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

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Abstract

Chemoimmunotherapy followed by consolidative high-dose therapy with autologous stem cell rescue was a standard upfront treatment for fit patients with mantle cell lymphoma (MCL) in first remission; however, treatment paradigms are evolving in the era of novel therapies. Lenalidomide is an immunomodulatory agent with known efficacy in treating MCL. We conducted a single-center, investigator-initiated, phase II study of immunochemotherapy incorporating lenalidomide, without autologous stem cell transplant consolidation, enriching for patients with high-risk MCL (*clinicaltrials gov. Identifier: NCT02633137*). Patients received four cycles of lenalidomide-R-CHOP, two cycles of R-HiDAC, and six cycles of R-lenalidomide. The primary endpoint was rate of 3-year progression-free survival. We measured measurable residual disease (MRD) using a next-generation sequencing-based assay after each phase of treatment and at 6 months following end-of-treatment. We enrolled 49 patients of which 47 were response evaluable. By intent-to-treat, rates of overall and complete response were equivalent at 88% (43/49), one patient with stable disease, and two patients had disease progression during study; 3-year progression-free survival was 63% (primary endpoint not met) and differed by *TP53* status (78% wild-type *vs*. 38% ALT; *P*=0.043). MRD status was prognostic and predicted long-term outcomes following R-HiDAC and at 6 months following end-of-treatment. In a high-dose therapy-sparing, intensive approach, we achieved favorable outcomes in *TP53*-wild-type MCL, including high-risk cases. We confirmed that sequential MRD assessment is a powerful prognostic tool in patients with MCL.

Introduction

An established standard of care for younger, fit patients with mantle cell lymphoma (MCL) has been frontline immunochemotherapy (IC) followed by consolidative high-dose therapy with autologous stem cell rescue (HDT/ASCR) and rituximab maintenance. However, the use of upfront HDT/ASCR in MCL was established in an era when rituximab and cytarabine were not routinely applied and there were limited treatment options for relapsed or refractory (R/R)

disease. Thus, it has been questioned whether HDT/ASCR should remain incorporated into frontline MCL therapy given the lack of clear overall survival (OS) benefit for this approach,[1-3] the rapidly evolving treatment landscape in MCL, and the substantial toxicity and intensive healthcare utilization associated with HDT/ASCR.[4] Furthermore, the outcomes among patients with high-risk MCL (e.g., *TP53* alteration high proliferation index, blastoid histology) treated with IC followed by HDT/ASCR are poor.[5,6] A number of novel therapies have shown promising efficacy for the treatment of MCL (thoroughly reviewed in [7]), including bortezomib, lenalidomide (len), Bruton tyrosine kinase inhibitors (BTKi), and venetoclax. Several studies have incorporated these novel agents into established IC regimens to evaluate if they can improve outcomes and potentially facilitate the safe omission of HDT/ASCR consolidation.

Len, an immunomodulatory agent with pleotropic anti-tumor effects, has established efficacy in newly diagnosed[8] and R/R MCL.[9] We designed a sequential frontline treatment approach for untreated MCL incorporating len to IC (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] followed by rituximab + high-dose cytarabine [R-HiDAC]) followed by R-len maintenance. We examined whether HDT/ASCR can be spared using this intensive induction treatment regimen in combination with len followed by R-len maintenance in a cohort of patients with MCL enriched for high-risk features (blastoid or pleomorphic histology, Ki67 ≥30%).

In addition to establishing the safety and efficacy of this treatment approach, we sought to investigate measurable residual disease (MRD) testing to augment response assessment and disease monitoring. The presence of MRD has been shown to offer prognostic information in MCL. However, comprehensive, prospective data in uniformly treated cohorts using contemporary, sensitive testing methodologies assays was lacking. MRD testing results do not currently guide treatment selection, intensification, or de-escalation for patients with MCL in clinical practice and further data are required before it can be incorporated into routine treatment decisions. We concurrently assessed the utility of sequential next-generation sequencing (NGS) for MRD detection using the clonoSEQ® Assay (Adaptive Biotechnologies, Seattle, WA) in the context of our prospective clinical study.

Methods

Patient enrollment

Eligible patients were age ≥18 years with untreated stage II-IV MCL. Eligibility required radiographically measurable disease, absent active infection, absent central nervous system involvement by MCL, and adequate performance status, blood counts, and organ function. Full eligibility requirements are detailed in the *Online Supplementary Appendix*. We aimed to enroll 2/3 high-risk patients, defined as Ki67 ≥30% or blastoid/pleomorphic histology. Eligibility for HDT/ASCR was not an enrolment criterion; subjects being considered for enrolment who intended to pursue HDT/ASCR were not permitted to enroll given the design of our study. This study was approved by our institutional review board (#15-196) and all trial conduct was in accordance with the Declaration of Helsinki with informed written consent. Our trial was registered with the National Clinical Trials Network (*clinicaltrials gov. Identifier: NCT02633137*).

Assessment of genomic alterations

In 43 instances, we performed molecular profiling on baseline tumor samples using a hybrid-capture, NGS panel interrogating >400 genes with the ability to detect mutations and copy number alterations.[10]

Treatment

Initial treatment consisted of four cycles of R-CHOP (len-R-CHOP; Figure 1) followed by two cycles of R-HiDAC. At

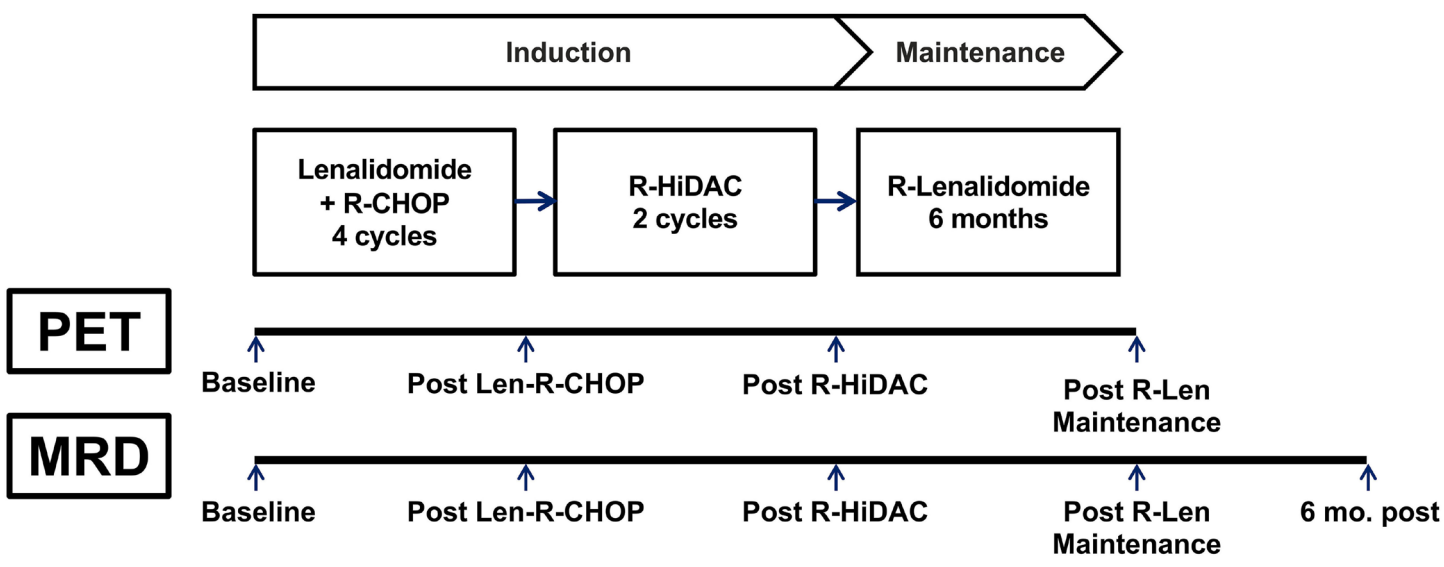

Figure 1. Study schema. MRD: measurable residual disease; PET: positron-emission tomography; len: lenalidomide; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HiDAC: rituximab + highdose cytarabine; mo: months.

interim evaluation with 16 patients, the 3,000 mg/m^2 dose of cytarabine was removed due to excess hematologic toxicity. Thereafter, patients received 6 months of rituximab-lenalidomide (R-len). We administered standard thromboprophylaxis concurrent with len, growth factor support for len-R-CHOP and R-HiDAC, varicella prophylaxis throughout treatment, and *Pneumocystis jirovecii* prophylaxis during len-R-CHOP and R-HiDAC.

^{18}FDG positron emission tomography/computed tomography (PET/CT) was performed after each phase of treatment. MRD testing occurred at these same time points and additionally at 6 months following end-of-treatment (EoT, the conclusion of R-len). We assessed radiographic response using the 5-point scale (5PS)[11] and classified responses using the Lugano Classification.[12] We used CTCAE version 4.0 to grade adverse events.

Measurable residual disease testing

The methodology for peripheral blood-based NGS MRD assay has been described previously.[13] Briefly, clonoSEQ® uses multiplex polymerase chain recation (PCR) and NGS to identify and track MCL-associated immunoglobulin receptor gene rearrangements (IgH, IgK, and IgL) with a lower detection limit of 1x10^{-6}. All MRD analyses were performed centrally (Adaptive Biotechnologies, Seattle, WA); any detectable tumor-associated clonal rearrangement was labeled 'detectable MRD' (dMRD) and the absence of detectable rearrangement, 'uMRD'.

Statistical analysis

The primary efficacy endpoint was 3-year progression-free survival (PFS) measured from study enrollment, with desirable cutoff 75% and undesirable 60%. The trial was powered at 80% with 47 patients. By protocol, patients who enrolled but did not complete the len-R-CHOP phase were removed and replaced. We report intent-to-treat outcomes including all 49 patients enrolled. Secondary objectives included PFS and OS, each measured from start of treatment. PFS was measured until progression or last follow-up and OS until death or last follow-up. Patients lost to follow-up or withdrawn from study are also counted as events. We conducted a landmark survival analysis to investigate the association between progression status at 24 months post-diagnosis (POD24) and OS and performed this only on those patients who were alive/not lost to follow-up at that time point. We conducted survival analyses using the Kaplan-Meier method. We evaluated prognostic variables using Cox proportional hazards. ED conducted biostatistical analyses using R (Version 4.0) and all authors had access to clinical data.

Results

Patient characteristics

We enrolled 49 total patients (Table 1) from January 2016 until

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 mutation, N (%)	10 (23)
Unknown	6
TP53 deletion, N (%)	12 (27)
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.

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, 14 were *TP53* altered (mutation and/or gene loss) (34%): three harbored mutated *TP53*, five harbored one copy of *TP53*, and

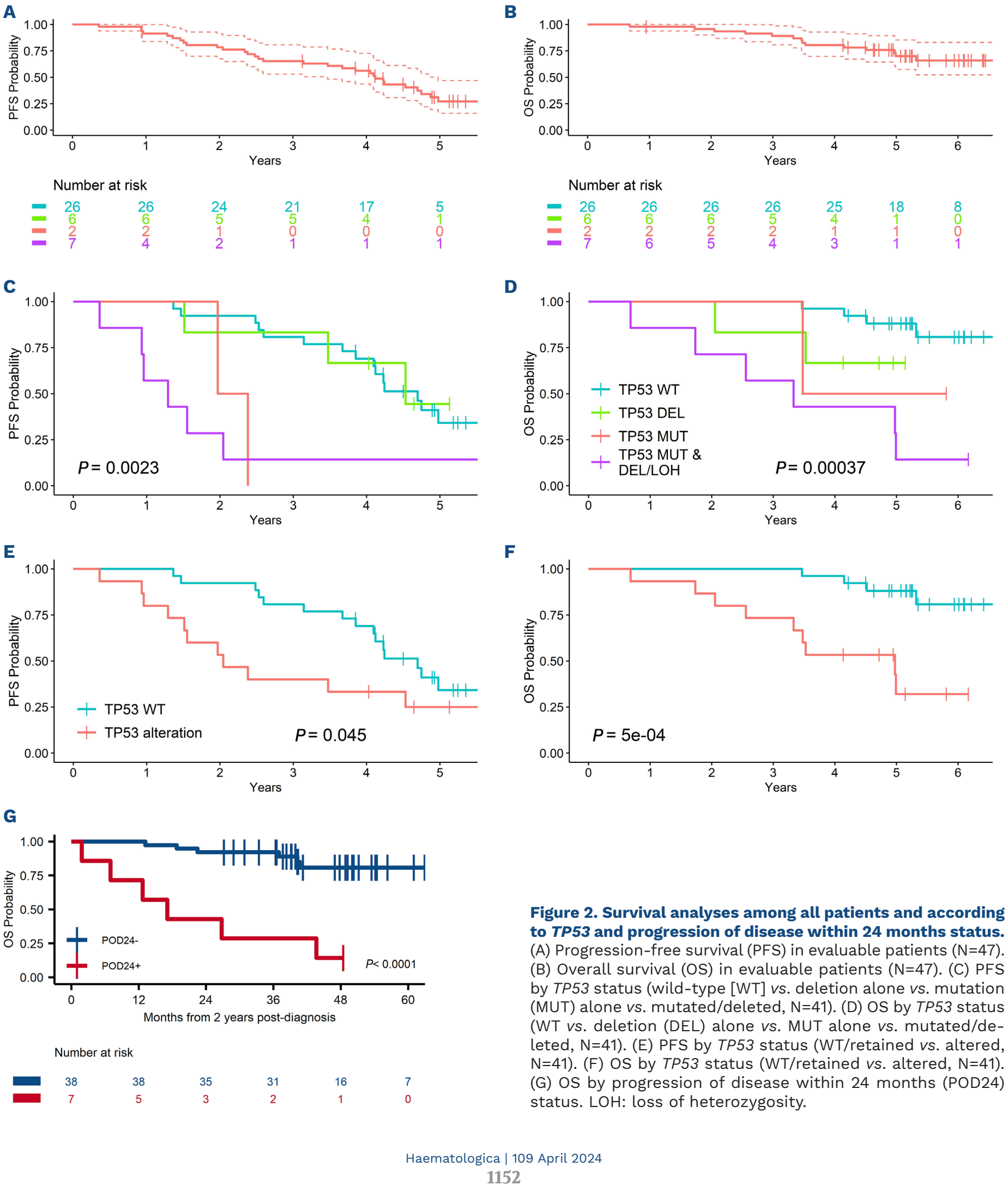

Figure 2. Survival analyses among all patients and according to *TP53* and progression of disease within 24 months status. (A) Progression-free survival (PFS) in evaluable patients (N=47). (B) Overall survival (OS) in evaluable patients (N=47). (C) PFS by *TP53* status (wild-type [WT] *vs.* deletion alone *vs.* mutation (MUT) alone *vs.* mutated/deleted, N=41). (D) OS by *TP53* status (WT *vs.* deletion (DEL) alone *vs.* MUT alone *vs.* mutated/deleted, N=41). (E) PFS by *TP53* status (WT/retained *vs.* altered, N=41). (F) OS by *TP53* status (WT/retained *vs.* altered, N=41). (G) OS by progression of disease within 24 months (POD24) status. LOH: loss of heterozygosity.

six harbored both. High-risk patients were enriched for MCL harboring *TP53* alterations (*Online Supplementary Table S1*).

Efficacy outcomes

By intent-to-treat (N=49), as of March 2023, the median follow-up among survivors was 63 months (range, 11-84). At EoT (N=47 patients), the overall response rate was 88% (*Online Supplementary Figure S1*), all complete responses (CR). Examining the three patients with stable disease or progressive disease on treatment, two had tumor *TP53* status assessed and both harbored deletion and mutation. Among 43 patients with CR at EoT, 32 have since relapsed at a median of 40 months (95% confidence interval [CI]: 33-49) from enrollment. The median PFS among all patients was 49 months (95% CI: 38-59; Figure 2A) and the median OS was not reached [NR]; Figure 2B); the rates of 3-year PFS and OS were 63% (95% CI: 50-78) and 85% (95% CI: 76-96), respectively. PFS and OS differed according to *TP53* status (Figures 2C-F): 3-year PFS, wild-type [WT] 78% (95% CI: 64-95) *versus* altered 38% (95% CI: 20-71; log-rank *P*=0.04); 3-year OS WT 96% (95% CI: 89-100) *versus* altered 69% (95% CI: 49-96) as well as MIPI-b14 and study risk category (PFS, not OS; Table 2). Median OS differed numerically by CR status (CR *vs.* <CR) post-len-R-CHOP (22 months *vs.* NR) but this did not meet the threshold for statistical significance (*Online Supplementary Table S5*).

At relapse/disease progression, all response-evaluable patients but three (with localized MCL amenable to radiation) received BTKi-based therapy (8 single-agent, 18 combination therapy), of which 19 (76% of response-assessed) had disease response. Nine patients had *TP53* mutation at relapse and received BTKi, of whom seven (78%) experienced disease response. The median survival among relapsing/progressing patients was 32 months (95% CI: 19-NR) from time of relapse/progression and 16 patients are deceased, including two patients deceased due to SARS-CoV2 infection coincident with responding MCL. Progression during study/within 1 year of EoT and relapse within 2 years of EoT were each associated with inferior OS (Table 3), as was POD24 (Table 3; Figure 2G). The seven patients who progressed within 2 years of diagnosis had a median OS of 17 months (95% CI: 7-NR) after the 2-year time point

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

Characteristic	Counts			PFS		OS	
	Overall[1]	PFS events[1]	OS events[1]	Median PFS in months (95% CI)	*P*[2]	Median OS in months (95% CI)	*P*[2]
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.* one-hit vs. biallelic					0.004		<0.001
WT	27	16	5	51 (49-NR)		NR	
MUT or DEL	8	5	3	48 (29-NR)		NR (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)	

[1]N; [2]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.

versus an unreached median for the 38 non-progressing patients (*P*<0.001).

Toxicity outcomes

Treatment-related toxicities of interest are displayed in Table 4. At interim evaluation following 16 total patients, the 3,000 mg/m^2 cytarabine dose was removed due to a pattern of excessive hematologic toxicity of grades 3/4 anemia and thrombocytopenia with one or both of these occurring in seven of ten patients who received 3,000 mg/m^2. Cycle 2 of cytarabine was dose-reduced or omitted in all but two such patients and no major bleeding events occurred during this period. For cycle 2 cytarabine dosing, one patient received 500 mg/m^2, two 750 mg/m^2, 13 1,000 mg/m^2, 24 2,000 mg/m^2, and two 3,000 mg/m^2.

No treatment-related deaths occurred; one patient withdrew during len-R-CHOP due to tumor lysis syndrome. The most common grade ≥3 toxicities were hematologic, most commonly neutropenia (37% of patients undergoing len-R-CHOP, 70% of patients undergoing R-HiDAC, and 42% of patients receiving R-len). The rates of febrile neutropenia were 14%, 21%, and 7% and grade ≥3 thrombocytopenia 22%, 83%, and 9% (one grade 1 bleeding event occurred) in the three treatment phases, respectively.

Treatment-related adverse events frequently led to dose reductions or delays (Table 4): 41% of patients receiving len-R-CHOP, 36% R-HiDAC, and 53% R-len. For the 20 patients requiring dose reduction/delay during len-R-CHOP, reasons included neutropenic fever (N=7), cytopenia (N=7), infection (N=3), rash (N=2), or other causes (N=2); see protocol in the *Online Supplementary Appendix* for lenalidomide and cytarabine dose reduction guidelines (R-CHOP dosing was not altered).

Rare grade ≥3 infections occurred, including four instances of pneumonia, one skin/soft tissue, and one sepsis. Non-hematologic grade ≥3 toxicities are detailed in the *Online Supplementary Table S4*; we did not observe malignancies ascribed to treatment. Notably frequent grade ≤2 toxicities across phases of treatment included fatigue (e.g., 35% during len-R-CHOP), peripheral sensory neuropathy (29% during len-R-CHOP), and rash (20% during both len-R-CHOP and R-len).

Measurable residual disease outcomes

Among 46 patients with an available pretreatment tumor sample, clonal rearrangement characterization was successful in 89% of patients; all baseline (pretreatment) blood samples were dMRD. An MRD result at the level of 1x10^{-5} sensitivity (1E-5) sensitivity was available at all four post-baseline time points in 28 patients (Figure 3A). At 1E-5, 32% (12/37) of patients remained dMRD following len-R-CHOP, of which 11 converted to uMRD following R-HiDAC thus 3% (1/37) were dMRD following both len-R-CHOP and R-HiDAC consolidation. PFS did not differ by MRD status at 1E-5 following len-R-CHOP and only one patient remained dMRD following R-HiDAC at 1E-5. At the level of 1x10^{-6} sensitivity (1E-6; Figure 3B; *Online Supplementary Table S2*), MRD status did predict median PFS following both len-R-CHOP (39 months [95% CI, 21-46] for dMRD *vs*. 54 months [95% CI, 28-NR] for uMRD; *P*=0.03) and R-HiDAC (19 months [95% CI, 11-NR] for dMRD *vs*. 45 months [95% CI, 27-NR] for uMRD; *P*=0.005).

Among 37 patients with MRD results at 1E-5 at EoT, four were dMRD, two of which were simultaneous (within 2 weeks of testing) with relapse; the remaining two patients dMRD had median PFS of 5 (95% CI, 4-NR) months *versus*

Table 3. Overall survival by progression status after end of treatment (among 49 patients, 4 came off study before end of treatment and 1 was lost to follow-up within 1 year of end of treatment).

Characteristic	Overall[1]	OS events[1]	36-month OS from EoT in months, % (95% CI)	Median OS from EoT in months (95% CI)	*P*[2]
<CR at EoT or progression/relapse within 1 year of EoT					<0.001
No	36	6	90 (80-100)	53 (53-NR)	
Yes	8	5	38 (15-92)	26 (19-NR)	
Progression/relapse within 2 years of EoT					<0.001
No	29	3	96 (88-100)	NR (53-NR)	
Yes	15	8	53 (33-86)	49 (28-NR)	
			24-month OS from 2 years post-diagnosis, % (95% CI)	**Median OS from 2 years post-diagnosis in months (95% CI)**	
POD24					<0.001
No	37	7	91 (82-100)	85 (41-NR)	
Yes	7	4	43 (18-100)	17 (7.0-NR)	

[1]N; [2]log-rank test. CR: complete response; EoT: end of treatment; OS: overall survival; CI: confidence interval; POD24: progression of disease within 24 months; NR: not reached.

Table 4. Significant (occurring in ≥5% of patients or resulting in treatment dose adjustment or delay) treatment-related adverse events.*

Timing† Toxicity	Len-R-CHOP N=49	R-HiDAC‡			R-len N=45
		All doses N=47	<3,000 mg/m² N=37	3,000 mg/m² N=10	
Hematologic, grades 3/4, N (%)					
Anemia	10 (20)	24 (51)	19 (51)	3 (30)	0
Thrombocytopenia	11 (22)	39 (83)	30 (81)	8 (80)	4 (9)
Neutropenia	18 (37)	33 (70)	25 (68)	7 (70)	19 (42)
Febrile neutropenia	7 (14)	10 (21)	8 (22)	2 (20)	3 (7)
Infection,§ grades 3/4, N (%)					
Any	1 (2)	1 (2)	1 (3)	0	5 (11)
Pneumonia	1	-	-	-	3
Skin/soft tissue	-	-	-	-	1
Sepsis	-	-	-	-	1
Metapneumovirus	-	1 (2)	1 (3)	-	-
Toxicity resulting in dose adjustment or delay,# N (%)					
Any toxicity	20 (41)	17 (36)	7 (19)	10 (100)	23 (53)
Due to febrile neutropenia	7	7	5	2	2
Due to cytopenia(s)	7	12	5	7	29
Due to infection	3	2	1	1	5
Due to rash	2	-	-	-	3
Due to other causes	2	3	2	1	4
Common toxicities, any grade, N (%)					
Gastrointestinal					
Constipation	16 (33)	-	-	-	1 (2)
Dysgeusia	7 (14)	1 (2)	-	-	2 (4)
Nausea	6 (12)	-	-	-	1 (2)
Diarrhea	6 (12)	2 (4)	-	-	6 (13)
Mucositis	5 (10)	1 (2)	-	-	4 (9)
General/metabolism					
Fatigue	17 (35)	8 (17)	-	-	7 (16)
Anorexia	3 (6)	-	-	-	-
Musculoskeletal/connective tissue					
Arthralgia	6 (12)	-	-	-	1 (2)
Myalgia	6 (12)	2 (4)	-	-	1 (2)
Edema	5 (10)	2 (4)	-	-	1 (2)
Nervous system					
Peripheral sensory neuropathy	14 (29)	6 (13)	-	-	8 (18)
Memory impairment	-	-	-	-	3 (7)
Respiratory					
Dyspnea	5 (10)	2 (4)	-	-	1 (2)
Hoarseness	3 (6)	-	-	-	1 (2)
Nasal congestion	3 (6)	1 (2)	-	-	
Skin/subcutaneous tissue					
Rash	10 (20)	-	-	-	9 (20)
Alopecia	5 (10)	2 (4)	-	-	-
Dry skin	4 (8)	-	-	-	4 (9)
Pruritus	3 (6)	-	-	-	-

*Data are presented as N patient (%) except for totaled toxicities which are at the toxicity instance (not patient) level. †Toxicities related to a phase of treatment affecting the next phase are ascribed to the preceding therapy; e.g., a patient with grade 3 anemia due to cycle 4 of len-R-CHOP causing delay in cycle 1 of R-HiDAC, this would be attributed to len-R-CHOP. ‡37 patients received only <3,000 mg/m², seven patients received 1 cycle of 3,000 mg/m² followed by 2,000 mg/m² for cycle 2, 2 patients received both cycles at 3,000 mg/m², and 1 patient received only 1 cycle total at 3,000 mg/m²; toxicities are listed under 3,000 g/m² if a patient received at least 1 dose at this level. §Instances of febrile neutropenia with an identified infectious source/agent are noted under both Infection and Febrile neutropenia categories. #Instances of dose reduction or delay due to multiple causes are listed under each category. Len-R-CHOP: lenalidomide plus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HiDAC: rituximab plus high-dose cytarabine; R-len: rituximab plus lenalidomide.

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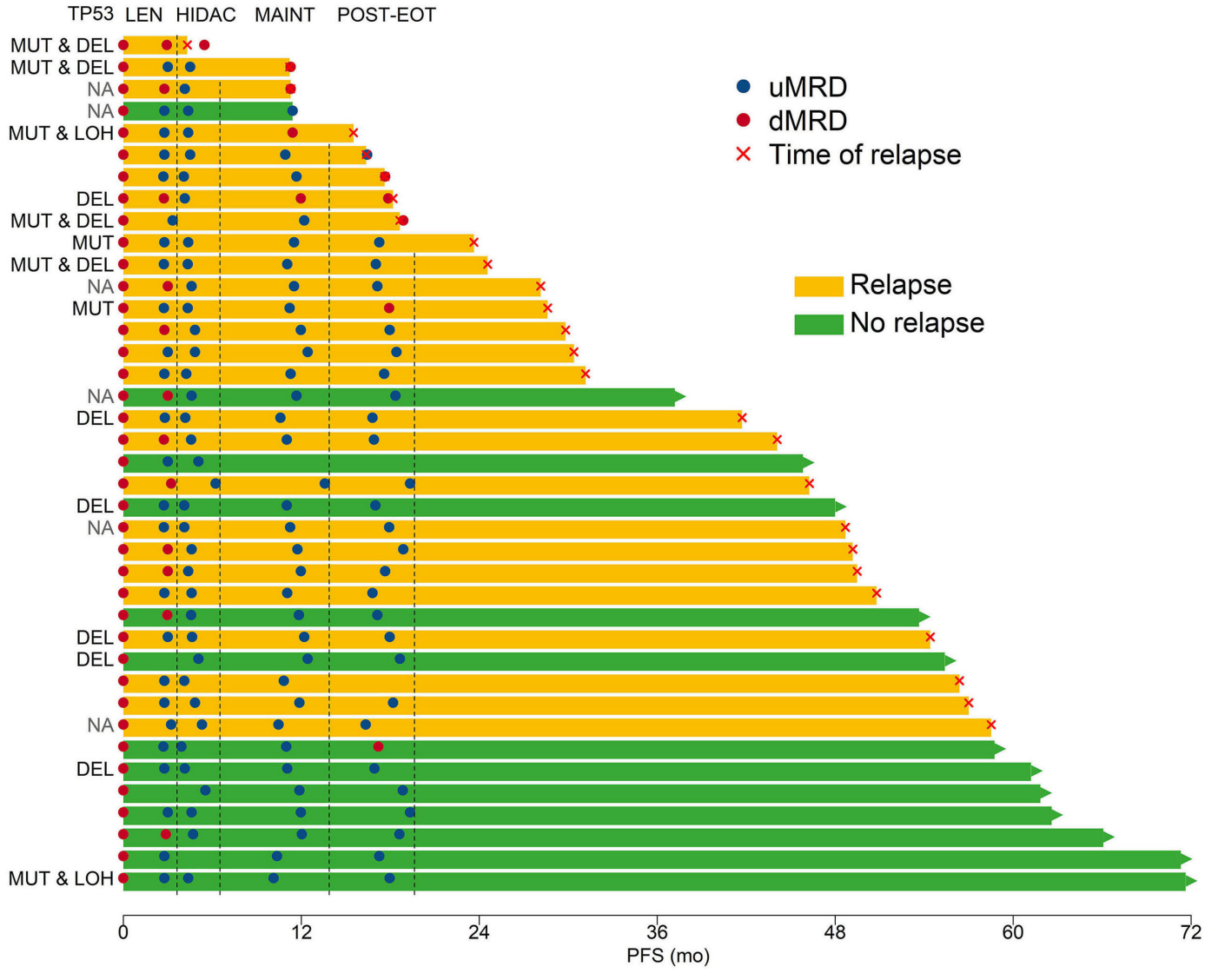

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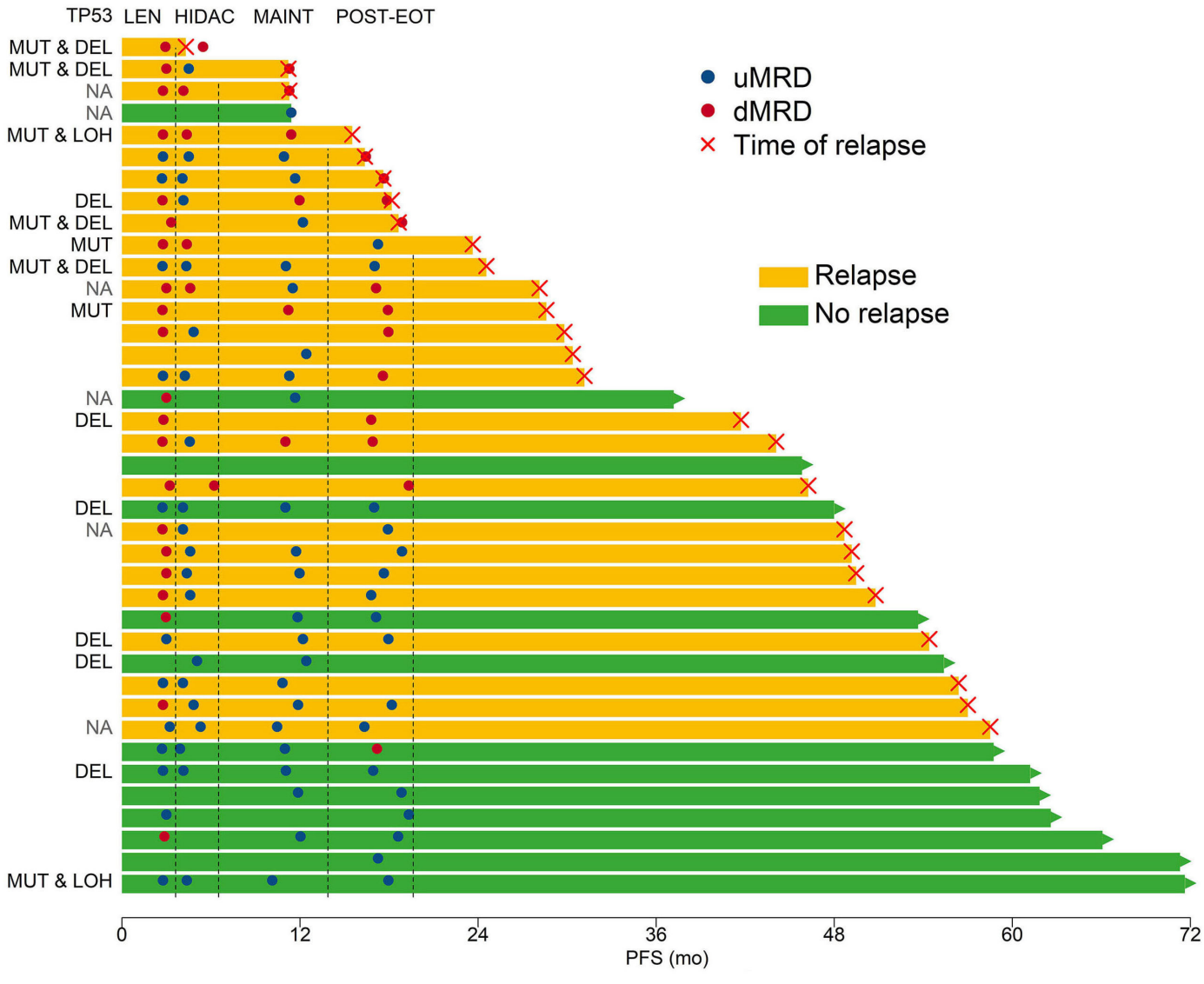

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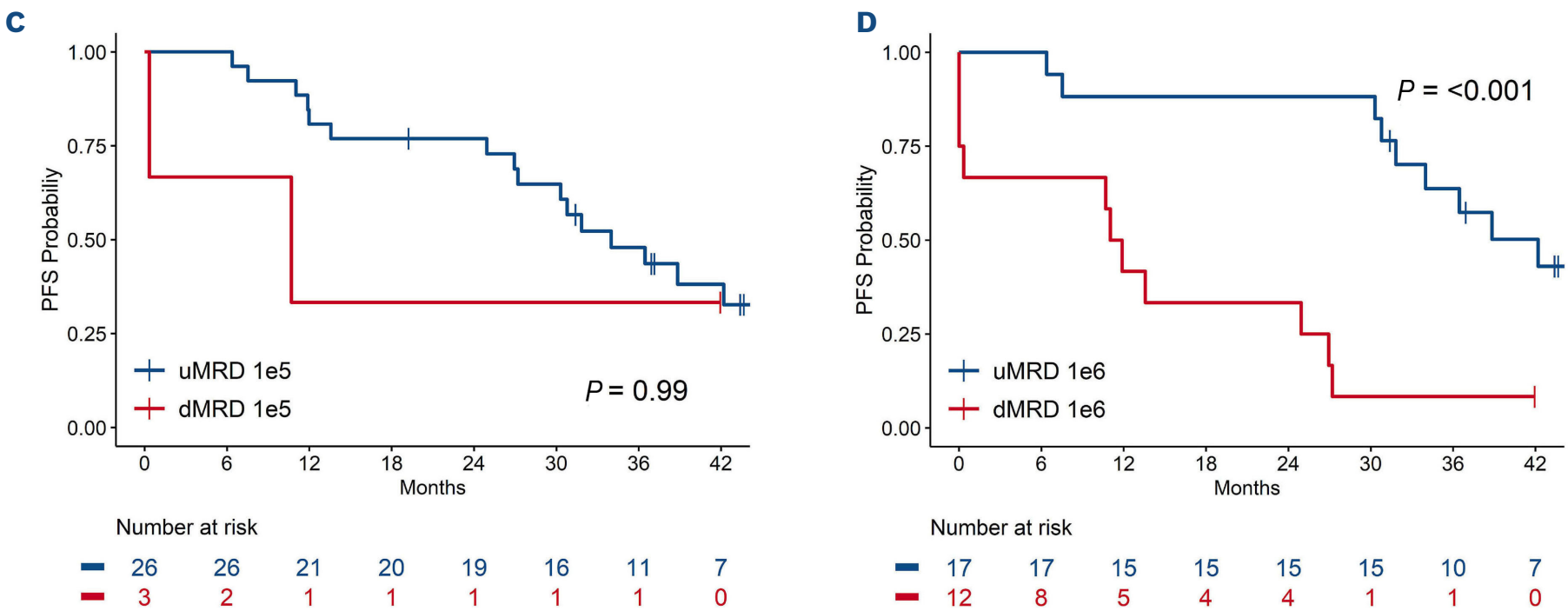

Figure 3. Measurable residual disease analyses. (A) Measurable residual disease (MRD) swimmer plot at $1x10^{-5}$ sensitivity. (B) MRD swimmer plot at $1x10^{-6}$ sensitivity. (C) Progression-free survival (PFS) by MRD status at $1x10^{-5}$ at 6 months post-end of treatment (EoT). (D) PFS by MRD status at $1x10^{-6}$ at 6 months post-EoT; DEL: deletion, MUT: mutation; LOH: loss of hetrozygosity; dMRD: detectable MRD; uMRD: absence of detectable MRD.

38 (95% CI, 33-NR) months for the 32 patients non-relapsed with uMRD (*P*<0.001). All six patients whose MCL was uMRD at 1E-6 at EoT and converted to dMRD at 6 months post-EoT eventually experienced disease relapse. MCL MRD status at 1E-6 at 6-months post-EOT was predictive of PFS (Figure 3C; *Online Supplementary Table S2*; *Online Supplementary Figure S2*): among the 29 patients with 1E-6 MRD results (12 dMRD, 17 uMRD), median PFS was 42 months (95% CI, 34-NR) for uMRD *versus* 11 months (95% CI, 0-NR) for dMRD (*P*<0.001). Examining concordance between PET/CT results and MRD status at 1E-5 (*Online Supplementary Table S3*), there were 111 coincident testing instances, of which most (86%) were concordant: six as PET^+/dMRD and 89 as PET^-/uMRD. Sixteen coincident tests showed discordant results: five PET^+/uMRD (all 5PS =4; 3 after len-R-CHOP and 2 after R-HiDAC) and 11 PET^-/dMRD. In all three instances of PET^+/uMRD discordance following len-R-CHOP, the patients' subsequent PET eventually was rated as 5PS ≤3. One patient with PET^+/uMRD discordance following R-HiDAC converted to PET- followed R-len maintenance whereas the other patient remained PET^+ and had conversion to dMRD. Both patients whose disease was PET^-/dMRD at EoT have experienced disease relapse.

Tumor genomic and cytogenetic alterations

Forty-five patients underwent NGS-based targeted exome sequencing (Figure 4) and 20 patients therein underwent analysis of paired tumor sequencing at relapse/progression. As shown in Figure 4A, besides *TP53* (N=8, 22%), commonly mutated genes at baseline included *ATM* (53%) and *KMT2D* (24%). A subset of 11 patients also had expanded cytogenetic testing at baseline (karyotype, N=7; SNP array, N=3; both, N=1) of whom two had complex karyotype (≥3 unrelated cytogenetic abnormalities beyond t(11;14)). Six of 20 patients with paired sequencing at time of disease relapse/progression demonstrated emerging *CDKN2A* and CDKN2B homozygous deletions compared to baseline (McNemar test for paired data, *P*=0.13). No gene besides *TP53* was prognostic when altered at baseline (hazard ratio [HR] for PFS =5.91; 95% CI: 2.35-14.84; HR for OS =7.87; 95% CI: 2.21-28.02).

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 consolidative 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

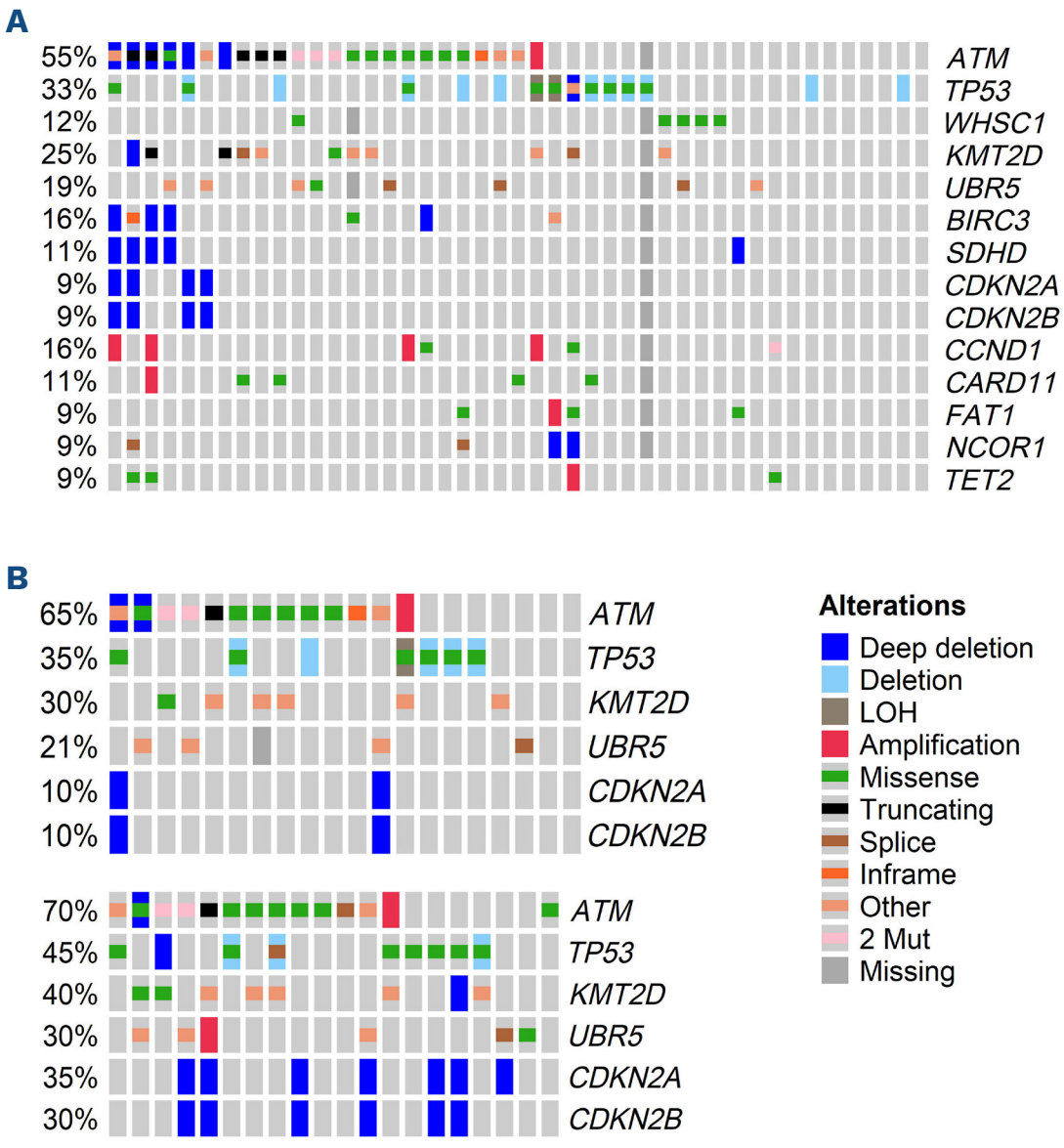

Figure 4. Genomic analyses. (A) Tile plot for baseline genomic alterations including all genes altered in cohort in at least 4 instances (N=45 patients). Source of *TP53* deletion status includes all possible testing modalities, including targeted sequencing and other cytogenetic studies (karyotype, single nucleotide polymorphism array, fluorescence *in situ* hybridization). (B) Tile plot displaying genomic alterations at progression evaluating the top 6 genes altered in relapsed samples (N=20 patients). LOH:loss of heterozygosity; Mut: mutations.

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 with this approach.[1,3,17] An updated analysis from the European Mantle Cell Lymphoma Network phase 3 clinical trial that established the role of HDT/ASCR 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.

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=12) 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 to 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 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 an of 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 in *CDKN2A* and *CDKN2B* loss at time of relapse, similar to enrichment 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.

Disclosures

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Contributions

AK and AZ designed the study. ZDE-P wrote the manuscript. ED conducted biostatistical analyses. UA and CH assisted with genomic and cytogenetic analyses. CLB, PC, PD, JG, PAH, MJM, AJM, CHM, CO, DJS, AY, ADZ, and AK enrolled patients, oversaw treatments, and graded toxicities. LL and AJ assisted with data collection and oversight. AD and CH provided pathology input. APJ and CM performed and provided input on MRD analyses. GS provided critical input on the manuscript. HS interpreted PET/CT scans. All authors read and approved the final manuscript for submission.

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Data-sharing statement

The data generated in this study are available upon request from the corresponding author.

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