Erratum to: Immunochemotherapy plus lenalidomide for high-risk mantle cell lymphoma with measurable residual disease evaluation

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This *erratum corrige* contains corrections to the text (in the Patient Characteristics section of the Results and in the Discussion) and tables (Tables 1 and 2) of our article published in *Haematologica* in April 2024, "Immunochemotherapy plus lenalidomide for high-risk mantle cell lymphoma with measurable residual disease evaluation".[1] These comments, shown below, relate to the patients' tumor *TP53* status in which the breakdown by *TP53* gene alteration status is revised and clarified.

References

1. Epstein-Peterson, Drill E, Aypar U, et al. Immunochemotherapy plus lenalidomide for high-risk mantle cell lymphoma with measurable residual disease evaluation. Haematologica. 2024;109(4):1149-1162.

Results

Patient characteristics

We enrolled 49 total patients (Table 1) from January 2016 until June 2018. Per protocol, efficacy-evaluable patients completed len-R-CHOP treatment. Two patients did not complete len-R-CHOP, one for progressive disease and one for toxicity. One patient withdrew from the study in remission following R-HiDAC to pursue HDT/ASCR. The median age among all patients was 63 years (range, 30-79) and 22 (45%) were ≥65 years old at enrollment. Thirty-one (65%) patients were high-risk by protocol including four patients with blastoid histology. Forty-one patients (84%) had tumor *TP53* mutation and deletion status assessed prior to treatment; of these, 16 were *TP53* altered (mutation and/or gene loss) (34%): two harbored mutated *TP53*, six harbored one copy of *TP53*, and eight harbored both abnormalities. High-risk patients were enriched for MCL harboring *TP53* alterations (*Online Supplementary Table S1*).

Discussion

We performed a single-center, investigator-initiated, phase II study examining a frontline intensive IC-based treatment regimen for MCL with the addition of len and omitting con-

solidative HDT/ASCR. Although the primary study endpoint of 3-year PFS was not met, this was primarily driven by the poor outcomes observed among patients with *TP53*-altered MCL, further establishing that *TP53*-altered MCL is associated with poor outcomes when treated with IC and len does not overcome this negative prognostic impact.[5] However, among patients with WT *TP53*, outcomes were more favorable, even among patients whose MCL harbored adverse disease features (elevated Ki67 and/or blastoid/pleomorphic histology). We further demonstrated the prognostic importance of MRD status in MCL within our approach, especially at the level of 1E-6 sensitivity, which can be achieved using the NGS-based MRD assay.

The frequency and severity of toxicities observed with our treatment regimen generally aligned with those expected based on prior studies investigating len-R-CHOP[15] and R-len.[16] The addition of lenalidomide did impact R-CHOP dosing, as 41% of patients required dose reduction (in len) or delay during len-R-CHOP, primarily due to cytopenias (7 instances) and neutropenic fever (6 instances). This frequency is higher than that observed (9%[15]) in treating diffuse large B-cell lymphoma with len-R-CHOP, which could be due to the higher incidence of bone marrow involvement in MCL predisposing to hematologic toxicity. At interim analysis of 16 patients, we observed excessive hematologic toxicity, primarily grades 3/4 thrombocytopenia without bleeding, with 3,000 mg/m^2 of cytarabine. Therefore, this dose level was removed for the remainder of our study. Numerous dose regimens of cytarabine have been utilized in treating MCL, notably: R-BAC - 500-800 mg/m^2 for 3 days, R-DHAX - 2,000 mg/m^2 every 12 hours for two doses, hyper-CVAD (age-based) - 1,000-3,000 mg/m^2 every 12 hours for 2 days, and Nordic (age-based) - 2,000-3,000 mg/m^2 every 12 hours for 2 days. In our study, many patients' MCL responded to cytarabine radiographically and based on conversion from dMRD to uMRD with cytarabine dosing of <3,000 mg/m^2, suggesting that efficacy may be maintained with dose attenuation for advanced age or comorbidity.

The role for consolidative HDT/ASCR in first remission in MCL has been questioned given several retrospective and real-world studies in the modern era which have not demonstrated an OS benefit associated with this approach.[1,3,17] Recent data from the European Mantle Cell Lymphoma Network show no statistically significant difference in PFS and OS in the rituximab-treated patient subset (N=68) between HDT/ASCR and interferon-α maintenance in first remission.[3] The rate of referral for HDT/ASCR in real-world datasets of patients in the United States is as low as 17%, suggesting incomplete uptake of this practice.[18,19] Although supportive care measures for patients undergoing HDT/ASCR have improved and the incidence of major toxicities or death with its use in contemporary practice is lower,[20] it still carries potential for substantial toxicity (especially in older patients in whom MCL is common), deep and lasting immunosuppression with potential infectious sequelae, high cost, and intensive exposure to healthcare facilities, much of which are especially undesirable during the ongoing COVID-19 pandemic.

Table 1. Patient characteristics at enrollment.

Characteristic	N=49*
Median age in years (IQR)	63 (57-68)
Sex: male, N (%)	35 (71)
Stage, N (%)	
II	4 (8.2)
III	4 (8.2)
IV	41 (84)
MIPI_b risk, N (%)	
High	29 (59)
Intermediate	18 (37)
Low	2 (4.1)
High-risk per protocol,** N (%)	31 (65)
Unknown	1
Ki67 ≥30%, N (%)	30 (62)
Unknown	1
Blastoid, N (%)	4 (8.2)
Elevated LDH, N (%)	16 (33)
Bone marrow involvement, N (%)	36 (75)
Unknown	1
GI tract involvement, N (%)	6 (14)
Unknown	5
TP53 alteration, N (%)	
Wild-type	27 (63)
Deletion	6 (14)
Mutation	2 (4.7)
Mutation and deletion or loss of heterozygosity	8 (19)
Unknown	6
Protocol risk/*TP53* alteration, N (%)	
Low risk/*TP53* WT	11 (26)
Low risk/*TP53* ALT	4 (9.5)
High risk/*TP53* WT	15 (36)
High risk/*TP53* ALT	12 (29)
Unknown	7
Method for *TP53* deletion assessment,† N (%)	
NGS-based sequencing assay	39 (80)
Fluorescence *in situ* hybridization	30 (61)
Karyotype	8 (16)
SNP array	4 (8.2)

*Percentages refer to evaluated patients. **One patient did not have Ki67 assessment at baseline; additionally, 1 patient's MCL displaying aggressive pathologic features not reaching the threshold for formally labeling as blastic morphology had Ki67 (<10%) only assessed from bone marrow sampling at baseline was classified as high-risk per protocol given these features at diagnosis and that subsequent biopsy specimens showed an elevated (≥30%) Ki67 concurrent with the same aggressive features. †Patients with evaluation via multiple methodologies are listed in each category. IQR: interquartile range; MIPI_b: biologic Mantle Cell Lymphoma International Prognostic Index; LDH: lactate dehydrogenase; GI: gastrointestinal; NGS: next-generation sequencing; WT: wild-type; ALT: altered; SNP: single nucleotide polymorphism.

Other notable studies have incorporated novel agents to frontline therapy with IC without HDT/ASCR consolidation.[21-24] Results from the WINDOW-1 study were published,[22] reporting outcomes from 131 patients treated with ibrutinib-rituximab followed by R-hyper-CVAD/methotrexate-cytarabine: among 97 PET/CT-evaluable patients, the overall response rate was 71% and complete response rate 69% to ibrutinib-rituximab alone; 3-year PFS was 79% (95% CI: 70-85), indicative of high clinical activity for this regimen. The Nordic MCL4 study[24] investigated len added to upfront bendamustine-rituximab in a non-transplant-eligible patient population (N=50) and demonstrated a median PFS of 42 months; importantly, patients whose MCL harbored altered *TP53* (N=16) had inferior survival outcomes in this study. Finally, abstract results have been reported for the Triangle study,[23] which randomized 870 patients to IC plus HDT/ASCR ('arm A') *versus* IC plus HDT/ASCR plus ibrutinib ('arm A+I') *versus* IC plus ibrutinib omitting HDT/ASCR ('arm I'). Similar to the WINDOW-1 study, only 15% of patients in Triangle were high-risk by MIPI. Although the 3-year PFS estimates from these studies (especially WINDOW-1 and Triangle) are higher than the 3-year PFS reported in the current study, our study included both younger and older patients and enriched for high-risk patients (59% with MIPI-b high risk and 23% with mutated *TP53*), thus limiting cross-trial comparison of outcomes. Collectively, these studies and our results show that frontline targeted therapies can build upon IC regimens and spare patients the toxicities associated with HDT/ASCR without a clear decrement in PFS.

Maintenance therapy has a clear role post-HDT/ASCR in prolonging remission duration based on results from the LYSA Group's randomized study demonstrating prolongation in PFS and OS with 3 years of rituximab maintenance.[25] Data from the Randomized European MCL Elderly Trial[26] reinforced the benefit of rituximab maintenance for older patients following R-CHOP. Multiple other groups have investigated the role for len-based maintenance with[27] or without[8] HDT/ASCR. The MCL R2 Elderly trial[8] reported improved PFS but not OS comparing R-len to rituximab alone as maintenance following induction (without HDT/ASCR) at the cost of increased toxicity; thus, along with waited results from the ongoing ECOG-ACRIN E1411 trial,[28] the optimal composition of maintenance therapy remains an unanswered question that warrants further inquiry. In our study, the re-emergence of detectable MRD and subsequent relapses that we observed in the 6 months following EoT suggest that a longer duration of maintenance beyond 6 months may have been

Table 2. Progression-free survival and overall survival estimates by risk factors.

Characteristic	Counts			PFS		OS	
	Overall N	PFS events N	OS events N	Median PFS in months (95% CI)	*P**	Median OS in months (95% CI)	*P**
Overall	49	32	16				
Ki67					0.034		0.5
<30%	18	9	5	60 (46-NR)		NR	
>=30%	30	23	11	38 (25-54)		NR (60-NR)	
MIPI_b risk					0.008		0.032
Low/intermediate	20	9	3	57 (49-NR)		NR	
High	29	23	13	30 (24-56)		NR (50-NR)	
High risk per protocol					0.015		0.3
No	17	8	4	60 (46-NR)		NR	
Yes	31	24	12	38 (24-54)		NR (60-NR)	
TP53 alteration					0.002		<0.001
WT	27	16	5	51 (49-NR)		NR	
DEL	6	3	2	54 (42-NR)		NR (42-NR)	
MUT	2	2	1	26 (24-NR)		56 (42-NR)	
MUT & DEL/LOH	8	7	7	14 (11-NR)		35 (21-NR)	
TP53 WT *vs.* altered					0.043		<0.001
WT	27	16	5	51 (49-NR)		NR	
ALT	16	12	10	24 (16-NR)		51 (31-NR)	
Protocol risk/*TP53* alteration					0.018		0.011
Low risk/*TP53* WT	11	5	2	60 (49-NR)		NR	
Low risk/*TP53* ALT	4	2	2	52 (18-NR)		52 (25-NR)	
High risk/*TP53* WT	15	11	3	49 (31-NR)		NR (64-NR)	
High risk/*TP53* ALT	12	10	8	21 (12-NR)		51 (31-NR)	
Overall				49 (38-59)		NR (64-NR)	

*Log rank test. PFS: progression-free survival; OS: overall survival; CI: confidence interval; MIPI_b: biologic Mantle Cell Lymphoma International Prognostic Index; WT: wild-type; ALT: altered; MUT: mutation; DEL: deletion; LOH: loss of heterozygocity; NR: not reached.

beneficial to sustain remissions in this high-risk patient population. However, such considerations would have to balance potential benefits with toxicity and further immunosuppression from R-len.

We evaluated MRD status at multiple points and our data comprise one of the largest experiences in MCL using the NGS clonoSEQ platform; most prior studies used ASO PCR. Overall, we have shown that MRD status carried prognostic importance in our sequential treatment regimen, especially at later time points such as 6 months following EoT, and that 1E6 is more strongly predictive of outcomes than 1E5 sensitivity. A key finding from our study is the different implications for MRD results at the level of 1E-5 *versus* 1E-6 sensitivity levels: a majority of patients' disease was uMRD at 1E-5 following R-HiDAC and MRD status at this sensitivity level and time point did not carry prognostic significance. However, MRD status at 1E-6 at this same time point did discriminate long-term PFS (median 22 months dMRD *vs*. 54 months uMRD). This supports the use of an NGS MRD assay which is a highly sensitive assay and can achieve a sensitivity level of $1x10^{-6}$. An additional key finding is that persistent or recurrent dMRD late in study treatment predicted long-term PFS: at 6 months following EoT, median PFS was 13 months for dMRD *versus* 39 uMRD at the level of 1E-6 sensitivity. This prompts consideration as to whether additional maintenance could have been beneficial in patients with dMRD. Furthermore, this finding of a later MRD time point carrying prognostic importance is concordant with results from a large, prospective effort using a PCR-based assay.[29] Therein, the authors showed that MRD status at 6 months post-HDT/ASCR was a particularly useful measure for predicting long-term outcome. MRD-based study designs based on these results could continue maintenance for patients with dMRD and/or terminate maintenance for patients with uMRD.

We substantiated existing literature correlating abnormalities in *TP53* and poor outcomes with IC-treated patients in MCL (this relationship was not firmly established at time of study conception). Our data correlating upfront sequencing results with clinical outcomes is one of the largest and most comprehensive in uniformly treated patients with MCL. We did not identify additional gene signatures predictive of outcomes. Through serial sequencing in 20 patients at baseline and relapse, we demonstrated stability in *TP53* alterations (Figure 4B) and identified an increase in *CDKN2A* and *CDKN2B* loss at time of relapse, similar to previously published findings.[30] The 3-year PFS rate among patients with *TP53*-altered MCL approximates data from the Nordic MCL2 study in which patients underwent HDT/ASCR, recognizing the limitations of cross-trial comparisons and differences between these cohorts.[5] The addition of len did not appear to abrogate this negative effect. There are ongoing studies without chemotherapy that are investigating the use of targeted therapies, such as BTKi with or without venetoclax, as upfront treatment of *TP53*-altered MCL (*clinicaltrials gov. Identifier: NCT03824483, NCT03112174*) and we await results from these studies to inform management for high-risk MCL patients.

Our study carries limitations. First, our study was devised and implemented prior to the extensive body of literature demonstrating the adverse prognostic effect of *TP53* abnormalities in MCL. Second, although there are clear patterns among our data from clinical and MRD perspectives, we caution firm conclusions given the relatively small numbers of patients treated at a single center that ultimately warrant confirmation in a multicenter effort.

We designed a non-HDT/ASCR-based frontline treatment approach for MCL and achieved generally favorable clinical outcomes in patients with WT *TP53* MCL with expected toxicity for cytarabine-containing induction regimens in treating MCL. Our clinical outcomes roughly align with those from other upfront HDT/ASCR-sparing approaches with novel agents, when accounting for our enriching for patients with high-risk MCL, and further substantiate the validity of this therapeutic approach. Additionally, we have redemonstrated the predictive power of MRD evaluation in defining disease trajectories longitudinally in patients with MCL and highlight the 1E-6 sensitivity level as particularly useful.

Although we are not further developing this treatment regimen, similar future approaches could consider developing a strategy with a longer maintenance treatment phase given the pattern of relapses that we observed post-maintenance. Based on the first formal evaluation in the Triangle study incorporating upfront BTKi, it is unclear whether or not upfront len + chemoimmunotherapy approaches will be further developed. Noteworthy ongoing upfront studies include venetoclax-lenalidomide-rituximab[31] and acalabrutinib-lenalidomide-rituximab[32] from which we await further results. Given len's immunomodulatory mechanism of action and the advent of chimeric antiden receptor T cell[33] and bi-specific antibodies[34] in treating MCL, there may be rational synergistic combinations that can be pursued wherein len augments the efficacy of these immune-based therapies.