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American Society of Hematology (ASH) 2021Annual Meeting Review

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WM

Real-world Evidence

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Evaluating Front Line Treatment Regimens for WM: A Systematic Review and Meta-Analysis

- Identified: 753 studies, Included: 12 (8 single arm, 1 phase II non-randomized non inferiority, 3 Phase III RCTs).
- PFS at 1- and 2-years were higher in BR (91%, 87%) and IR (93%, 82%), compared to BDR (87.5%, 66.8%) and CRD (82%, 64%).
- Combined complete response (CR) and very good partial response (VGPR) rates were also superior with BR (35%) and IR (26%) compared to BDR (9%), Bortezomib-Rituximab (8%) and CRD (7%).
- The bortezomib bendamustine rituximab (BBR) regimen was evaluated in only one study but showed an impressive CR/VGPR rate of 47% and a PFS at 3 years of 75%.
- Adverse event profile:
  - Bleeding and atrial fibrillation were more common with IR
  - Neuropathy was more prevalent with bortezomib-based regimens

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Survival Trend of WM over Last 3 Decades Shows Health Disparities in Minority Population

- National SEER Database (1992-2018)
  - N=5690 (Whites: 86%, Other races: 14%)
  - Survival Trends:

Variables		Survival (years)	Relative Survival %			Z Value. *(>1.65 / p<0.05)*	
			1992-2000	2001-2010	2011-2018	1992-2000 vs. 2001-2010	2001-2010 vs. 2011-2018
Age	>18 years	1	87.3	92.0	94.7	3.8	2.9
		5	67.7	81.3	85.7	6.8	3.3
	18-64 years	1	91.2	95.0	97.2	2.5	1.9
		5	78.3	87.5	94.2	3.9	3.2
	≥65 years	1	85.0	90.2	93.5	3.0	2.7
		5	60.8	77.3	81.1	5.3	2.6
Race	White	1	87.3	92.6	95.1	4.1	2.4
		5	68.2	82.1	86.3	6.6	2.8
	Other	1	86.5	86.9	90.4	0.1	1.4
		5	64.3	72.3	78.1	1.3	1.5

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Dose Reductions Related to Adverse Effects in Patients with WM Treated with the BTK-Inhibitor Ibrutinib

- 385 patients (May 2012-Oct 2020)
  - 1/3 were treatment naïve
  - 95 patients (25%) required at least one dose reduction
  - 23 patients (6%) required a second dose reduction
  - Patients requiring a dose reduction were older at the time of ibrutinib initiation (median age 71 years vs. 66 years, p<0.001).
  - Median time to first dose reduction was 7.3 months from the time of ibrutinib initiation
  - Most common reasons for dose reductions: myalgia, arthralgia, arrythmia, hypertension, palpitations, cytopenias, skin changes, diarrhea, nausea, reflux, bleeding/bruising
  - After dose reduction:
    - 65% had some improvement or resolution of adverse events
    - 27% had no change in adverse events
  - Majority (94%) of patients with follow up data had stabilization or improvement of their hematological response after dose reductions.

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Real-World Disease Burden, Costs and Resource Utilization of Hospital-Based Care Among MCL, WM, MZL and CLL: Disparities and Risk Factors

- Population-based from hospital-based claims data
  - Nearly 52,000 patients; 1,811 with WM
  - Patients with WM were significantly older
  - The most common comorbidities included: chronic pulmonary disease (27.1%), gastroesophageal reflux disease (17.6%), moderate-severe renal disease (16.6%), congestive heart failure (15.7%), diabetes without chronic complications (15.2%)
  - During hospitalizations, the use of steroids alone was higher among whites compared to non-white patients (69.5% vs. 60.4%), the use of chemo-immunotherapy was lower in whites compared to non-whites (11.9% vs. 16.2%).
  - Non-white WM patients had significantly longer mean length of stay days compared with white patients (19.0 vs. 14.5 days)
  - Higher hospitals costs were associated with patients who were non-white, Hispanic/Latino, treated in hospitals located in the Northeast or West, or had Medicaid
  - Statistically significant increased cost of care was also noted for patients who received targeted therapy or supportive care, such as blood transfusion or GCSF.

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Evaluating Patients' Preferences Regarding Treatment Options for WM, a Discrete-Choice-Experiment *(Holland)*

- A discrete-choice experiment questionnaire was developed including 5 treatment-related attributes: 5-year progression-free survival (PFS), frequency/route of administration (IV/SC or oral)/setting (clinic or home) of treatment, adverse events (nausea & vomiting and fatigue, neuropathy and atrial fibrillation), risk of future secondary malignancies (low vs high), and type of treatment agent (chemotherapy or targeted therapy).
- Each respondent was presented with 16 choice cards and was asked to choose between two hypothetical but realistic treatment options.
- 347 respondents, 214 included in analysis (based on complete responses).
  - Efficacy (high 5-year PFS rate) was the most important attribute
  - Followed by a low risk of future secondary malignancies.
  - Neuropathy was the adverse event patients most wanted to avoid.
  - Patients preferred a fixed-duration IV/SC treatment over an ongoing oral regimen.
- Socio-demographic characteristics such as age, gender and treatment status did not significantly influence patients' preferences with the exception of educational status.

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Global WM Patient-Derived Data Registry, Whimsical, Highlights Real-World Treatment Outcomes and COVID-19 Data

- 558 patients from 20 countries (50% from USA, 22% from Australia, 9% from UK)
- Median age at diagnosis: 61 years, median follow up ~3 years
- 371 patients had 1st line therapy with 54 unique combinations. Most common: BR, Rituximab, RCd, Ibrutinib, BDR, Rit-Cyt-Vin-p, chlorambucil
  - More patients with BR listed higher comorbidities (37%) and least with ibrutinib (19%)
  - Pretreatment disease burden tended to be higher in BR and RCd groups
  - TTNT: BR was superior to RCd or rituximab, and trended to superior to ibrutinib
  - BTK treated group tended to have better QoL than BTK naïve group.
- COVID-related data:
  - Small numbers.
  - <10% non-vaccinated.
  - None of the vaccinated tested positive for COVID.

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Productivity Loss and Indirect Costs Among Non-Hodgkin Lymphoma Patients and Their Caregivers

- MarketScan Commercial and Health and Productivity Management databases
- 394 WM patients among a total of 5344 patients studied
- 190 WM caregivers among a total of 2233 caregivers studied
- WM patients: 82% absentee claims, 17% short-term and 3% long-term disability
- WM caregivers: 75% absentee claims, 8% short-term disability
- Average illness-related absentee hours in WM: 18.2 in patients vs. 8.1 in caregivers
- Average per-patient-per-month indirect (productivity time loss) cost for WM:
  - $2056 for long-term disability
  - $1177 for short-term disability
  - $662 for absentee claims
  - Short-term disability and absentee claims higher in caregivers

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WM

Management of Relapsed Disease

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Treatment of Relapsed/Refractory WM Patients: Final Clinical and Molecular Results of the Phase II Brb (Bendamustine, Rituximab and Bortezomib) Trial *(Italy)*

- Single-arm phase II study (n=38), 6 cycles
- Median age 66.8 years
- 30 patients completed 6 cycles. 7 patients stopped due to toxicity
- Overall response rate: 82% (11% CR, 39% VGPR, 32% PR)
- 30-month PFS 79%
- 50% experienced grade ≥3 hematological toxicity, and 31.5% grade ≥3 non-hematological toxicity
- 6 patients (16%) had bortezomib-related neurological toxicity (mostly grade 1-2)
- Mutational screening and MRD assessment in blood and bone marrow – good concordance.

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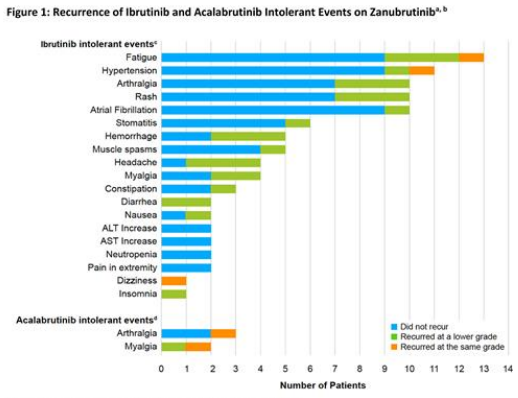
Phase 2 Study of Zanubrutinib in BTK Inhibitor-Intolerant Patients (Pts) with Relapsed/Refractory B-Cell Malignancies

- Patients intolerant to ibrutinib and/or acalabrutinib
- N=57 (WM: 10)
- Median duration of treatment: ~8 months
- Overall *(not just WM)* 73% of pts did not experience recurrence of their ibr or acala intolerant events and 79% of recurrent events recurred at a lower severity.
- Zanu has less off-target binding as compared to ibr or acala



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Newer BTK inhibitors and…

- Pirtobrutinib (LOXO-305) Is Active and Overcomes ERK Related Pro-Survival Signaling in Ibrutinib Resistant, BTK^{Cys481} Mutant Expressing WM and ABC DLBCL Lymphoma Cells Driven By Activating MYD88 Mutations
  - *Blood* (2021) 138 (Supplement 1): 2261.
- Efficacy and Safety of Orelabrutinib in Relapsed/Refractory WM Patients
  - *Blood* (2021) 138 (Supplement 1): 46.
- Two -Year Follow-up Data of Phase II Study of Tirabrutinib, a Second-Generation Bruton's Tyrosine Kinase Inhibitor, in Patients with Treatment-Naïve or Relapsed/Refractory WM
  - *Blood* (2021) 138 (Supplement 1): 1352.
- Preliminary Clinical Response Data from a Phase 1b Study of Mavorixafor in Combination with Ibrutinib in Patients with WMwith *MYD88* and *CXCR4* Mutations
  - *Blood* (2021) 138 (Supplement 1): 1362.

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WM (and some other lymphoproliferative disorders) and COVID

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COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and WM

- Methods:
  - Prospective clinical trial of MM and WM patients vaccinated.
  - Primary endpoint: SARS-CoV-2 spike protein (S) antibody (Ab) detection 28 days after final vaccination.
- Results:
  - 141 patients enrolled, 137 (91 MM and 46 WM) of whom had an S Ab assessment.
  - S Ab response rate was 91% (83/91) in MM and 56% (27/46) in WM.
  - Responses achieving S Ab >250 U/mL were 47.3% (43/91) in MM and 26.1% (12/46) in WM.
  - Among WM patients, S Ab responses >250 U/mL occurred in 63.6% (7/11; $p<0.05$) previously untreated; 0% (0/9; $p<0.05$) who received rituximab within 12 months; 10% (2/20); $p<0.05$) on an active Bruton Tyrosine Kinase (BTK) inhibitor; and 20% (3/15; p=NS) who received other therapies.
  - Age >75 years associated with significantly lower rates and vaccination with Moderna elicited significantly higher S Ab response rates than other vaccines.

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Increase in Antibody Titers Following Sars-Cov-2 Vaccination Remains Limited for More Than 3 Years after Final Dose of Anti-CD20 Antibody

- Study in Japan
- 36 patients enrolled who had been previously treated with anti-CD20 monoclonal Ab
- Median time since prior monoclonal Ab treatment 571 days (range 48-1320 days)
- Antibody levels checked 14 days after the 2nd COVID vaccine.
- No patient vaccinated within close to one year or sooner after the last anti-CD20 antibody administration showed an increase in titers.
- Titers in most patients were lower than in healthy volunteers even among those vaccinated more than three years after the last administration.
- No relationship between the percent of B-cells (CD19-positive cells) and antibody titers.
- Patients with total IgG level below lower normal limit had low S1 antibody titers.

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More COVID Vaccine and WM data…

- *Blood* (2021) 138 (Supplement 1): 816.
  - Efficacy of Pfizer vaccine in Australia.
  - Treatment naïve patients had a better response than treated patients.
  - Patients on BTKi had a significantly reduced response compared to treatment-naïve patients
  - No similar lack of response in patients with chemo-rituximab but no data regarding time since treatment.
- *Blood* (2021) 138 (Supplement 1): 185.
  - LLS study of booster vaccine – very small numbers. Heterogenous data.
- *Blood* (2021) 138 (Supplement 1): 1335.
  - Prospective exploratory analysis in CLL and B-cell lymphoma patients to evaluate antibody and T-cell responses to the commercially available Covid-19 vaccines.
  - Virus-responsive T-cells can be readily detected, even in the absence of antibodies.

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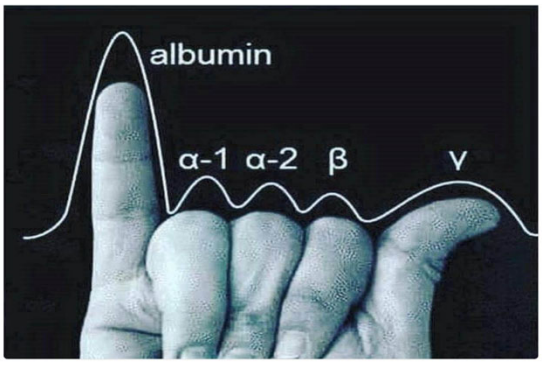

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