Highlights in lymphoma

S. Snauwaert, MD, PhD

SUMMARY

This non-comprehensive summary of abstracts dedicated to lymphoma that were presented at ASH 2017, will focus on Hodgkin lymphoma (HL), follicular lymphoma (FL), primary central nervous system lymphoma (PCNSL) and diffuse large B-cell lymphoma (DLBCL). Although this selection of abstracts is of course biased by personal interest, it aims to give you a relevant overview for daily clinical practice.

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HODGKIN LYMPHOMA

Based on very high response rates in the relapsed/refractory setting, both brentuximab vedotin and checkpoint inhibitors are quickly proceeding to clinical trials for first-and second-line therapy of HL. The ultimate goal is to improve, cure rate and avoid toxicities associated with subsequent treatments (e.g. radiotherapy or autologous stem cell transplantation, ASCT).[1] A plethora of phase 1 and 2 studies were presented, but we strongly believe that the benefit of these agents should be confirmed in phase 3 trials.

ECHELON-1 is a phase 3, open-label, multicenter, randomized controlled trial, involving patients (18 years of age or older) with previously untreated stage III or IV classical HL. In total, 664 patients were assigned to receive A+AVD (brentuximab vedotin 1.2 mg/kg, doxorubicin, vinblastine, and dacarbazine), and 670 were assigned to receive classical ABVD (bleomycine instead of brentuximab vedotin), each for 6 cycles. The primary endpoint of the study was modified progression-free survival (mPFS), defined as the time to progression, death, or non-complete response with subsequent use of anticancer therapy. After a median follow-up of 24.9 months, the rate of mPFS was significantly higher in the A+AVD group than in the ABVD group (2-year mPFS 82.1% *vs.* 77.2% with a hazard ratio [HR] of 0.77 and p= 0.03), corresponding to a 23% risk reduction (*Figure 1*). Data concerning overall survival (OS), a key secondary endpoint, were immature at the time of the analysis. Neutropenia and febrile neutropenia were observed more frequently in the experimental arm, leading to the recommendation during enrollment to use primary prophylaxis with granulocyte-colony stimulating factor (G-CSF) for all patients yet to be enrolled in the A+AVD arm. Peripheral neuropathy, including grade 2 and 3 were also more frequent in the A+AVD arm. Omission of bleomycin led to less interstitial lung disease in the A+AVD arm. The authors concluded that a pharmaco-economic analysis is warranted, in view of the high costs of this treatment strategy.[2]

The BREACH trial analysed the PET-based response after 2 cycles of A+AVD as first-line treatment for patients with unfavourable (EORTC criteria) early-stage HL. Results from the first planned interim analysis were reported. Patients were randomly assigned in a 2:1 ratio to receive 4 cycles of A+AVD or ABVD, followed by 30 Gy involved node radiation therapy (INRT). The experimental arm showed an improved negative PET2 rate (82.3% *vs.* 75.4%), with the primary objective met, this is a lower boundary of the 90% confidence interval greater than 75% in the experimental arm. Longer follow-up is required to evaluate the impact on PFS and OS.[3]

Nivolumab, a programmed-death 1 (PD-1) inhibitor, was also investigated in newly diagnosed advanced-stage (stage IIB, III and IV) classical HL. In the phase 2 CheckMate 205 study, patients were treated with 4 cycles of nivolumab monotherapy, followed by 6 cycles of combination of nivolumab + AVD (N-AVD). With a median follow-up of 11.1 months, N-AVD was associated with an overall response rate (ORR) of 84% and a complete response rate of 67%. The mPFS rate of 94% at 9 months. The therapy was well tolerated with a safety profile consistent with historical analyses, without new safety signals.[4]

In conclusion, new agents might have the potential to im-

AZ Sint-Jan Brugge Oostende

Please send all correspondence to: Dr. Sylvia Snauwaert, Department of Hematology, AZ Sint-Jan Brugge Oostende, Campus Sint-Jan, Ruddershove 10, 8000 Brugge, E-mail: Sylvia.Snauwaert@azsintjan.be

Conflict of interest: The selection of the abstracts discussed here is the sole responsibility of the author and was not influenced by third parties.

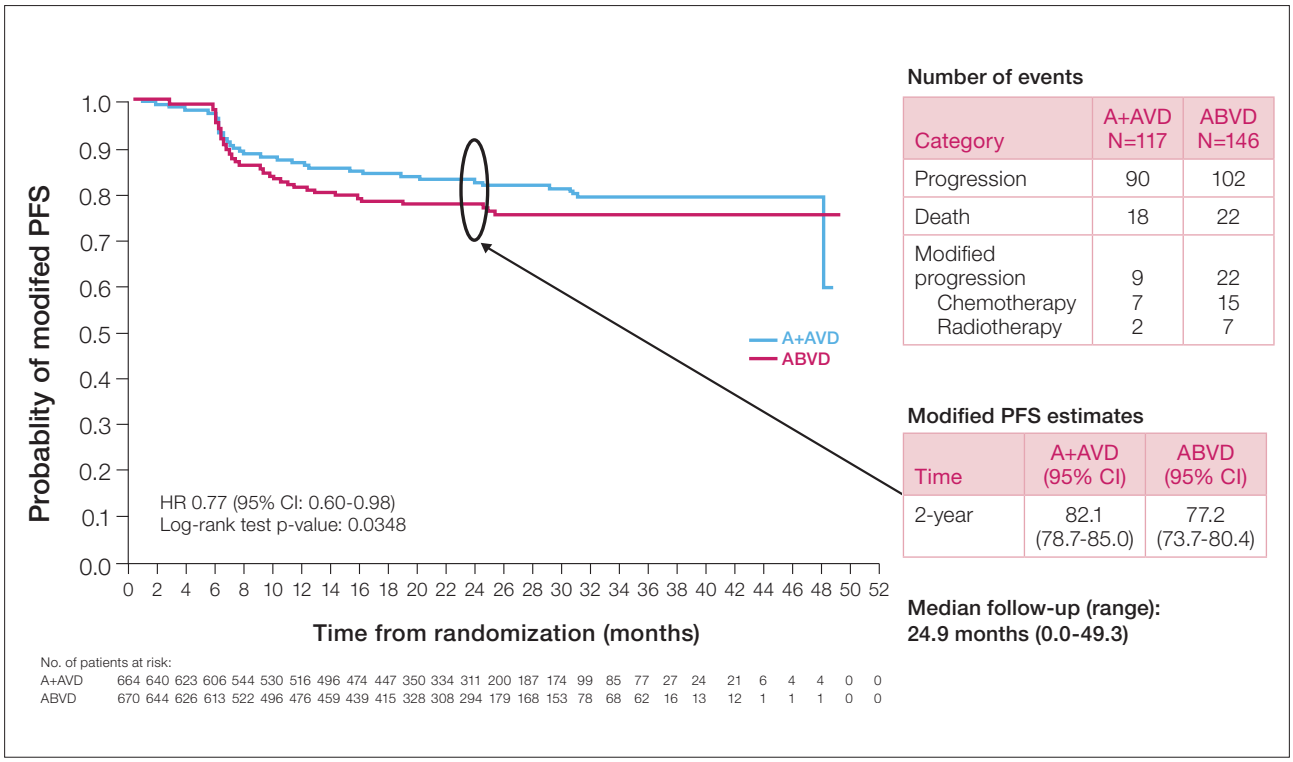

FIGURE 1. Modified progression free survival per independent review in the phase III ECHELON-1 trial.[2]

prove outcomes for cHL patients even further. Nevertheless, many challenges remain: how to safely combine new agents with conventional chemotherapy? What about the costs?

FOLLICULAR LYMPHOMA

The tumour-microenvironment is increasingly recognized as playing a crucial role in sustaining malignant B-cell survival and growth, subclonal evolution, and drug resistance. Moreover, the complex set of bi-directional interactions between B-cells and their microenvironment has been proposed as a promising therapeutic target. Especially in FL, tumoral B-cells are extremely dependent on these interactions.[5] Many studies presented at ASH aim to target this microenvironment in B-cell non Hodgkin lymphoma (NHL) and more specifically in FL. *Nastoupil et al. (MD Anderson Cancer Center)* presented a phase II study investigating the combination of rituximab (375 mg/m^2 IV on d1, 8, 15, 22 of cycle 1) with pembrolizumab (200 mg IV every 3 weeks for up to 16 infusions) in patients with relapsed/refractory FL after 1 or more therapies. Patients included in the study had to be rituximab-sensitive, defined as having a complete or partial response lasting at least 6 months after the most recent rituximab therapy. The authors hoped for a synergistic effect, as blocking PD-1 has shown to enhance the antibody dependent cellular toxicity (ADCC) effect of NK cells, one of the mechanisms of action of rituximab. The trial revealed a promising efficacy with a a clinically meaningful ORR of 67% and a CR rate of 50% for the 30 patients in the study. The median PFS was reported to be 11.4 months. PD-L1 status was not a significant predictor of response. The combination showed a favourable toxicity profile, with 3 subjects discontinuing the study due to diarrhoea, 2 due to pneumonitis and 1 due to rash.[6]

The median OS in FL is 20 years, but there is a significant clinical heterogeneity. Data from the National Lymphocare Study and others identified that progression of disease within 24 months of initiation of treatment (POD24) by chemo-immunotherapy is associated with a poor subsequent OS.[7] At ASH 2017, *Casulo and colleagues* revalidated POD24 as a robust early clinical endpoint of poor OS in FL by a retrospective pooled analysis of the prospectively collected data from 5,453 patients included in 13 randomized clinical trials (both from the pre and post rituximab era) within the FLASH (FL analysis of surrogacy hypothesis data set) collaboration. POD24 was independently associated with an increased risk of death after adjusting for gender, FLIPI score, performance status and beta-2 microglobuline with a HR of 5.65 (95%CI: 4.72-6.76). In a landmark analysis for OS by first response, researchers showed that the adverse impact of POD24 seems to be independent of the response to treatment (assessment by CT, not PET-CT) before progression.[8]

However, POD24 is a post-hoc marker, and lots of efforts have been made to identify predictive parameters at diagnosis, which could identify these early progressors upfront and thereby allow a risk-adapted therapeutic strategy in FL.[7] *Bachy et al*. presented a simplified scoring system (the PRIMA-prognostic index or PRIMA-PI) for FL patients treated with chemo-immunotherapy, using the PRIMA cohort. It comprises 3 categories: high, low, and intermediate risk, according to beta-2 microglobulin (cut-off 3), and bone marrow involvement. In this discovery cohort, the score outperformed FLIPI or FLIPI2.[9] Together with FLIPI, FLIPI2, m7-FLIPI (a clinico-genetic risk model for failure free survival using the FLIPI score and the mutation status of 7 genes) and POD24-PI (another clinico-genetic prognostic model based on FLIPI and mutation status of 3 genes: *EP300, FOXO1, EZH2*), this PRIMA-PI comprises one of the possible, but imperfect measures that can be applied to a patient with FL to estimate his/her risk at diagnosis. An ideal model, which classifies all POD24 patients within the high-risk category, has not yet been developed. The m7 FLIPI has the highest specificity, positive predictive value (PPV) and accuracy to predict POD24. The POD24-PI has a higher sensitivity and negative predictive value (NPV) but is far less accurate and specific. Therefore, both PPV and NPV will need to improve before clinicians would be comfortable making treatment allocations based upon these risk scores.[7]

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

The current frontline treatment for PCNSL consists of high-dose methotrexate-based polychemotherapy. Evidence supporting the addition of an alkylating agent is growing, and in 2016, *Ferreri and colleagues* published the results of the randomized, phase 2 IELSG32 trial demonstrating that the combination of methotrexate, cytarabine, thiotepa and rituximab (MATRix regimen) was associated with a significantly better OS.[10] The MATRix protocol (4 cycles repeated every 3 weeks) followed by consolidation with high-dose chemotherapy and autologous stem cell transplant or whole-brain radiotherapy (WBRT) is now widely regarded as a new treatment standard and benchmark for future randomized trials. However, treatment associated toxicity is common, and many patients encountered in routine practice are older and frailer than those treated in the IELSG32 trial. At ASH 2017 *Schorb et al*. presented a multicentre retrospective analysis on the feasibility and effectiveness of the MATRix regimen in routine clinical practice. Eighty-eight patients were included, with a median age of 61 years (range 28-76). Twenty-three patients (26%) would not have met the inclusion criteria of the IELSG32 trial. They noticed that dose modifications were often necessary, with the most frequent adverse event being infections (e.g. 55% of patients, with 16% severe infections, and 4.5 % need for intensive care support during the first cycle of therapy). Treatment related deaths occurred in 7% of patients, most frequently due to infections. After 4 induction cycles the ORR was 83% with a CR in 41% of patients, compared to an ORR of 87% and a CR rate in 49% reported in the IELSG32 trial. The MATRix protocol is thus feasible and effective in routine practice, and can be delivered to patients aged >70, with reduced PS and/or co-morbidity to produce similar clinical outcomes to the IELSG32 trial. However, dose reductions and infections are common.[11]

Concerning the role of rituximab in PCNSL, IELSG32 and other phase 2 and retrospective trials, suggest that the addition of rituximab to the chemotherapy backbone is associated with a significant improvement in ORR with unchanged tolerability. The role of rituximab in the upfront treatment of PCNSL was further investigated in the randomized phase 3 HOVON 105/ALLG NHL 24 study. Patients up to 70 years old were randomized to induction with 2 cycles of MBVP (high dose methotrexate, BCNU, teniposide, prednisone) with (arm B, N= 99) or without (arm A, N=100) rituximab. Rituximab (375 mg/m^2) was given weekly during MBVP cycle 1 and every other week during cycle 2 to a total of 6 administrations (compared to 8 in total in the IELSG32 trial: day -5 and 0, for 4 cycles). The CR/CRu rate was 66% in arm A and 68% in arm B with an ORR of 87% in both arms. The event-free survival (EFS) did not differ between the two arms: 1 year EFS rate 49% in arm A and 52% in arm B (HR[95%CI]: 1.00[0.70-1.43], p= 0.99) (*Figure 2*). An unplanned subgroup analysis suggests a possible effect of rituximab in younger patients. Longer follow-up is needed to evaluate the impact of rituximab on OS.[12]

DIFFUSE LARGE B-CELL LYMPHOMA

Although recent years have brought significant insights into the biology of DLBCL, (e.g. the identification of prognostic heterogeneous subgroups), progress in therapeutic management has been disappointing. In 2017, R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) still remains the gold standard. Many efforts have been made to improve outcomes, by intensification of induction chemotherapy or by introducing next-generation anti-CD20 antibodies in front-line therapy.[13]

At ASH 2017, the final results of the LYSA initiated GAINED trial were presented. This phase 3, randomized, prospective trial compared obinutuzumab (G) versus rituximab (R) in combination with 4 cycles of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone)-14 or

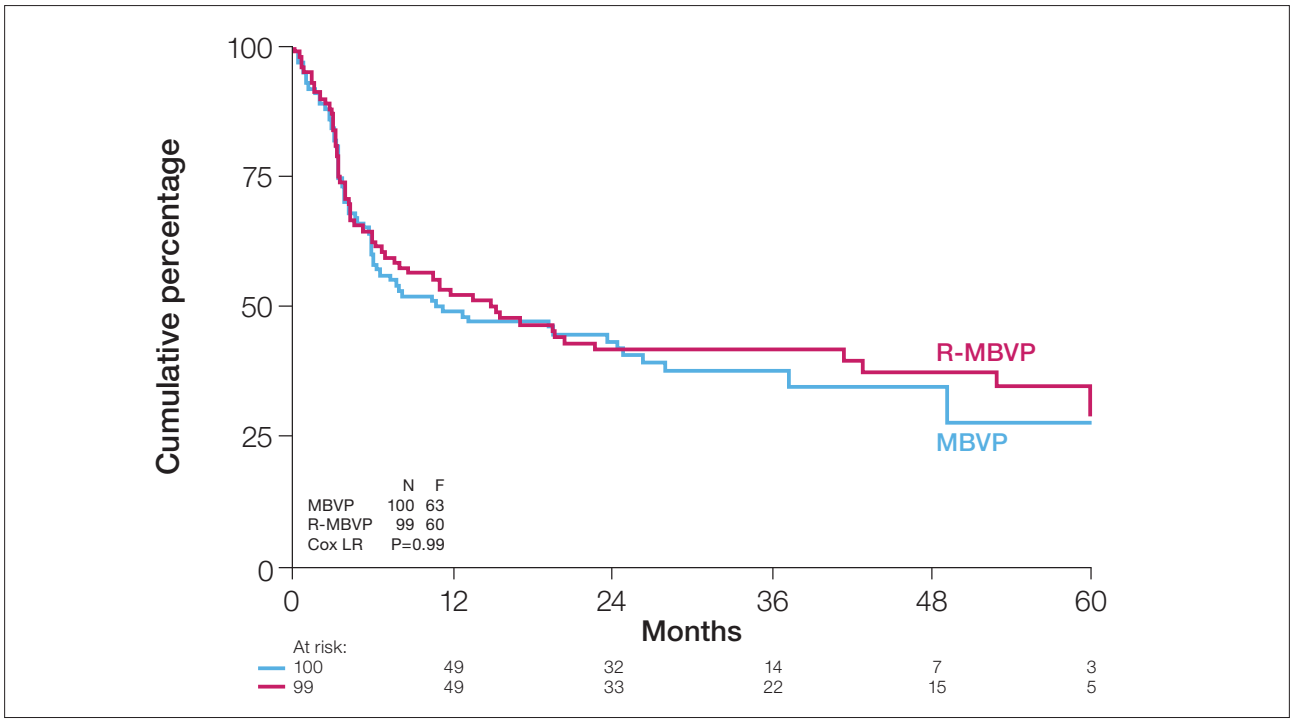

FIGURE 2. Similar EFS with rituximab-MBVP in the randomized phase 3 HOVON 105/ALLG NHL 24 study.[12]

CHOP-14 followed by a PET-driven consolidation strategy in age adjusted (aa-)IPI 1-3 DLBCL patients younger than 60. PET2-/PET4- patients were assigned to immunochemotherapy consolidation with either rituximab or obinutuzumab (G-chemo) according to the randomization arm. PET2+/PET4-patients received HDT-ASCT, PET4+ were treated according to the investigator's choice. The primary endpoint was 2-year EFS and with a median follow-up of 25.2 months, G-chemo (60% [54.4-65.1]) did not improve the EFS compared to R-chemo (57% [51.5-62.2]). G-chemo did also not improve PFS and OS. However, obinutuzumab was associated with a higher incidence of adverse events, serious adverse events and fatal toxicity events (10 fatal AE in G arm *vs.* 1 in R arm). In this trial, cell of origin was not found to be a prognostic factor for PFS, but the frequency of the ABC subtype was relatively low in this trial. The PET-driven consolidation strategy based on ΔSUVmax was shown to be feasible and allowed the identification of 69% PET2-/PET4- patients with a good outcome (2-year PFS 90%) with immunochemotherapeutic consolidation. Sixteen percent of patients were PET4+ and had a poor outcome, despite salvage therapy (2-year PFS 61%). Fifteen percent were PET2+/PET4- patients who appeared to benefit from ASCT consolidation with an outcome similar to PET2- patients (2-year PFS 85%).[14]

Patients with refractory DLBCL experience poor outcomes with the currently available therapies. Several chimeric antigen receptor (CAR) T-cell trials in this setting were presented at ASH 2017. CTL019 (tisagenlecleucel, Novartis) is an anti-CD19 CAR T-cell therapy studied in the single-arm, open-label, multicenter, phase 2 JULIET trial in adults with highly pre-treated relapsed/refractory DLBCL. In total, 147 patients were enrolled and 99 were infused with a single dose of CTL019 transduced cells (median 3.1 x 10^8 cells). Prior to infusion, patients received lymphodepleting chemotherapy (73% received fludarabine and cyclophosphamide and 19% received bendamustine). At month 3, the CR rate was 32% and the PR rate 6%, with 95% of CRs at 3 months being sustained at 6 months. The median duration of response was not reached; the 6-month probability of being relapse free was 73.5% (95%CI: 52.0% to 86.6%). Cytokine release syndrome (CRS) occurred in 58% of infused patients, with 15% grade 3 and 8% grade 4. Fifteen percent of patients received anti-IL6 therapy, tocilizumab, for CRS management with good response and 11% of patients received corticosteroids.[15]

JCAR017 (Juno Therapeutics) is a CD19-directed 4-1BB CAR T-cell product administered in a defined composition at a precise dose of CD8 and CD4 CAR T-cells. TRANSCEND NHL 001 is the first multicenter Phase 1 trial of JCAR017 in relapsed/refractory B-cell NHL. Patients received lymphodepletion with fludarabine and cyclophosphamide, followed by a single flat dose of JCAR017 at one of two dose levels (DL1, 5 x 10^7 CAR T-cells; DL2, 1 x 10^8 CAR T-cells).

Amongst others, 69 patients with DLBCL, including at least 16 patients with double/triple hit lymphoma, were treated. Only 21 patients had CRS, with a single serious CRS event (grade 4). The 3-month and 6-month CR rates were 40% and 37%, respectively. Among 16 double/triple hit lymphoma patients, the 3-month CR rate was 60%. Responses seemed durable.[16]

Finally, the long-term follow-up data (median follow-up of 15 months) from the ZUMA-1 study were presented. This trial studied Axicabtagene Ciloleucel (Axi-Cel; KTE-C19, Kite Pharma) in patients with refractory aggressive NHL. Earlier efficacy and safety results were confirmed.[17]

Taken together, CAR T-cell therapy is an emerging and promising treatment strategy for relapsed/refractory DBLCL, but many challenges remain, including costs, the management of the cytokine release syndrome, and the highly-personalized character and complexity of the product. Of note, less than 10% of the ongoing CAR T-cell clinical trials are performed in Europe. As for marketing, four CAR T-cell products from three pharmaceutical companies (KTE-C19, Kite Pharma; CTL019, Novartis; JCAR015 and JCAR017, Juno Therapeutics) have been granted access to EMA's Priority Medicines (PRIME) scheme, under which developers will have enhanced interaction and early dialogue with EMA, to optimize development plans and speed up evaluation.[18]

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