VENETOCLAX, IBRUTINIB, PREDNISONE, OBINUTUZUMAB, AND LENALIDOMIDE (VIPOR) IN RELAPSED/REFRACTORY (R/R) AND TREATMENT-NAÏVE (TN) MANTLE CELL LYMPHOMA (MCL)

R. Lakhotia MBBS[1], S. Pittaluga MD, PhD[1], J. Phelan PhD[1], Y. Yang PhD[1], T. Davies-Hill[1], J. Simard MD[1], J. Muppidi MD, PhD[1], D. Huang MD[1], C. Thomas PhD[2], M. Ceribelli PhD[2], F. Tosto MS[2], A. Pradhan NP[1], A. Juanitez RN[1], L. Rimsza MD[3], A. Jacob MS[4], H. Simmons PhD[4], S. Steinberg PhD[1], E. Jaffe MD[1], L. Staudt MD, PhD[1], M. Roschewski MD[1], W. Wilson MD, PhD[1], and C. Melani MD[1]

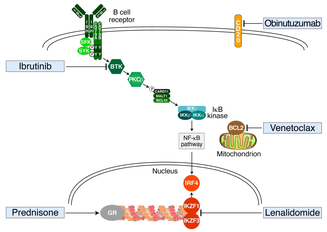
1. National Cancer Institute, Bethesda, MD USA
2. National Center for Advancing Translational Sciences, Bethesda, MD USA
3. Mayo Clinic, Scottsdale, AZ USA
4. Adaptive Biotechnologies, Seattle, WA USA

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INTRODUCTION

- MCL is biologically and clinically heterogeneous, and incurable with standard chemotherapy
- Novel targeted agents can disrupt key survival pathways in lymphoma **(Figure 1)**

Figure 1: ViPOR Targets Multiple B-Cell Survival Pathways

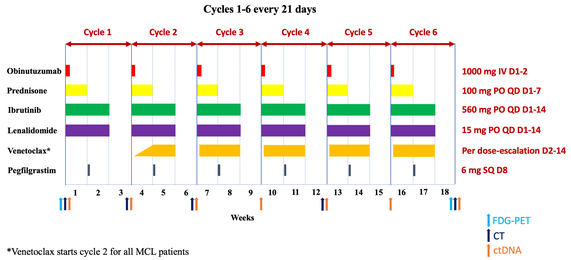


- Oral targeted monotherapy does not induce deep remission and requires extended duration
- ViPOR is a multiagent targeted regimen that is safe and induces durable complete responses (CRs) in R/R B-cell lymphomas (Melani et al. Blood. 2020).
- Herein, we present the data for the MCL cohort of the ongoing phase 1b/2 ViPOR study

METHODS

- R/R and TN MCL patients with adequate organ function were eligible.
- One prior rituximab-containing regimen was required for R/R patients.
- Ph 1 (R/R only): 3+3 design to determine the MTD of 2 DLs of dose-escalated venetoclax (200 mg and 400 mg) with fixed-doses of ibrutinib, prednisone, obinutuzumab, and lenalidomide **(Figure 2)**

Figure 2: ViPOR Regimen and Study Schema



*Venetoclax starts cycle 2 for all MCL patients

- Phase 2: Dose expansion cohorts of R/R and TN MCL at the MTD.
- Maximum 6 cycles of ViPOR q21 days were administered without maintenance or consolidation.
- All patients were admitted for C2 for 12-day venetoclax ramp-up with TLS prophylaxis/monitoring.
- All patients received PCP and G-CSF prophylaxis with VTE prophylaxis per investigator discretion.
- Plasma for ctDNA collected at baseline, prior to each cycle, at each follow-up visit, and at disease progression, and assessed via NGS of rearranged VDJ segments of Ig receptor genes (clonoSEQ®).

RESULTS

Table 1: Patient Characteristics

Characteristic	R/R MCL (N=12)	TN MCL (N=14)	All MCL (N=26)
Age – median (range) yr.	71 (57-79)	66 (41-82)	67 (41-82)
Male sex – no. (%)	8 (67%)	11 (79%)	19 (73%)
Simplified MIPI – no. (%)			
Low-risk (0-3)	1 (8%)	7 (50%)	8 (31%)
Intermediate-risk (4-5)	7 (58%)	4 (29%)	11 (42%)
High-risk (6-11)	4 (33%)	3 (21%)	7 (27%)
MCL35 Risk Category – no. (%) (N=20)			
Low-risk	2 (25%)	5 (42%)	7 (35%)
Standard-risk	5 (63%)	5 (42%)	10 (50%)
High-risk	1 (13%)	2 (17%)	3 (15%)
Stage IV disease – no. (%)	11 (92%)	14 (100%)	25 (96%)
BM involvement	9 (75%)	14 (100%)	23 (88%)
EN involvement	10 (83%)	13 (93%)	23 (88%)
Both	8 (67%)	13 (93%)	21 (81%)
Blastoid or pleomorphic – no. (%)	2 (17%)	5 (36%)	7 (27%)
KI-67 ≥30% - no. (%)	5 (42%)	5 (36%)	10 (38%)
TP53 IHC >50% – no. (%)	3 (25%)	1 (7%)	4 (15%)
TP53 mutation – no. (%) (N=21)	4 (50%)	2 (15%)	6 (29%)
Prior therapies– median (range)	3 (1-4)	--	--
Prior therapy – no. (%)			
Rituximab	12 (100%)	--	--
Anthracycline	6 (50%)	--	--
Bendamustine	6 (50%)	--	--
BTKi	5 (42%)	--	--
ASCT	3 (25%)	--	--
CAR-T	1 (8%)	--	--
Refractory to last therapy – no. (%)	8 (67%)	--	--

Table 2A: Hematologic Adverse Events (% Cycles)

Adverse Event (AE) Term	ViPOR cycles (N=140)			
	All Grade	Grade 1-2	Grade 3	Grade 4
Thrombocytopenia	88 (63%)	67 (48%)	17 (12%)	4 (3%)
Anemia	54 (39%)	42 (30%)	12 (9%)	0
Neutropenia	19 (14%)	7 (5%)	8 (6%)	4 (3%)
Febrile neutropenia	0	0	0	0

Table 2B: ≥G3 Non-Hematologic Adverse Events (% Patients)

Adverse Event (AE) Term	MCL patients (N=26)	
	Grade 3	Grade 4
Hypokalemia	6 (23%)	0
Rash	3 (12%)	0
Fatigue	2 (8%)	0
Atrial fibrillation	2 (8%)	0
Syncope	2 (8%)	0
Alk. Phos. increased	1 (4%)	0
AST increased	1 (4%)	0
Bilirubin increased	1 (4%)	0
ALT increased	1 (4%)	0
Hypomagnesemia	1 (4%)	0
Fever	1 (4%)	0
Infusion related reaction	1 (4%)	0
Lung infection	1 (4%)	0
Hypotension	1 (4%)	0
Skin infection	1 (4%)	0
Spinal fracture	1 (4%)	0
Thromboembolic event	1 (4%)	0
Urinary tract infection	1 (4%)	0
Dehydration	1 (4%)	0
Shingles	1 (4%)	0
VZV meningitis	1 (4%)	0
Tumor lysis syndrome	0	0

Dose Reductions: 27% pts
- 87% lenalidomide
- 11% venetoclax

- 38% for G4 thrombocytopenia
- 25% for G4 neutropenia

86% pts completed 6C

0 of 9 pts experienced DLTs
- Venetoclax 400mg → RP2D for expansion

Figure 3: Change in Tumor Burden and Outcomes

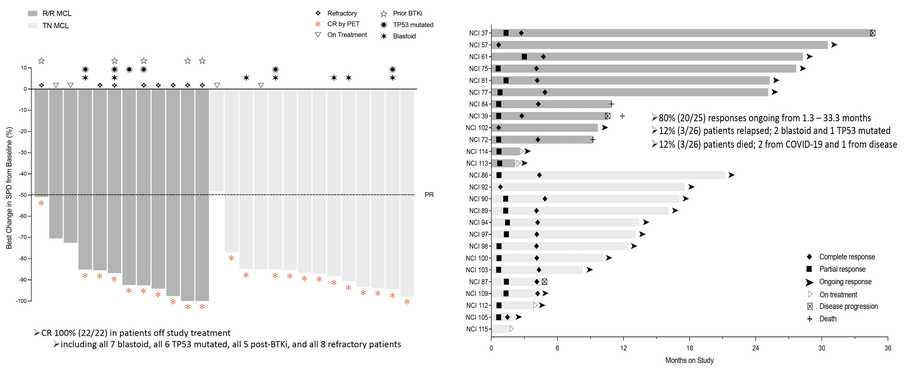


Figure 4: Time to Progression (TTP) in All MCL and by Subgroup

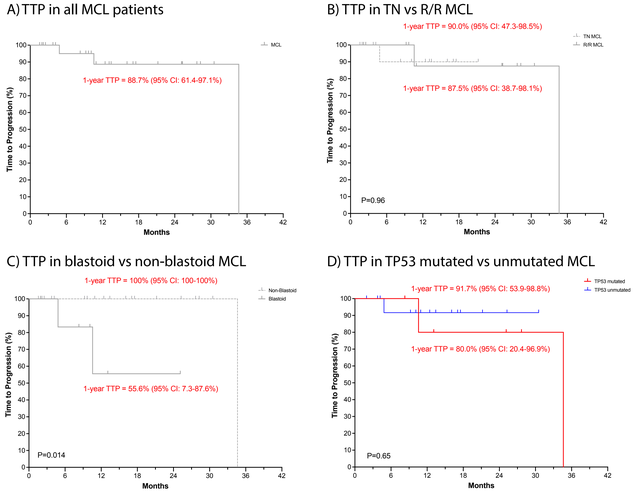
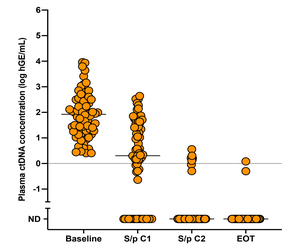


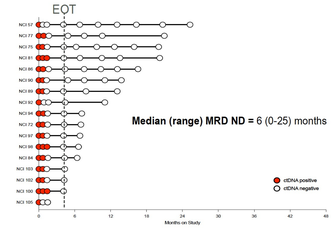
Figure 5A: Interim Minimal Residual Disease

95% (21/22) had calibrating rearrangement (Sensitivity 1x10^{-6})



uMRD: (%/No. Pts)	Baseline	S/p C1	S/p C2	EOT
	0% (0/20)	15% (3/20)	80% (16/20)	95% (19/20)

Figure 5B: Surveillance MRD in CRs without Relapse



Median (range) MRD ND = 6 (0-25) months

CONCLUSIONS & DISCUSSION

- Fixed-duration ViPOR x 6 cycles induces a high rate of uMRD CRs in MCL
  - CR rate 100% with uMRD 95% in off-treatment patients
  - Includes blastoid, *TP53* mutated, post-BTKi, and refractory patients
- ViPOR is safe in MCL patients of all ages without significant TLS or DLTs
  - 12-day **venetoclax** ramp-up to **400 mg** on C2 feasible without TLS
  - Hematologic AEs manageable with G-CSF and no febrile neutropenia
- Accrual continues in Ph 2 dose expansion cohort in both TN and R/R MCL
- Future development: Randomized Ph 2 study of ViPOR vs BTKi in R/R MCL

DISCLAIMER & DISCLOSURES

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Correspondence: christopher.melani@nih.gov