ASH Highlights and Commentary: Chronic Lymphocytic Leukemia and Lymphomas

**Abstract 125**

Five-Year Analysis of MURANO Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

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**Introduction:** The randomized Phase III MURANO study (NCT02005471) compared fixed-duration VenR with standard bendamustine-rituximab (BR) in R/R CLL. Deep responses with uMRD were associated with superior progression-free survival (PFS) of VenR vs BR with 48 months (mo) follow-up (f/u). We now report long-term MRD kinetics and updated efficacy outcomes, including re-exposure to VenR (to be presented), with a 5 year (yr) median follow-up (clinical cutoff date May 8, 2020).

**Methods:** As published, pts were randomized to VenR (Ven 400 mg daily for 2 yrs + standard dose R for the first 6 mo) or B (70 mg/m2)R (6 mo). A sub-study was introduced in 2018, allowing pts who developed progressive disease (PD) following Tx with BR or VenR to receive the MURANO VenR regimen. PFS was based on investigator assessment. Peripheral blood MRD was analyzed centrally by allele-specific oligonucleotide polymerase chain reaction and/or flow cytometry. Pts were categorized by MRD status as previously reported, using <10-4 threshold for uMRD. MRD conversion was defined as 2 consecutive assays detecting MRD or PD in pts who previously had uMRD. Genomic complexity (GC) and del(17p) status were assessed by array comparative genomic hybridization. GC was defined as ≥3 copy number variations (CNV). All p-values are descriptive.

**Results:** 389 pts were enrolled (VenR, n=194; BR, n=195). With a median f/u of 59.2 (range, 0-71.5) mo, the PFS benefit with VenR over BR was sustained (HR, 0.19 [95% CI: 0.15-0.26]; p<0.0001). Median PFS was 53.6 (95% CI: 48.4-57.0) mo for VenR and 17.0 (95% CI: 15.5-21.7) mo for BR. For pts who completed the full 2 yrs of Ven Tx (n=130), PFS estimates 36 mo post-end of treatment (EOT) were ~51.1% (95% CI: 40.2-61.9). Overall survival (OS) benefit was maintained for pts treated with VenR vs BR (HR, 0.40 [95% CI: 0.26-0.62]; p<0.0001), with 5-yr OS estimates of 82.1% (95% CI: 76.4-87.8) for VenR and 62.2% (95% CI: 54.8-69.6) for BR.

Improved OS outcome was observed among the VenR pts that reached EOT without PD and had uMRD (83/118) compared with those with MRD (35/118), with 3-yr post-EOT survival estimates of 95.3% (95% CI: 90.0-100.0) vs 85.0% (95% CI: 72.8-97.2), respectively (Figure 1). Of the pts with uMRD at EOT, 32/83 had not shown PD and remained uMRD at the 5-yr update, 4/83 had PD without prior confirmed MRD conversion and 47/83 had MRD conversion. Median time to MRD conversion from EOT was 19.4 (95% CI: 8.7-28.3) mo.
mo. Of the 47/83 pts with confirmed MRD conversion, 19 subsequently developed PD by International Workshop on CLL criteria with a median time to PD from MRD conversion of 25.2 (95% CI: 19.4-30.4) mo. These 19 pts exhibited more rapidly increasing rates of MRD post-EOT than pts that had MRD conversion but were PD-free (Figure 2).

Among pts that were uMRD at EOT, the baseline presence of del(17p), GC and unmutated immunoglobulin heavy chain gene (IGVH) were each associated with increased risk of MRD conversion and subsequent PD post-EOT (Table 1). All 4 pts with del(17p) experienced MRD conversion with subsequent PD. 8/18 (44%) pts with GC vs 8/40 (20%) pts without GC eventually converted to MRD and developed PD. The rate of MRD conversion with eventual PD was also higher among those with unmutated IGVH (21/56; 37%) than those without (1/23; 4%). Once uMRD at EOT was achieved, pts without del(17p) or GC, or with mutated IGVH, were more likely to maintain uMRD or experience MRD conversion without subsequent PD at this follow-up (Table 1).

No new safety signals were identified. Excluding non-melanoma skin cancers, 2 second primary malignancies (VenR [acute myeloid leukemia and multiple myeloma]) were reported since the previous update. Rates of Richter transformation remained balanced between treatment arms (7 on VenR, 6 on BR).

Following PD on the main study, 29 pts were enrolled in the sub-study (re-treatment; n=21, crossover; n=8). Further data on their biologic profile, updated response rates, and MRD in the re-treatment cohort will be presented.

**Conclusions:** Five-yr data from MURANO demonstrate sustained PFS and OS benefit with VenR vs BR. In the VenR cohort, uMRD at EOT is associated with improved OS. Unmutated IGVH, del(17p) and GC (≥3 CNV) are associated with higher rates of MRD conversion and subsequent PD after attaining uMRD at EOT. Overall, a substantial proportion of pts who completed Ven Tx retained uMRD 36 mo after treatment cessation, displaying durable response following 2-yr fixed-duration VenR.

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**The Advanced Practitioner Perspective:**

*Sara Tinsley, PhD, APRN, AOCN*

Is cure within reach for patients with chronic lymphocytic leukemia (CLL)? This is an ongoing discussion among CLL experts. The MURANO study added evidence to the debate based on a 5-year analysis of data presented at the 62nd American Society of Hematology Annual Meeting and Exposition. A subset of patients with undetectable minimal residual disease (uMRD) treated with venetoclax and rituximab (VenR) remained without evidence of progressive disease for 36 months following 24 months of treatment. Continued follow-up of these patients will define whether they are cured. The results are encouraging for the treatment of relapsed/refractory CLL patients with VenR.

The randomized phase III MURANO study consisted of fixed-duration VenR compared with standard-dose bendamustine and rituximab (BR) in patients with relapsed or refractory CLL. There were 194 patients in the VenR arm and 195 patients in the BR arm. In the BR arm, patients were treated with bendamustine and rituximab for 6 months. In the VenR arm, venetoclax 400 mg daily was given for 24 months with 6 monthly treatments with rituximab. The superior regimen was VenR, with median progression-free survival (PFS) of 53.6 months compared with a PFS of 17 months with BR. Overall survival (OS) estimates at 5 years for VenR vs. BR were 82.1% and 62.2%, respectively.

The subset of patients that experienced improved OS in the VenR arm had uMRD at the end of treatment (83/118) compared with those with MRD (13/118). For patients with MRD conversion (47/83), 19 later developed progressive disease with median time from MRD conversion of approximately 25 months.

A separate group of CLL patients including del 17p, genomic complexity, and unmutated immunoglobulin heavy chain variable region experienced higher rates of MRD conversion and eventual progressive disease after attaining uMRD at the end of treatment. This group also experienced faster MRD doubling time following end of treatment. Continued research is needed for this distinct group of CLL patients.

**Implications for the Advanced Practitioner**

For the advanced practitioner, this abstract from ASH provides evidence for the clinical
utility of measuring MRD, with patients with CLL who obtained uMRD at end of treatment having improved PFS and OS. In addition, there is strong evidence of the benefit of targeted therapy in combination with immunotherapy, and the potential for cure in a subset of patients with CLL. In addition, VenR has a clear treatment duration, which is appealing to our patients.

**Disclosure:** Dr. Tinsley has served as a consultant for Agios, Celgene, Incyte, Jazz Pharmaceuticals, and Novartis, and on the speakers bureaus for Astellas Pharma, Celgene, Incyte, and Jazz Pharmaceuticals.

**Abstract 598**

**Phase 1b/2 Study of ViPOR (Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide) in Relapsed/Refractory B-Cell Lymphoma: Safety, Efficacy and Molecular Analysis**

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**Background:** Aggressive B-cell non-Hodgkin lymphoma (NHL) can be cured with chemoimmunotherapy; however, those who fail primary therapy and those with indolent NHL are rarely curable. Targeted agents can disrupt key survival pathways in NHL such as regulation of apoptosis (BCL2: venetoclax), B-cell receptor signaling (BTK: ibrutinib), and NF-κB survival pathways (IRF4/SPIB: lenalidomide). These agents are active as monotherapy but fail to induce deep responses and require continuous therapy. Also, genetically defined subtypes of NHL that best respond to these targeted agents are undefined. Synergistic cytotoxicity has been shown with these targeted therapies and corticosteroids in DLBCL cell lines. We hypothesized that combining agents that target multiple survival pathways will leverage efficacy and time-limited, cyclic dosing will limit toxicities.

**Methods:** Relapsed/refractory (R/R) B-cell NHL pts, excluding MCL and CLL/SLL, with adequate organ function were eligible. A phase I “3+3” design was used to determine the maximum tolerated dose (MTD) of 4 dose-levels (DLs) of escalated venetoclax (200mg, 400mg, 600mg, and 800mg) PO D2-14 (starts cycle 2 for DL1) in combination with fixed-dose ibrutinib 560mg PO D1-14, prednisone 100mg PO D1-7, obinutuzumab 1000mg IV D1-2, and lenalidomide 15mg PO D1-14. A phase II expansion in R/R DLBCL and FL was included at the MTD. Up to 6 cycles of ViPOR every 21-days was given without maintenance. TLS and PCP prophylaxis was given to all pts and VTE prophylaxis and G-CSF use was per investigator discretion. Baseline CT, PET, BM and tumor biopsy was performed with CT scans after cycles 1, 2, 4, and 6 and PET after cycle 6 or at time of suspected CR. Surveillance CT was performed q3m for 1y, q4m x 1y, q6m x 1y, then annually x 2y.

**Results:** 53 pts were enrolled and treated; 17 in dose-escalation and 36 in dose-expansion. NHL subtypes included DLBCL (23), FL (19), HGBCL “double-hit” (9), and MZL (2). Of 32 aggressive pts, 34% transformed from indolent NHL. Median age was 57y (range 29-83) with stage III/IV disease in 89%, elevated LDH in 68%, and >2 EN sites in 57%. Median prior therapies was 3 (range 1-9) with 45% of pts refractory (i.e. <PR) to last therapy. A single dose-limiting toxicity (DLT) of G3 intracranial hemorrhage occurred at DL1 with concomitant enoxaparin and ASA. No other DLTs occurred in venetoclax 800mg was used in expansion. Heme AEs (% cycles) were most common and included thrombocytopenia (23%), neutropenia (23%) and anemia (7%). G-CSF was used in 92% of pts and 89% of cycles with only 3 (6%) cases of febrile neutropenia. Non-heme AEs (% pts) were mainly G1-2 and included diarrhea (67%), hypokalemia (56%), nausea (52%), and rash (42%). Most common G3-4 non-heme AEs included hypokalemia (19%), diarrhea (8%), and a.fib/flutter (6%). G4 TLS occurred in 1 pt with HGBCL after the first venetoclax dose and was successfully treated without further TLS upon continued
treatment. Dose reductions and delays occurred in 8% and 9% of cycles, respectively.

Of 53 total patients, 51 completed 1C of therapy with restaging CT and tumor reduction occurred in 90% of pts overall (Fig 1A). Of 44 pts who are now off therapy, 43 were evaluable for response with an ORR of 70% and 49% CR, with responses across all DLs and NHL subtypes. In 27 pts with aggressive NHL, ORR was 56% with 37% CR. Based on DLBCL subtype by IHC, ORR and CR rate was 62% (8/13) and 54% (7/13) in non-GCB and 50% (7/14) and 21% (3/14) in GCB DLBCL, respectively. In 16 pts with indolent NHL, ORR was 94% with 69% CR. ORR and CR rate was 52% (11/21) and 29% (6/21) in refractory pts and 86% (19/22) and 68% (15/22) in relapsed pts, respectively. ORR was 40% with 30% CR in 10 patients who failed prior CAR-T and completed ViPOR therapy. With a median potential f/u of 13m, median TTR and DOR was 0.8m and NR, respectively, with 25 (69%) of 36 responses ongoing. 5 pts relapsed after CR, including 2 non-GCB at 3m and 6m, 1 HGBCL at 5m, 1 FL at 6m, and 1 MZL at 16m. Median PFS and OS was 9m and NR, respectively; 20m and NR in indolent NHL, 3m and 13m in GCB, and 7m and 13m in non-GCB DLBCL (Fig 1B).

**Conclusions:** ViPOR is safe without unexpected toxicities observed. Most common AEs were hematologic with rare febrile neutropenia and no severe infections observed when given with G-CSF prophylaxis. ViPOR induces durable CRs without maintenance therapy, including refractory and post CAR-T pts. Molecular analyses are ongoing and will be presented at the meeting.

**The Advanced Practitioner Perspective:**

**Sara Tinsley, PhD, APRN, AOCN**

This abstract presented the results of an early phase 1b/2 study of venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide (ViPOR) in patients with relapsed and refractory B-cell lymphoma. ViPOR targets several key survival pathways in indolent and aggressive B-cell non-Hodgkin lymphoma (NHL). Patients with mantle cell lymphoma and CLL were excluded.

A phase 1 3 × 3 design was used to determine the maximum tolerated dose of four dose levels of venetoclax at 200 mg, 400 mg, 600 mg, and 800 mg given on days 2 to 14. Ibrutinib was given at 560 mg on days 1 to 14, prednisone 100 mg on days 1 to 7, obinutuzumab 1000 mg IV on days 1 and 2, and lenalidomide 15 mg on days 1 to 15. This combination was given for up to 6 cycles every 21 days. There was no maintenance phase. Venetoclax 800 mg was used in the expansion groups.

The eligibility criteria included patients with relapsed, refractory NHL who had adequate vital organ function. There was a total of 53 patients; 17 were included in the dose escalation group and 36 in the dose expansion group. Most patients were diagnosed with diffuse large B-cell NHL. The median number of prior treatment cycles was three.

**Implications for the Advanced Practitioner**

It is important for the advanced practitioner to appreciate the adverse events to tailor the visits to focus on potential problems and educate patients and their caregivers. Most side effects were hematologic, with neutropenia and thrombocytopenia at 23%. Anemia occurred at a rate of 7%. Neupogen was used in 92% of patients. Febrile neutropenia was rare at 6%. Nonhematologic adverse events were gastrointestinal, primarily grades 1 and 2. These included diarrhea (67%), hypokalemia (19%), nausea (52%), and rash (42%). The most common grade 3 to 4 nonhematologic adverse events included hypokalemia (19%), diarrhea (8%), and atrial fibrillation/flutter (6%). Only one instance of grade 4 tumor lysis occurred and was successfully treated.

Forty-three patients were evaluable for response, with an overall response rate of 70% and a 49% complete response rate. The responses occurred in all NHL subtypes. In 27 patients with aggressive NHL, the overall response rate was 56%, with a 37% complete response rate. In 16 patients with indolent NHL, the overall response rate was 94% with a 69% complete response rate. It is impressive that this study included patients who had failed chimeric antigen receptor T-cell therapy and front-line therapy, which meets a need for salvage treatment.

This regimen includes new agents with a high price tag but also with impressive results in relapsed/refractory NHL. There is a defined treatment period, followed by regu-
lar restaging at defined time intervals with observation, and no maintenance immunotherapy or chemotherapy.

For the advanced practitioner, it is important to be aware of this study for NHL patients who may need another treatment option and are willing to participate in clinical trials. This would require coordination of care with the National Cancer Institute. If this combination becomes a treatment option in the future, clear communication with patients about the multiple oral medications included in the treatment at specified time intervals is essential.

Disclosure: Dr. Tinsley has served as a consultant for Agios, Celgene, Incyte, Jazz Pharmaceuticals, and Novartis, and on the speakers bureaus for Astellas Pharma, Celgene, Incyte, and Jazz Pharmaceuticals.
The Burkitt Lymphoma International Prognostic Index (BL-IPI)

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Background. BL is a rare, high-grade B-cell lymphoma that is often studied in trials with small sample sizes. Historical definitions of “low-risk BL” vary between studies, use arbitrary cutoffs for lactate dehydrogenase (LDH), and identify a small favorable group, leaving >80-90% of patients (pts) in an undifferentiated “high-risk” category. A validated prognostic index will help compare study cohorts and better define good-prognosis pts for whom reduced treatment would be appropriate vs a poor-prognosis group in need of new approaches. Herein, we constructed and validated a simplified prognostic model for BL applicable to diverse clinical settings across the world.

Methods. We derived the BL-IPI from a large real-world evidence cohort of US adults treated for BL in 2009–2018 (Evans A, Blood 2020). Progression-free survival (PFS) from diagnosis until BL recurrence, progression, death, or censoring was the primary outcome. We first determined the best prognostic cutoffs for age, LDH (normalized to local upper limit normal, ULN), hemoglobin (Hgb), and albumin. Independent risk factors were ascertained by forward stepwise selection into Cox regression from candidate variables: age, sex, HIV+ status, ECOG performance status (PS) ≥2, advanced stage (3/4), involvement of >1 extranodal site, bone marrow, central nervous system (CNS), values of LDH, Hgb, and albumin. Derivation models used multiple imputation to mitigate bias from missing data and reported hazard ratios (HR) with 95% confidence interval (CI). BL-IPI groups, defined by inspection of survival curves, were compared using log-rank test for trend. We validated performance of the BL-IPI in an external retrospective dataset of BL pts treated contemporaneously in centers from the United Kingdom, Scandinavia, Canada, and Australia.

Results. Characteristics of pts in the derivation (N= 633) and validation (N=457) cohorts are shown in the Table. Age ≥40 years (yr), LDH >3xULN, Hgb <11.5 g/dL, and albumin <3.5 g/dL were determined as optimal prognostic cutoffs. Age ≥40 yr, PS ≥2, stage 3/4, involvement of marrow, CNS, LDH >3xULN, low Hgb, and low albumin were associated with inferior PFS in univariate tests. In the multivariable model age ≥40 yr, LDH >3xULN, PS ≥2, and CNS involvement were selected as 4 independent prognostic factors; adding stage did not enhance the model. The model was simplified to 3 groups with 0 (low risk; 18% of pts), 1 (intermediate risk; 36% of pts; HR=3.14; 95%CI, 1.61-6.14), or 2-4 factors (high risk; 46% of pts; HR=6.52; 95%CI, 1.61-6.14), or 2-4 factors (high risk; 46% of pts; HR=6.52; 95%CI, 3.48-12.20; Fig A) with 3 yr PFS of 92%, 72%, and 53%, respectively (P<.001, Fig. B); median PFS was reached only in the high-risk group (46 months, 95%CI, 19-53). BL-IPI was similarly prognostic for overall survival (OS, P<.001; Fig. C).

Among pts with stage III/IV (historically classified as “high-risk” and constituting 78% of all pts in the cohort), the BL-IPI further discriminated subgroups with 3 yr PFS of 87%, 71%, and 52%, respectively (P<.001; Fig. D), and OS of 95%, 75%, and 57%, respectively (P<.001; Fig. E). In addition, BL-IPI was prognostic regardless of HIV status, in the subcohort treated with rituximab (3 yr PFS: 92%, 73%, and 55%, respectively, P<.001), and among pts treated with specific regimens: CODOX-M/IVAC+R (3 yr PFS: 88%, 67%, 61%, respectively, P=.004), DA-EPOCH-R (3 yr PFS, 87%, 73%, 51%, respectively, P<.001), or hyperCVAD/MA+R (3yr PFS: 100%, 80%, 54%, respectively, P<.001).

In the international validation cohort, fewer pts had CNS involvement; most received CO-
DOX-M/IVAC+R; and PFS/OS estimates at 3 yr were higher. BL-IPI categories were of similar size (low-risk 15%, intermediate-risk 35%, high-risk 50%), and provided similar risk discrimination (Harrell's C=.65 in both datasets). PFS at 3 yr was 96%, 82%, and 63%, respectively (P<.001; Fig. F), and OS was 99%, 85%, and 64%, respectively (P<.001; Fig. G). In the validation cohort, BL-IPI remained prognostic in the subsets receiving rituximab (P<.001) and in advanced stage (P<.001).

**Conclusions.** BL-IPI is a novel prognostic index specific to Burkitt lymphoma, which was validated to allow for simplified stratification and comparison of risk distribution in geographically diverse cohorts. The index identified a low-risk group with PFS >90%–95%, which could be targeted with future strategies for treatment de-escalation. Conversely, only about 55-60% of pts in the high-risk group achieved cure with currently available immunochemotherapy.

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**The Advanced Practitioner Perspective:**

**Sandra E. Kurtin, PhD, ANP-C, AOCN**

Non-Hodgkin lymphomas (NHL) represent more than 60 different diagnoses. Accurate tissue diagnosis is key to confirming the diagnosis and selecting the best available therapy. Risk stratification based on established factors that have statistical significance in determining survival allow for tailored treatment. There are a number of risk stratification models to estimate survival for NHL: The International Prognostic Index (IPI) for Diffuse Large B-Cell Lymphoma (DLBCL), the Follicular Lymphoma International Prognostic Index (FLIPI), and the Mantle Cell Lymphoma International Prognostic Index (MIPI). While these share some prognostic indicators, each model has been refined over the years and tailored to each disease.

Although Burkitt lymphoma (BL) represents a potentially curable subtype of lymphoma, it remains a heterogenous and rare disease, thus generating data from prospective clinical trials is impractical. As a result, clinical trial data is limited to subset analyses of trials for aggressive lymphomas. Retrospective analysis of real-world data provides an alternative to prospective clinical trials for the analysis of rare diseases. This requires sophisticated statistical modeling to ensure that missing data is accounted for and individual data elements (in this case, proposed risk attributes) are tested in these models. For this analysis, attributes considered to represent risk were derived from other aggressive NHL models but adapted to the much younger BL population. In the multivariable model, age 40 years or older, lactate dehydrogenase > 3 × upper limit of normal, performance status ≥ 2, and central nervous system involvement were selected as four independent prognostic factors; adding stage did not enhance the model.

**Implications for the Advanced Practitioner**

In this analysis, 633 BL cases over 9 years across four countries were compiled for analysis. The authors emphasize that a subset of BL patients do very well and can be cured, with an estimated overall survival of 90% to 95% (p < .001). This raises the question of the option to de-escalate treatment. Importantly, this study also identified a subset of BL patients who did not do as well, with a 40% to 45% overall survival with advanced disease, which indicates that we need to continue to look for better treatments. Using indexes such as the BL-IPI and other indexes that are commonly applied in other lymphomas is critical for the advanced practitioner to effectively discuss individual risk with patients and to risk stratify patients for treatment.

**Disclosure:** Dr. Kurtin has no conflicts of interest to disclose.