short review

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ASH 2018—aggressive lymphoma

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Summary At the American Society of Hematology Meeting (ASH) 2018 promising data were presented reflecting the impressing advances of clinical research in aggressive lymphoma. Besides promising and partially practice-changing therapies in first-line treatment, there was a focus on Chimeric Antigen Receptor T Cell (CART) therapy for patients with relapsed/refractory (r/r) diffuse large B cell lymphoma (DLBCL): longer follow-up, real world data and new developments were reported. A bit overshadowed by CART therapy hype promising data for adding venetoclax to chemoimmuntherapy, bispecific antibodies, antibody drug conjugates and new monoclonal antibodies were presented. Important data to detect patients at high risk for R/CHOP (Rituximab/Cyclophospamide, Doxorubicin, Vincristine, Prednisone) failure and to detect possible targets for this high-risk subgroup were shown. The focus of phase III studies in the future should be on this high-risk population as the next phase III trial—the PHOENIX study adding ibrutinib to R/CHOP in non GCB DLBCL—failed to improve standard first-line therapy with R/CHOP.

Keywords Diffuse large B cell lymphoma · CART therapy · Bispecific antibodies · Venetoclax · Ibrutinib

Take home message

- For young low-risk patients outcome with 4x R-CHOP+ 2xR is non-inferior compared to the previous standard 6x R-CHOP. Thus, chemotherapy can be spared without compromising prognosis in this population
- Long-term follow-up, real world data and data for high-risk patients confirmed CART therapy as a big hope for r/r patients
- New promising therapeutic strategies were presented at ASH 2018, e.g. adding venetoclax to chemoimmuntherapy, antibody drug conjugates, bispecific antibodies, CD19 antibody MOR208, new developments in CART technology

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Risk stratification

A large transatlantic cooperation—the Luneburg Lymphoma Biomarker Consortium (LLBC)—addressed the question of the prognostic relevance of myc rearranged diffuse large B cell lymphoma (DLBCL) in combination with bcl and/or bcl6 rearrangements in the context of the myc translocation partner [1]. In all, 2380 patients of 5118 patients from registry cohorts and prospective trials treated with rituximab (R)/cyclophosphamide, doxorubicin, vinristine and prednisone (CHOP) or R/CHOP like therapy had full data for analysis. Only patients with myc translocation partner immunoglobulin (IG) and bcl2 and/or bcl6 rearrangement had poor outcome—these double or triple hit lymphoma (DHL/THL) patients should be evaluated for alternative therapeutic strategies. In fact, 50% of all myc arrangements had translocations with non IG partner—these patients are not at high risk for R/CHOP failure.

Horn et al. presented a new stromal signature applicable to formalin fixed paraffin embedded tissues [2]. The method was validated in a cohort of 466 patients from 7 prospective trials. High expression of the stromal signature is an independent risk factor for event-free survival (EFS), progression-free survival (PFS) and overall survival (OS) underlining the impor-

tance of the microenvironment in DLBCL. In addition this stromal signature may provide a rationale for targeted therapies (e.g.—Imides) in patients at risk.

First-line therapy phase III studies

The German FLYER trial for young (18–60 years) DLBCL patients with good prognosis (i.e. aaIPI0 without bulk >7.5 cm) evaluated the efficacy of 4 cycles CHOP with 6 cycles rituximab versus standard chemoimmunotherapy with 6 cycles R/CHOP [3]. A total of 592 patients were randomized and 588 evaluable for the final analysis: there was no difference in 3a EFS (both cohorts 89%) and 3a OS (99% 4x R/CHOP + 2x R vs 98% 6x R/CHOP). Nonhematological grade 3/4 toxicities could be reduced by a third in the experimental arm. The new standard of car for this (rare) subgroup of young low-risk patients is 4x R/CHOP + 2x R.

In the PHOENIX trial 838 patients with nongerminal center B (GCB) DLBCL were randomized 1:1 into ibrutinib R/CHOP vs placebo R/CHOP [4]. There was no significant difference in the intent to treat (ITT) population concerning overall response rates (ORR) (89.3% vs 93.1%) and complete response (CR) rates (77.3% vs 68%). In elderly patients (>60 years) in the ibrutinib arm only 69% received 6 cycles R/CHOP, in the standard arm 91%—the combination of ibrutinib with chemoimmunotherapy is too toxic in patients >60 years. In younger patients ibrutinib R/CHOP was tolerable: 90.4% received preplanned 6 cycles of R/CHOP. Ibrutinib + R/CHOP improved EFS and OS significant versus placebo + R/CHOP in this subgroup. The PHOENIX trial is the next phase 3 trial that failed to improve R/CHOP in first line—the impressive OS delta in young patients (12% better 44 month OS) was diminished by the toxicity in elderly patients. Unfortunately this is the next negative phase III trial with novel agents in DLBCL trying to improve R/CHOP: bortezomib (REMoDL-B and Pyramid) [5, 6], obinutuzumab (GOYA) [7], everolimus (PILLAR-2) [8], enzastaurin (PRELUDE) [9] and now ibrutinib failed to improve R/CHOP. On the other hand high-risk patients for R/CHOP failure—e.g. high-risk NCCN IPI, double expressor lymphoma (DEL), double hit lymphoma (DHL)—can easily be detected at the time of diagnosis. Further phase III trials should target these high-risk patients.

First-line phase II studies

The addition of venetoclax (Ven) 800 mg to R/CHOP was tested in the single arm phase II CAVALLI trial [10]. In all, 211 patients were enrolled; 208 received any treatment and were included in efficacy and safety analysis. The R/CHOP arm from the GOYA trial was selected as historical comparator [7]. Especially in bcl2 FISH positive and in double hit lymphoma the PET CR rate was significant in favor of Ven + R/CHOP: PET CR rates were 71% for DHL ($n = 7$, no data on myc rearrangement partner) and 70% for FISH bcl2 positive patients ($n = 40$) in the CAVALLI trial, in GOYA PET CR rates were 25% ($n = 8$) in DHL and 48% in FISH bcl2 positive patients. As expected the addition of venetoclax led to higher rates of hematotoxicity with a febrile neutropenia rate of 31%. As presented by Morschhauser Ven + R/CHOP should be further tested in bcl2+ DLBCL.

In a prospective trial of the HOVON group the addition of lenalidomide to R/CHOP (R2/CHOP) in DLBCL harbouring a myc rearrangement led to an 1a PFS of 66% with an acceptable safety profile for R2/CHOP [11]. This data has to be interpreted on the background of above mentioned data from the LLBC [1]: patients with myc single hit and patients with myc non-IG translocation partners (as mentioned 50% of all myc rearrangements) should not be considered as high-risk patients.

Relapsed/refractory patients

In patients with relapsed/refractory DLBCL the hope of Chimeric Antigen Receptor T Cell (CART) destroying the dogma of DLBCL as a “single shot cancer” was supported by updated data of ZUMA 1, real world data in patients receiving CART as SOC and by new developments in CART cells. Besides CART promising data for venetoclax in addition to salvage therapy, bispecific antibodies, CD19 antibodies, updated data for polatuzumab were presented.

A PFS plateau at 40% was confirmed after 2 years of follow-up in an update of ZUMA 1, only 10 of 101 patients relapsed later than 6 months after CART infusion ([12]; Fig. 1). Several studies confirmed efficacy and toxicity in a real world setting: in 124 patients with r/r DLBCL 3 month CR rate was 57% with cytokine release syndrome (CRS) (≥grade 3) rate of 7% and neurotoxicity (≥grade 3) rates of 33% [13]. Noteworthy 43% of these patients would not have been eligible for ZUMA-1. In a subgroup analysis of ZUMA-1 patients with double hit or double expressor lymphoma—a subgroup with an especial poor prognosis in relapse—half of the patients (18/37) had a sustained CR after 1 year showing similar outcome in comparison to “standard risk” patients [14]. New developments in CART therapy are on the way: multitargeted CART [15], armored CART [16], allogenic CART [17], combinations of CART with checkpoint inhibitors [18, 19]. We are at the promising beginning of a new era in DLBCL with CART therapy but of course there are major issues to be resolved, e.g., the applicability to all r/r DLBCL on the background of practical/cost implications, patients becoming resistant, intention to treat and not per protocol analysis is warranted, toxicity issues.

In the single arm L-Mind trial, 81 relapsed DLBCL patients ineligible for salvage therapy with autologous stem cell transplantation (ASCT) received

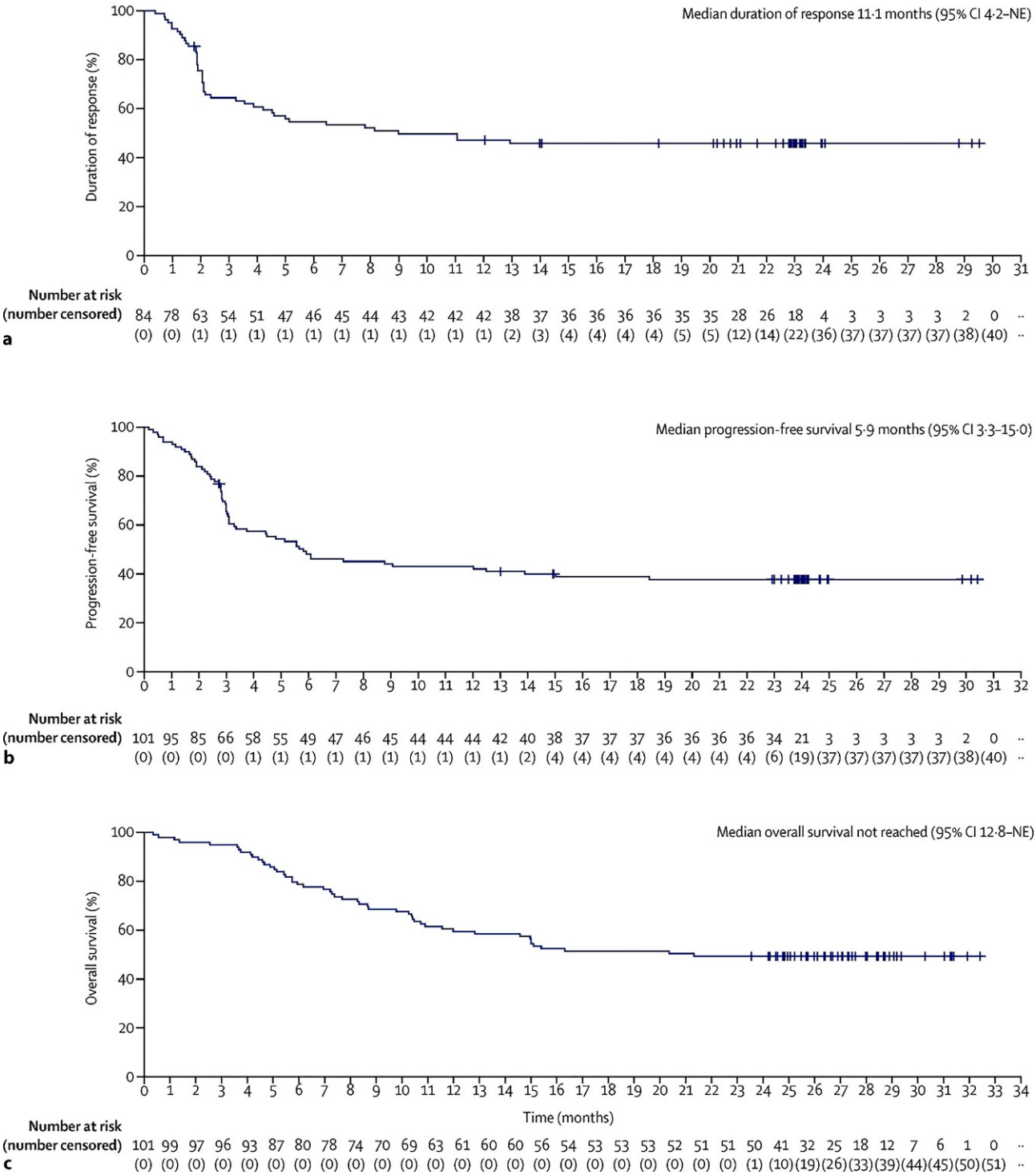

Fig. 1 Long term (27.1 month) FU of ZUMA 1. Kaplan–Meier estimates of investigator-assessed duration of response (**a**), progression-free survival (**b**), and overall survival (**c**). All 101 patients assessable for activity in phase 2 are shown. The x-axis shows time since infusion of chimeric antigen receptor T cells [12]. *FU* follow up, *CI* confidence interval, *NE* not estimable © Reprinted from The Lancet Oncology, 20, Frederick L. Locke et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial, 31-42, © 2019, with permission from Elsevier

chemotherapy free treatment with the anti CD19 antibody MOR208 in combination with lenalidomide; chemorefractory patients were excluded [20]. Besides dose reductions of lenalidomide in half of the patients the therapy was well tolerated. With an ORR of 58% a CR rate of 33% and median PFS of 16 months results are promising for this cohort.

The VICER regimen—the addition of venetoclax to R/ICE—led in a phase I trial to a CR rate of 78%; 13 of 16 patients proceeded to autologous stem cell transplantation without any unexpected toxicity [21]. This regime should be further tested in comparison to standard salvage regimens like R/DHAP, R/ICE or R/GDP.

Laurie Sehn presented an updated analysis of a phase Ib/II trial for patients ineligible for salvage chemotherapy with ASCT comparing the antibody drug conjugate polatuzumab in combination with R/bendamustine versus R/bendamustine the original results were maintained with a significant OS benefit in favor for the polatuzumab arm of 12.4 versus 4.7 months [22]. After a median observation time of 22 months in the randomized comparison the median duration of response in the ADC arm had yet to be reached.

Preliminary result of two bispecific antibodies targeting CD20 and CD3—mosunetuzumab and CD20-TCB RG6026—are promising and will be further tested in combination therapies [23, 24]. For example ORR for RG6026 at doses from 1000–1600 microgram was 55% with a CR rate of 27% in r/r DLBCL, CR were sustained after a median follow-up of 96 days. An ongoing CR in a patient relapsing after multiple lines of therapy including CART therapy in combination with pembrolizumab receiving mosunetuzumab was reported. Mild and manageable CRS, neurotoxicity (only mosunetuzumab), neutropenia and pyrexia (only RG6026) were the main (manageable) toxicities.

Conflict of interest M. Panny declares that he has no competing interests.

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