further investigation into combination treatment with second-generation BTK inhibitors, such as acalabrutinib.

A 2-part, multicenter, open-label phase 1b study (NCT02717624) assessed the efficacy and safety of acalabrutinib plus bendamustine and rituximab or acalabrutinib plus venetoclax and rituximab (AVR) in TN patients diagnosed with MCL. Data from part 1 of this phase 1b study that assessed acalabrutinib plus bendamustine and rituximab are reported separately.[20] An initial report of part 2 of the study that assessed AVR showed high rates of clinical and molecular responses after a median follow-up of 16 months (range, 8.0-26.2).[21] We present here the updated results on safety and efficacy after a median follow-up of 27.8 months.

Methods

Study design and population

This multicenter, open-label study was designed to assess the safety and efficacy of acalabrutinib administered concomitantly with venetoclax and rituximab in patients with TN MCL. The study design is depicted in supplemental Appendix 1.

This trial included adult patients (≥18 years old) with a pathologically confirmed diagnosis of MCL without previous systemic therapies and an Eastern Cooperative Oncology Group performance status ≤2. Approximately 20 to 32 patients were planned to be enrolled in this study. There was no sample size calculation performed for this study. A planned sample size of ~20 to 32 patients was considered sufficient for this phase 1b study. Therefore, no formal statistical testing of the hypotheses was performed. Patients with any history of central nervous system lymphoma, leptomeningeal disease, or significant cardiovascular disease were excluded from enrollment. Detailed inclusion and exclusion criteria are described in supplemental Appendix 2.

Treatment regimen

Starting on cycle 1 day 1, acalabrutinib 100 mg twice daily was administered orally until disease progression or discontinuation caused by undue toxicity. Rituximab was administered via IV infusion at 375 mg/m^2 on day 1 of each cycle for up to 6 28-day cycles, followed by maintenance rituximab treatment every other cycle until disease progression or discontinuation caused by undue toxicity, for a maximum of 9 additional doses for patients who achieved a complete response (CR) or partial response (PR).

Acalabrutinib plus rituximab were initiated in cycle 1 to reduce and debulk the tumor burden and decrease the risk of tumor lysis syndrome. The oral administration of venetoclax was started on cycle 2, day 1 with an initial 5-week ramp-up schedule (20, 50, 100, 200, and 400 mg daily) to 400 mg daily through cycle 25. The complete treatment scheme is depicted in supplemental Appendix 1.

End points and assessments

The primary objective was to characterize the safety profile of AVR in patients with TN MCL. The safety end point was assessed by monitoring adverse events (AEs), which were mapped using the Medical Dictionary for Regulatory Activities thesaurus terms and graded according to the Common Terminology Criteria for Adverse Events version 4.03.

The secondary objective was to evaluate the efficacy of AVR in the treatment of TN MCL. Investigator-assessed efficacy end points included the overall response rate (ORR), progression-free survival (PFS), and duration of response (DOR). All end points were evaluated per Lugano criteria for NHL, which require a positron emission tomography/computed tomography (PET/CT) scan and bone marrow (BM) biopsy for confirmation of CR.[22] The Investigators' assessment of ORR was confirmed using PET/CT alone without BM biopsy.

Patients were evaluated by clinical examination and laboratory tests every cycle, CT scans every 3 cycles starting with day 1 of cycle 4 for the first year and every 6 cycles thereafter, PET/CT scans after completion of 3 and 6 cycles, and/or to confirm CR at any time during the study.

MRD testing was performed on peripheral blood using the clonoSEQ assay (Adaptive Biotechnologies) at PR, CR, every 6 cycles after CR, and treatment end. MRD negativity was defined as 10^{-6}.

Statistical analyses

Descriptive statistics were used to summarize the baseline demographic and disease characteristics, study drug administration, efficacy, and safety outcomes.

The ORR was summarized by the number and percentage of patients, and its corresponding 95% confidence interval (CI) was calculated using an exact binomial test (Clopper-Pearson). The best ORR by Lugano criteria and PET/CT alone were summarized by the number and percentage of patients for each response category (CR, PR, stable disease, progressive disease [PD], nonevaluable, and unknown). For patients achieving CR or PR, descriptive statistics were calculated for the time to the initial response and best response.

Kaplan-Meier (K-M) estimates of PFS in months and the corresponding 2-sided 95% CIs were calculated and presented for the median, with a K-M curve used to estimate the distribution of PFS. A sensitivity analysis for PFS was carried out by censoring patients who died due to the coronavirus disease 2019 (COVID-19) infection, and the corresponding K-M plots were provided.

Only patients who achieved objective response (CR or PR) were included in the analysis of DOR. K-M estimates of DOR in months and the corresponding 2-sided 95% CIs were calculated and presented for the median. A sensitivity analysis for DOR was carried out by censoring patients who died due to COVID-19 infection.

Correlations between MRD in BM and treatment outcomes were performed.

This study was funded by AstraZeneca and conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. The study protocol was approved by the institutional review boards or independent ethics committees, and all patients provided written informed consent. The data cutoff date for the current analysis was 15 June 2022.

Results

In total, 21 patients were enrolled from 7 sites in 2 countries (the United States, n = 14; Poland, n = 7) between December 2018 and March 2020. Baseline patient and disease characteristics are summarized in Table 1. Fifty-seven percent (n = 12) of the enrolled patients were 65 years or older, Mantle Cell Lymphoma International Prognostic Index (MIPI) score was high in 4 (19%) patients, and 19 (90%) patients were classified as Ann Arbor stage IV. The median time from the initial diagnosis to the first dose of acalabrutinib was 1.4 months (range, 1.0-73.1).

Table 1. Baseline patient and disease characteristics

Characteristic	N = 21
Age, median (range), y	66 (51-85)
Male, n (%)	17 (81)
White race, n (%)	19 (91)
ECOG PS, n (%)	
0	11 (52)
1	9 (43)
2	1 (5)
Bulky lymph nodes, n (%)	
>5 cm	7 (33)
≥10 cm	1 (5)
BM involvement, n (%)	15 (71)
Extranodal disease, n (%)	13 (62)
Ann Arbor stage IV disease, n (%)	19 (90)
Simplified MIPI score, n (%)*	
Low risk (0-3)	5 (24)
Intermediate risk (4-5)	11 (52)
High risk (6-11)	4 (19)
Missing	1 (5)
Blastoid/pleomorphic MCL, n (%)	1 (5)
Ki-67 proliferation index, n (%)†	
<30%	10 (48)
≥30%	10 (48)
Missing	1 (5)

ECOG PS, Eastern Cooperative Oncology Group performance status.
*Simplified MIPI score calculated from 4 prognostic factors: age, ECOG PS, lactate dehydrogenase level, and white cell count at baseline.
†Total percentage exceeds 100% due to rounding.

Twenty (95.2%) patients completed the first 6 cycles of induction with AVR per study protocol; 1 patient discontinued venetoclax between cycles 1 and 6 due to COVID-19 and subsequently died of the infection. During treatment, the median relative dose intensity achieved for each drug was 96.2% (range, 52.2%-100.0%) for acalabrutinib, 97.1% (range, 53.1%-100%) for venetoclax, and 100.5% (range, 90.8%-108.8%) for rituximab. The median number of cycles administered was 27 (range, 7.0-43.0) for acalabrutinib, 21.5 (range, 5.0-24.0) for venetoclax, and 15.0 (range, 6.0-16.0) for rituximab.

Overall, at the time of data cutoff, 12 (57.1%) patients remained in the study, and 9 (42.9%) patients discontinued the study (supplemental Appendix 3). The most common reason for study discontinuation was death (n = 6 [PD, n = 1, 4.8%; other causes of death, n = 5, 23.8%]), followed by reasons not specified (n = 2, 9.5%) and investigator decision (n = 1, 4.8%).

At the time of the data cutoff, 11 patients discontinued all treatments. For treatment discontinuation by individual study drug, see supplemental Appendix 4. After the induction phase between cycles 7 and 25, the most common reason for discontinuation of acalabrutinib (n = 4, 19.0%) and venetoclax (n = 3, 14.2%) was COVID-19 infection (supplemental Appendix 5).

Safety

The most common any-grade AEs reported were diarrhea (n = 15, 71.4%), headache (n = 11, 52.4%), and fatigue (n = 10, 47.6%), most of which were grades 1 to 2 (Table 2). Grade 3 to 4 AEs were reported in 13 (61.9%) patients, most commonly neutropenia (n = 7, 33.3%), pneumonia (n = 2, 9.5%), and seizures (n = 2, 9.5%).

Serious AEs (SAEs) of any grade were observed in 12 (57.1%) patients, and 11 (52.4%) were grade ≥3. The most common SAE reported was COVID-19 infection. Overall, 7 (33.3%) patients were diagnosed with COVID-19 infection: 6 (28.6%) were reported as SAEs, and 5 (23.8%) patients died of the infection, 4 (19.0%) during the treatment-emergent period (defined as up to 30 days after the last dose of study medication), and 1 after the treatment-emergent period. Other SAEs affecting ≥2 patients were pneumonia (n = 2, 9.5%) and seizures (n = 2, 9.5%). Among the 2 SAEs of seizure, 1 was due to brain metastatic lesions, and the other was determined by the investigator to be related to acalabrutinib.

Table 2. Treatment-emergent AEs occurring in more than or equal to 15% of patients

	N = 21			
	Any grade	Grade 1-2	Grade 3-4	Grade 5
Patients with an event, n (%)*	21 (100)	4 (19.0)	13 (61.9)	4 (19.0)
Diarrhea	15 (71.4)	14 (66.7)	1 (4.8)	0
Headache	11 (52.4)	11 (52.4)	0	0
Fatigue	10 (47.6)	10 (47.6)	0	0
Neutropenia	8 (38.1)	1 (4.8)	7 (33.3)	0
COVID-19	7 (33.3)	1 (4.8)	2 (9.5)	4 (19.0)†
Dizziness	7 (33.3)	7 (33.3)	0	0
Cough	6 (28.6)	6 (28.6)	0	0
Paresthesia	6 (28.6)	6 (28.6)	0	0
Dyspnea	5 (23.8)	4 (19.0)	1 (4.8)	0
Hypoesthesia	5 (23.8)	5 (23.8)	0	0
Myalgia	5 (23.8)	5 (23.8)	0	0
Memory impairment	4 (19.0)	4 (19.0)	0	0
Peripheral edema	4 (19.0)	3 (14.3)	1 (4.8)	0
Pruritus	4 (19.0)	4 (19.0)	0	0
Upper respiratory tract infection	4 (19.0)	4 (19.0)	0	0
Blurred vision	4 (19.0)	4 (19.0)	0	0

Regardless of causality assessment.

*A patient with multiple severity grades for a given AE is counted only once under the maximum severity.

†A fifth patient died from COVID-19 infection outside the treatment-emergent period (30 days after discontinuation of all study drugs).

The impact of the COVID-19 vaccine on patient outcomes was assessed. None of the patients who died received the COVID-19 vaccine (Figure 1). Additionally, none of the vaccinated patients died, and 1 case of COVID-19 that occurred in a vaccinated patient was of grade 2.

Nine (42.9%) patients had SAE related to acalabrutinib, most commonly grade 3 to 4 pneumonia (n = 2, 9.5%). Venetoclax- and rituximab-related SAEs were reported in 8 (38.1%) and 5 (23.8%) patients, respectively.

Five (23.8%) patients discontinued acalabrutinib due to COVID-19 infection, and 1 (4.8%) patient discontinued the drug due to grade 3 seizures. COVID-19 infection also led to discontinuation of venetoclax in 4 (19.0%) patients; 1 (4.8%) patient discontinued due to grade 1 osteoarthritis, and 1 (4.8%) patient required a dose reduction due to grade 2 diarrhea. Permanent discontinuation of rituximab was reported in 4 (19.0%) patients secondary to COVID-19 infection.

Overall, AEs led to temporary dose withholding of any study drug in 15 (71.4%) patients. AEs led to temporary dose withholding of acalabrutinib in 14 (66.7%) patients, venetoclax in 11 (52.4%) patients, and rituximab in 3 (14.3%) patients.

Most treatment-emergent events of clinical interest were grade 1 to 2. Treatment-emergent events of clinical interest of grade ≥3 affecting ≥20% patients were leukopenia (42.9%) and infections (38.1%; Table 3). There were no cardiac events of grade ≥3 and no events of atrial fibrillation or ventricular tachyarrhythmia were reported. None of the patients in the study had a major hemorrhage or tumor lysis syndrome.

Efficacy

At the data cutoff date, the investigator-assessed ORR by Lugano criteria was 100% (95% CI, 83.9-100.0) with 71.4% CR, and the ORR by PET/CT alone was 100% (95% CI, 83.9-100.0) with 90.5% CR (Figure 2).

Overall, 19 (90.5%) patients achieved CR or PR after the first 6 cycles. The 2 patients who missed the assessment on the first day of cycle 7 achieved a confirmed PR at cycle 10.

The median (range) times to record an initial response and best response were 2.8 (range, 0.7-3.7) and 3.0 (range, 0.7-18.3) months, respectively. At the time of data cutoff, the median DOR was not reached and the estimated 12- and 36-month DOR were 90.5% (95% CI, 67.0-97.5) and 53.3% (95% CI, 24.0-75.8), respectively. After censoring the 5 patients who died due to COVID-19 infection, the median DOR was not reached and the estimated 12- and 36-month DOR were 95% (95% CI, 69.5-99.3) and 79.2% (95% CI, 31.8-95.4), respectively. The maximum change in the sum of the products of the perpendicular diameters is presented in Figure 3.

At a median follow-up of 27.8 months (range, 8.0-39.8), median PFS and overall survival (OS) were not reached (Figures 4-5). PFS rates at 1 year and 2 years were 90.5% (95% CI, 67.0-97.5) and 63.2% (95% CI, 34.7-82.0), respectively; both were 95% (95% CI, 69.5-99.3) after censoring for the 5 deaths due to COVID-19 infection. OS rates were 95.2% (95% CI, 70.7-99.3) at 1 year and 75.2% (95% CI, 50.3-88.9) at 2 years; both were 100% after censoring for COVID-19 deaths.

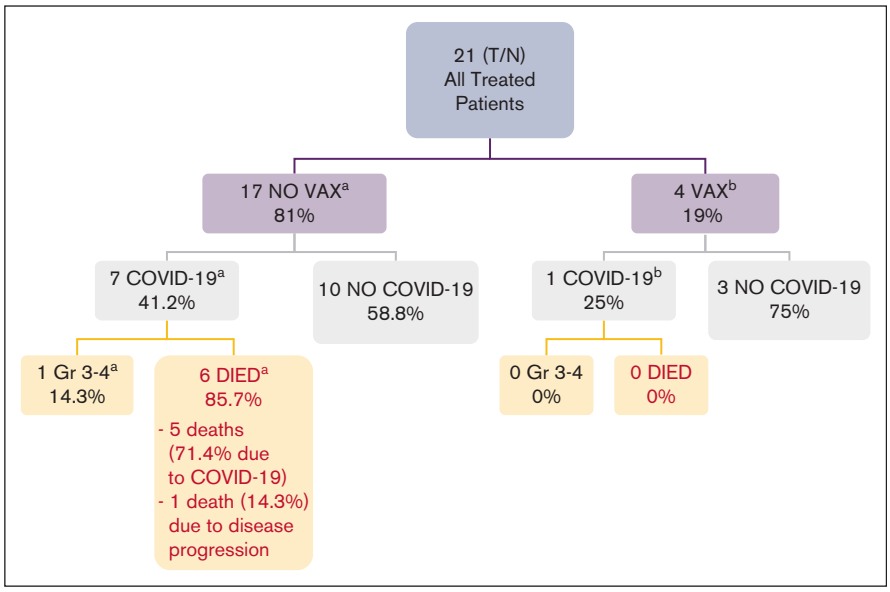

Figure 1. Impact of COVID-19 vaccine on patient outcomes. [a]Among 17 patients who did not receive a COVID-19 vaccine, 7 contracted COVID-19. The dates of onset of COVID-19 infection were between 21 July 2020 and 9 April 2022, and the end dates of COVID-19 infection were between 5 August 2020 and 29 April 2022. Of the 7 patients who did not receive a COVID-19 vaccine and contracted COVID-19, 1 patient experienced grade 3 COVID; this patient received cefepime IV transfusion for 7 days and remdesivir IV transfusion for 4 days, and their COVID-19 resolved. The 6 other patients who did not receive a COVID-19 vaccine and contracted COVID-19 died; 5 deaths were due to COVID-19 and 1 death was due to disease progression. [b]Among the 4 patients who received the COVID-19 vaccine, 1 patient received 3 doses of the Pfizer messenger RNA vaccine on 5 March 2021, 9 June 2021, and 7 January 2022, and then contracted grade 2 COVID-19 on 9 March 2022, which resolved on 20 March 2022. The other 3 patients did not contract COVID-19. Gr, grade; VAX, vaccination.

MRD analysis

MRD data were available for 16 of the 21 patients enrolled in the study (Figure 6) and were missing for 5 patients due to the lack of available baseline tumor tissue samples. The best MRD-negative response rate was 87.5% at 10^{-6}. Among patients with available samples at the respective time point, at cycle 6, 12 (100%) of 12 patients were MRD-negative, and at cycle 12, 11 (78.6%) of 14 patients were MRD-negative.

Of the 15 patients who achieved CR on PET/CT at any time during the study, 13 (86.7%) were MRD-negative at least once during treatment, and 1 patient had no follow-up for MRD assessment. At the last follow-up, 11 of these patients (73.3%) remained in CR (8 [53%] were MRD-negative), 3 patients (20%) remained in PR or better (2 had missing BM biopsies, achieved CR per PET/CT, and were MRD-negative, and 1 patient had no MRD follow-up), and 1 patient (6.7%) had PD.

Table 3. Events of clinical interest

Event, n (%) ECI category ECI subcategory	N = 21	
	All grades	Grades ≥3
Cardiac events*	5 (23.8)	0
Atrial fibrillation	0	0
Ventricular tachyarrhythmias	0	0
Leukopenia	12 (57.1)	9 (42.9)
Neutropenia	10 (47.6)	8 (38.1)
Other leukopenia	4 (19.0)	2 (9.5)
Thrombocytopenia	1 (4.8)	0
Hemorrhage†	7 (33.3)	0
Hepatotoxicity	1 (4.8)	0
Hypertension	1 (4.8)	1 (4.8)
Infections‡	14 (66.7)	8 (38.1)
Interstitial lung disease/pneumonitis	1 (4.8)	0
Second primary malignancies	1 (4.8)	0
Second primary malignancies (excluding skin)	1 (4.8)	0

ECI, event of clinical interest.

*Cardiac events included 2 patients with tachycardia (both grade 2), 1 patient with cardiac failure and mitral and tricuspid valve incompetence (all grade 1), 1 patient with pericarditis (grade 1) and chronic cardiac failure (grade 2), and 1 patient with arrhythmia (grade 2).

†Hemorrhage was reported in 1 patient with petechiae (grade 1), 2 patients with hemorrhagic diathesis (both grade 1), 3 patients with contusion (n = 3, grade 1; n = 1, grade 2), and 1 patient with epistaxis (grade 1).

‡Six of the 8 grade ≥3 infections were related to COVID-19: 4 were grade 5 and 2 were grade 3.

Discussion

Treatment with triple combination AVR has shown high efficacy rates, durable molecular responses, and a manageable safety profile in patients with TN MCL.

Despite the ample variety of therapies available for MCL, no single treatment can be considered as the standard. Characteristics such as age, fitness, baseline comorbidities, disease stage, and molecular profile, among others, must guide the decision-making process and often preclude the use of high-intensity induction chemoimmunotherapy.[23]

Chemotherapy-free combinations have been previously investigated as treatment options for patients with R/R MCL,[14-16,19,24] and in recent years for TN patients as well.[3,19,25,26] As with any antineoplastic therapy, safety, tolerability, and deep and durable responses are key aspects to be considered when choosing chemotherapy-free treatment.

Jain et al reported that a combination of ibrutinib and rituximab administered to 50 older patients (median age, 71 years; range, 69-76) with TN MCL resulted in a 42% discontinuation rate of ibrutinib, mainly due to grade 3 atrial fibrillation (10 patients, 20%), bleeding (3 patients, 6%; 2 grade 3), and other grade 3 toxicities (8

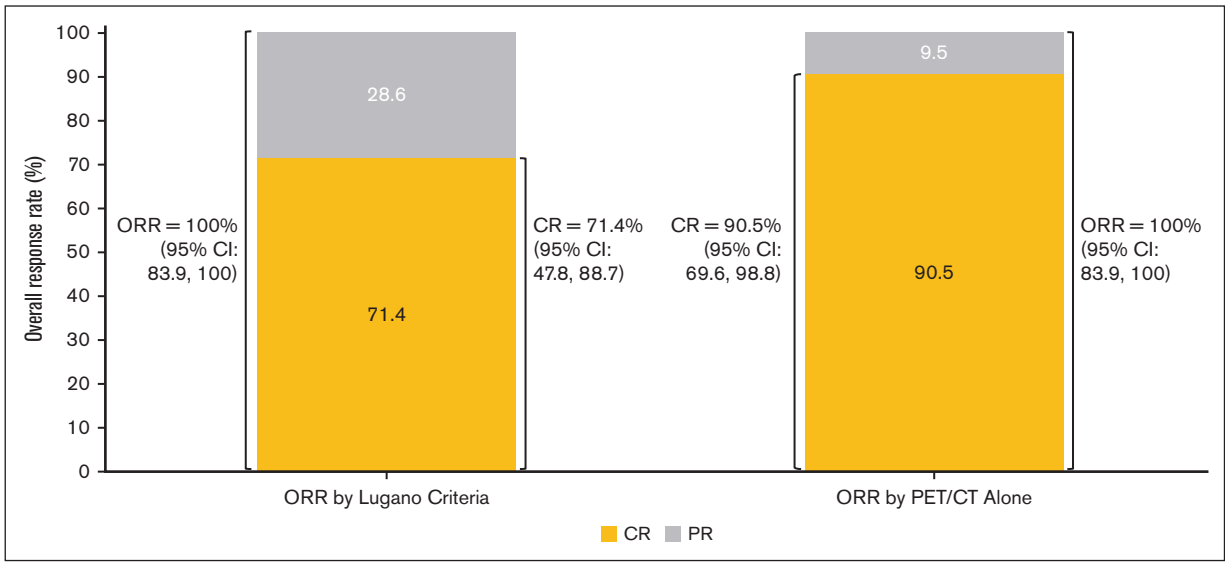

Figure 2. ORR per Lugano criteria and by PET/CT alone with corresponding 95% CI based on the Clopper-Pearson exact binomial test. Four of the 6 patients had PR per Lugano and were counted as CR by PET/CT because BM biopsy was missing to confirm CR per Lugano.

patients, 16%).[3] In addition, 58% of the patients in that study required dose reduction of ibrutinib due to AEs.[3] The investigator-assessed ORR reported in that study was 96%.[3] Similarly, a phase 3 study demonstrated improved PFS, CR rates, and time to next treatment for patients with R/R MCL treated with a combination of ibrutinib plus venetoclax compared with patients treated with ibrutinib plus placebo, although 84% and 76% of patients experienced grade ≥3 AEs with ibrutinib plus venetoclax and ibrutinib plus placebo, respectively.[16]

More recently, Jain et al reported that combination treatment with acalabrutinib and rituximab in 50 older patients (median age, 69 years; range, 65-81) with TN MCL resulted in an 18% study discontinuation rate, mainly due to AEs (syncope, atrial fibrillation, and intolerance; 1 patient each) and disease progression (3 patients).[27] The ORR reported for doublet acalabrutinib-rituximab treatment was 94%. These data and the data presented in this study demonstrated that both doublet acalabrutinib-rituximab therapy and triplet AVR combination therapy are active in patients with TN MCL.[27] Other BTK inhibitor–based triplet combination therapies are being explored in TN MCL. In a recent phase 2 trial, the combination of zanubrutinib, obinutuzumab, and venetoclax treatment in TN patients with *TP53*-mutated MCL demonstrated tolerable safety, high response rates, and high rates of Undetectable MRD (uMRD).[28] Long-term follow-up of doublet vs triplet BTK inhibitor–based therapies is needed to assess the balance between durability of response and toxicity.

With regard to the impact of COVID-19 on study outcomes, patients were enrolled in the study beginning December 2018 through March 2020, which encompasses the early stages of the COVID-19 pandemic when there were no clearly established clinical management guidelines.[29] In this study, all 5 patients who died due to COVID-19 were not vaccinated. Severe COVID-19–related infections and deaths have been shown to occur more frequently in patients with hematologic malignancies than in those without cancer (28.8% vs 19.6%).[30] Additionally, patients with MCL from a large European MCL registry were shown to have an overall COVID-19 mortality rate of 44.4%, which is increased compared with other pooled lymphoma cohorts that demonstrated

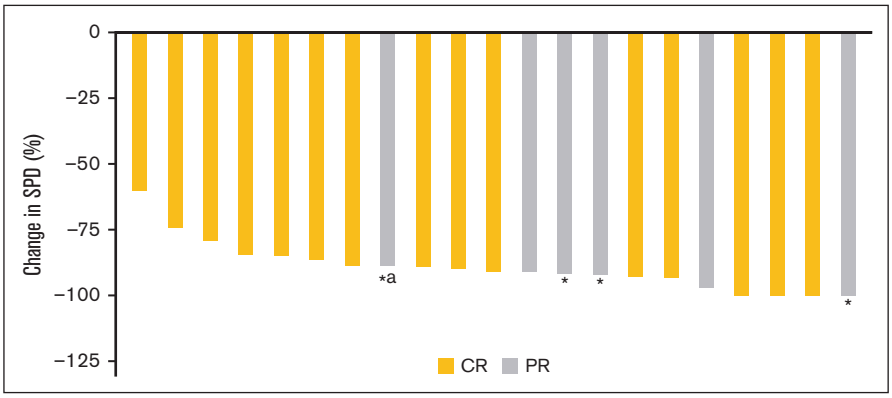

Figure 3. Maximum change from baseline in SPD, including 4 patients with missing BM biopsies reported as CR by PET/CT. Asterisks (*) denote the missing BM biopsies reported as CR by PET/CT. Among the 4 patients with CR per PET/CT only, 1 patient had missing postscreening measurements for 2 of the 6 target lesions. Only 4 of the 6 target lesions were calculated for SPD, denoted by *a. SPD, sum of the products of perpendicular diameters.

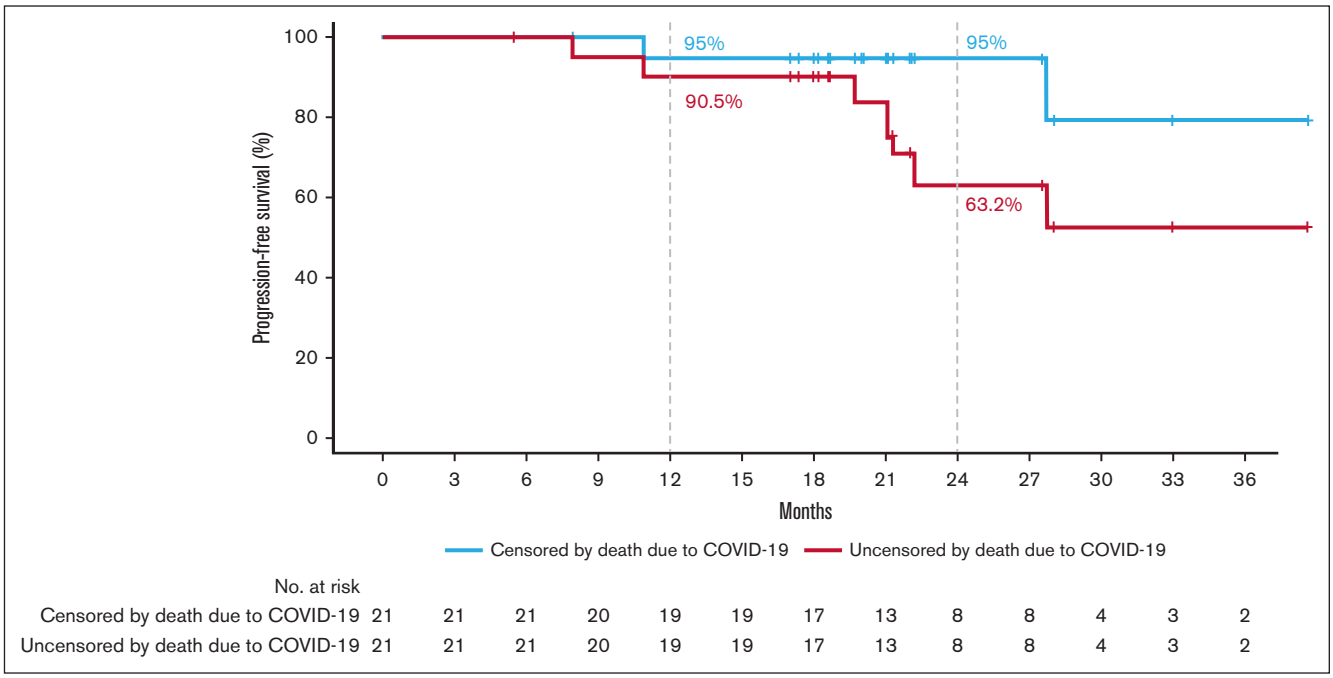

Figure 4. PFS after a median follow-up of 27.8 months, with and without censoring for 5 deaths due to COVID-19 infection.

a COVID-19 fatality rate of 13.8%.[30,31] In this study, 1 case of COVID-19 that occurred in a patient who was vaccinated was grade 2 and resolved, which is consistent with a recent study that demonstrated the protective benefits of COVID-19 vaccination in patients with hematologic malignancies with low rates of COVID-19–related hospitalization and death.[32] Without a controlled study in a large population of patients with MCL, the possibility of immunosuppression with AVR cannot be excluded.

All patients treated with AVR had a 100% ORR both by Lugano criteria and by PET/CT alone, and >90% of patients achieved CR by PET/CT. Unavailable BM biopsy results precluded the confirmation of CR by Lugano criteria in 4 patients who were otherwise classified as CR by PET/CT alone. Of these 4 patients, 1 died due to COVID-19, 1 discontinued the study before obtaining the biopsy, and 2 declined the procedure. Moreover, responses to the AVR combination appeared to be long lasting; after >2 years of

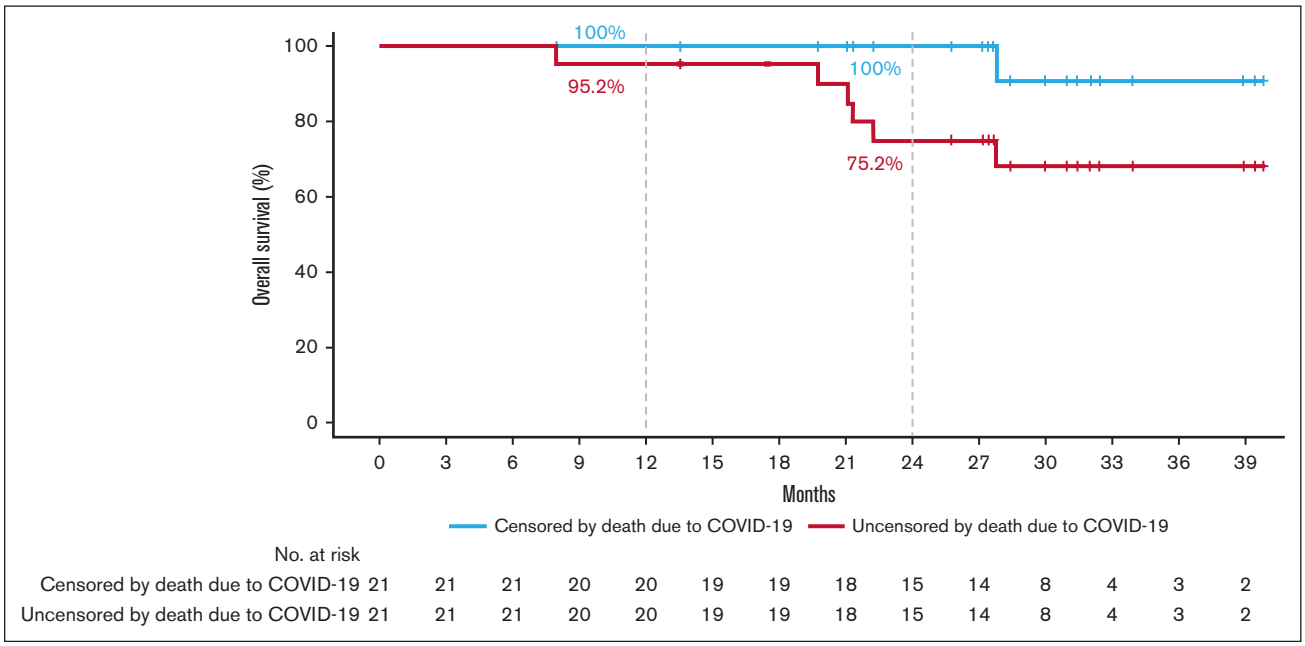

Figure 5. OS after a median follow-up of 27.8 months, with and without censoring for 5 deaths due to COVID-19 infection.

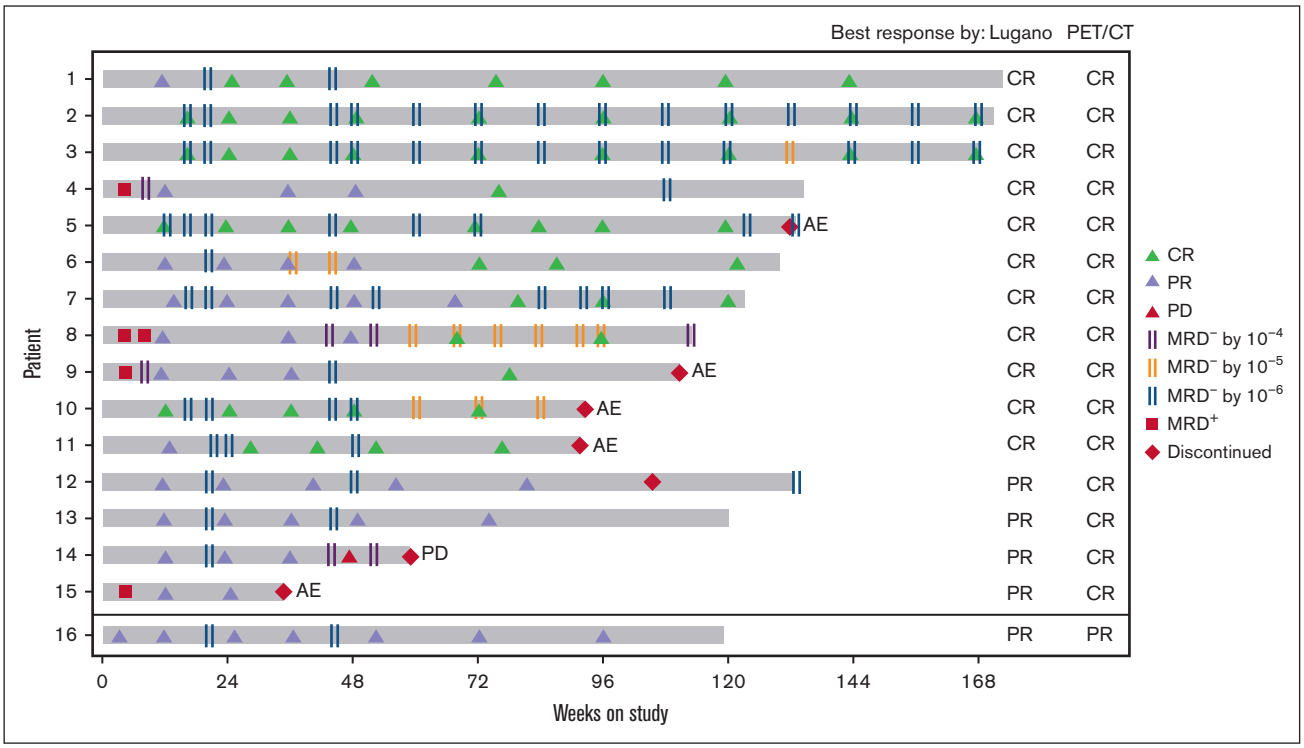

Figure 6. Longitudinal MRD analysis using NGS with clinical data. NGS, next-generation sequencing.

median follow-up, the median DOR, PFS, and OS were not reached.

The prognostic impact of MRD in patients with MCL has been previously established.[33] Data collected from 2 clinical trials conducted by the European MCL Network Clinical Intergroup, a consortium of 15 national lymphoma study groups, showed that patients achieving molecular remission after induction therapy had a significantly improved response duration compared with patients with residual disease (remission rates at 2 years: 87% vs 61%, respectively; $P = .0043$).[33] Positive MRD at 6 months was an independent predictor of the risk of relapse in patients with MCL who received ASCT.[34] Furthermore, persistently positive MRD or alternating positive and negative MRD results at different time points of follow-up outperformed CR as a predictor of time-to-progression in these patients.

Treatment with AVR resulted in high rates of molecular responses. At cycle 6, MRD data were available for 12 patients, all of whom achieved MRD negativity at a threshold of 10^{-6}. At cycle 12, MRD data were available for 14 patients and 11 (79%) patients continued to be MRD-negative. One patient was MRD-negative at cycle 6, with a threshold of 10^{-6}. At cycle 12, this patient progressed and became MRD-positive.

The durable responses and high rates of MRD negativity achieved with the AVR regimen presented in this study are consistent with previous results reported for combination therapies that included a BTK inhibitor, BCL2 inhibitor, and/or anti-CD20 antibodies.

The limitations of this study include the open-label, single-cohort study design with a small sample size, which limits the ability to compare it with a standard-of-care control. Most patients had a low-to-intermediate MIPI score, with 19% of patients having a high-risk MIPI score. Additionally, data on cytogenetic or molecular features, such as *TP53* mutation or del(17p), were not collected.

In conclusion, AVR is a promising, highly effective, and well-tolerated chemotherapy-free treatment option for patients with TN MCL. The AVR combination is being evaluated in a phase 2 TrAVeRse study for patients with TN MCL (NCT05951959).

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Authorship

Contribution: C.-C.W., R.C., M.W., and T.P. contributed to the study design; T.R., W.J., M.W., S.D.S., T.P., and K.J.M. contributed to the study investigation; T.R., W.J., C.-C.W., M.W., S.D.S., T.P., and K.J.M provided patients or study materials; T.R., W.J., V.M., C.-C.W., S.D.S., and M.W. contributed to the collection and assembly of data; V.M., C.-C.W., M.W., T.P., and K.J.M. contributed to the data analysis; W.J., V.M., C.-C.W., R.C., D.G., M.W., S.D.S., T.P., and K.J.M. contributed to the data interpretation; W.J., V.M., R.C., M.W., S.D.S., T.P., and K.J.M. contributed to the manuscript preparation; and all authors participated in the critical review and revision of this manuscript and provided approval for manuscript submission.

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