The best of ASH 2017

R. Schots, MD, PhD

SUMMARY

The selection for this best of ASH article was based on the studies that were selected for presentation during the presidential symposium, the late breaking abstract session and the "best of ASH" session at the 2017 annual meeting of the American Society of Hematology (ASH). The selection is primarily targeted at clinicians and the information from these sessions was grouped into 5 chapters: studies likely to have an impact on our clinical practice on the short term, early clinical trials with promising new treatments, therapeutic advances in rare hematological diseases, new insights in mechanisms of disease and innovative applications for next generation sequencing (NGS).

(BELG J HEMATOL 2018;9(1):3-7)

CLINICAL PRACTICE CHANGING

VENETOCLAX PLUS RITUXIMAB IN RELAPSED/REFRACTORY CLL

Venetoclax (V) is an orally administered highly selective BCL-2 inhibitor. BCL-2 overexpression is frequently observed in hematological malignancies, including B-cell chronic lymphocytic leukemia (B-CLL). *Seymour et al*. presented the results from an open-label, randomized, phase 3, multinational trial where V + rituximab (R) was compared to bendamustine (B) (70 mg/m^2 days 1&2) + R in 389 patients with relapsed/refractory (R/R) B-CLL.[1] The dose of V was gradually increased to avoid tumor lysis syndrome and treatment was continued for a maximum of 2 years, or until disease progression. After a median follow-up of 24 months, V+R was found to be superior in terms of progression-free survival (PFS) (2 year PFS rate: 84.9% *vs*. 36.3%), the rate of complete response and complete response with incomplete recovery of blood counts (CR/CRi) (26.8% *vs*. 8.2%) and the rate peripheral blood MRD negativity as assessed by ASO-PCR or flow cytometry (83.5% *vs*. 23.1%). These benefits were observed in all evaluated subgroups, including in patients with a del(17p) and in patients harboring a *TP53* mutation. In terms of toxicity, there was only more grade 3-4 neutropenia noted in the V+R arm.[1] Based on these findings, V+R is likely to become a standard of care regimen in R/R B-CLL.

DARATUMUMAB-VMP IN NEWLY DIAGNOSED MYELOMA

VMP (Velcade, melphelan and prednisone) (9x 6-week cycles) is a standard first-line regimen in multiple myeloma (MM) patients who are ineligible for high-dose therapy. *Mateos et al*. presented data from the ALCYONE study comparing VMP with VMP + daratumumab (D-VMP) (D weekly x 4 weeks followed by q3wks for cycles 2-9 followed by maintenance until progression for previously untreated, symptomatic MM patients (N= 706).[2] After a median follow-up of 16.5 months the risk of progression was reduced by 50% in the D-VMP arm which also induced a higher CR rate (42.6% *vs*. 24.4%) and minimal residual disease (MRD) (PCR, level 10-5) rate (22.3% *vs*. 6.2%). The latter is of particular interest given the fact that previous myeloma studies, both in first-line and in more advanced disease, indicate that MRD negativity correlates with improved survival. There were no concerns about safety when combining D with VMP. D-VMP is likely to become a new standard of care first-line regimen in MM patients who are ineligible for high-dose therapy.[2] The study was also published in the NEJM on December 12th 2017.[3]

FIRST-LINE BRENTUXIMAB PLUS AVD IN ADVANCED HODGKIN LYMPHOMA

The combination of adriamycin, bleomycin, vinblastine and dacarbazide (ABVD) is the gold standard first-line schedule

UZ Brussel

Please send all correspondence to: Prof. Rik Schots, Department of Hematology, UZ Brussel, Laarbeeklaan 101, 1090 Brussel

Tel: +32 (0)2 477 62 11, E-mail: Rik.Schots@uzbrussel.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.

for Hodgkin lymphoma. Bleomycin has well-known pulmonary toxicity and brentuximab (anti-CD30 antibody-drug conjugate) has marked activity in advanced Hodgkin lymphoma patients. *Connors et al.* presented results from the ECHELON-1 trial in which 1,334 patients were randomized to receive ABVD or A (for Adcetris = brentuximab) +AVD. As primary endpoint, a modified PFS (mod-PFS) was used defined as time to progression, death or change of anti-cancer treatment as the result of incomplete response. There was a 23% reduced mod-PFS in favor of the A+AVD arm (*Figure 1*). There was more neuropathy in the A-AVD arm (67% *vs* 43% overall and 11% *vs* 2% grade ≥3) of which 67% improved or resolved. There was more pulmonary toxicity in the ABVD arm (3% *vs* <1% grade ≥3). The authors propose A+AVD as a standard first-line option in advanced Hodgkin lymphoma.[4] However, it remains to be seen if overall survival (OS) will be improved and whether the increased neurotoxicity outweighs the modest benefit in terms of pulmonary toxicity.

EARLY CLINICAL TRIALS WITH NEW COMBINATIONS OR NOVEL THERAPIES

VENETOCLAX PLUS LOW-DOSE CYTARABINE IN ELDERLY AML

Venetoclax 600 mg PO daily was combined with low-dose cytarabine (LDAC, 20 mg/m^2/day days 1-10 of each 28-day's cycle) in previously untreated patients ≥65 years of whom 44% had an antecedent hematological disorder, mostly MDS. A CR/CRi was achieved in 62% with a median duration of 14.9 months and the observed 12-month OS was 46%. The median OS was 11.4 months. Patients with *NPM1, DNMTRA, FLT3-ITD* and *SRSF2* mutations had the best responses. The most pronounced toxicity was hematological in nature. Based on these encouraging results, a phase 3 study is ongoing.[5]

CAR T-CELLS IN DIFFUSE LARGE B CELL LYMPHOMA

CTL019 (tisagenlecleucel) is a CAR T-cell therapy targeting CD19-expressing B-cells. In this multinational (27 sites in 10 countries) study, patients with diffuse large B cell lymphoma (DLBCL) failing ≥2 lines of chemotherapy and ineligible or failing autologous stem cell transplantation were provided with centrally manufactured CAR T-cells (JULIET trial). Cryopreservation of the products was feasible. Patients received lymphodepleting chemotherapy before cell infusion, mostly fludarabine in combination with cyclophosphamide. In a cohort of 81 patients having received a single infusion of CAR T-cells and a minimum follow-up of 3 months, the CR/PR rate was 39.5%/13.6% and the 6-month OS rate was reported to be 64.5%. Toxicity was considerable: cytokine release syndrome occurred in 58% of infused patients (15% grade 3 and 8% grade 4) and grade 3-4 neurological adverse events were noted in 12% of cases, none of which were fatal.[6] The study is ongoing in Europe and USA.

CAR T-CELLS IN MYELOMA

In a study reported by *Berdeja et al.*, bb2121 CAR T-cells directed against the BCMA antigen were infused after lymphodepleting chemotherapy (fludarabine + cyclophosphamide) in R/R MM patients (median 7 lines of treatment) with >50% BCMA expression on malignant plasma cells. The overall response rate in 18 evaluable patients was 89% and 100% in patients treated with a higher doses of CAR T-cells. First responses were noted after 1 month and best responses after 3-4 months. A CR was noted in 56% (MRD negativity in 90%) and a VGPR or better in 89% of cases. Not much information was available on the duration of the responses. There were no major toxicities with only few, and mostly mild, cytokine release syndromes.[7] Based on these promising results a global trial will be opened soon.

ANTI-BCMA DRUG CONJUGATE IN MYELOMA

GSK2857916 is a humanized IgG1 anti-BCMA antibody conjugated to a microtubule disrupting agent. During ASH 2017, phase 1 results in 35 patients with R/R myeloma (57% received ≥ 5 prior lines) treated with the standard 3.4 mg/kg dose were presented.[8] The drug is administered every 3 weeks as a 1 hour IV infusion. The ORR was 60% (43% in patients previously treated with daratumumab) (1 sCR and 15 VGPR) and the median PFS was 8 months. As such, responses were durable in this heavily pretreated cohort. The most frequent adverse events were corneal (blurred vision, dry eyes, photophobia), mostly mild and reversible. The use of this antibody conjugate proved to be relatively easy and safe with promising results to be explored in further clinical trials.

THERAPEUTIC ADVANCES IN RARE DISORDERS

CAPLACIZUMAB IN ACQUIRED TTP

Acquired or immune-mediated thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease characterized by severe thrombocytopenia, microangiopathic anemia and organ ischemia caused by inhibitory antibodies against the von Willebrand factor (vWF) cleaving enzyme ADAMTS13. Standard treatment is based on plasma exchange (PE) and immunosuppression. Caplacizumab (CAP) is a bivalent nanobody targeting the A1 domain of vWF and inhibiting the interaction between the vWF multimeres and platelets. In the phase 3 HERCULES study, *Scully et al.* showed the efficacy of CAP which was started as a daily SC therapy in addition to daily PE + corticosteroids after the first PE. CAP led to

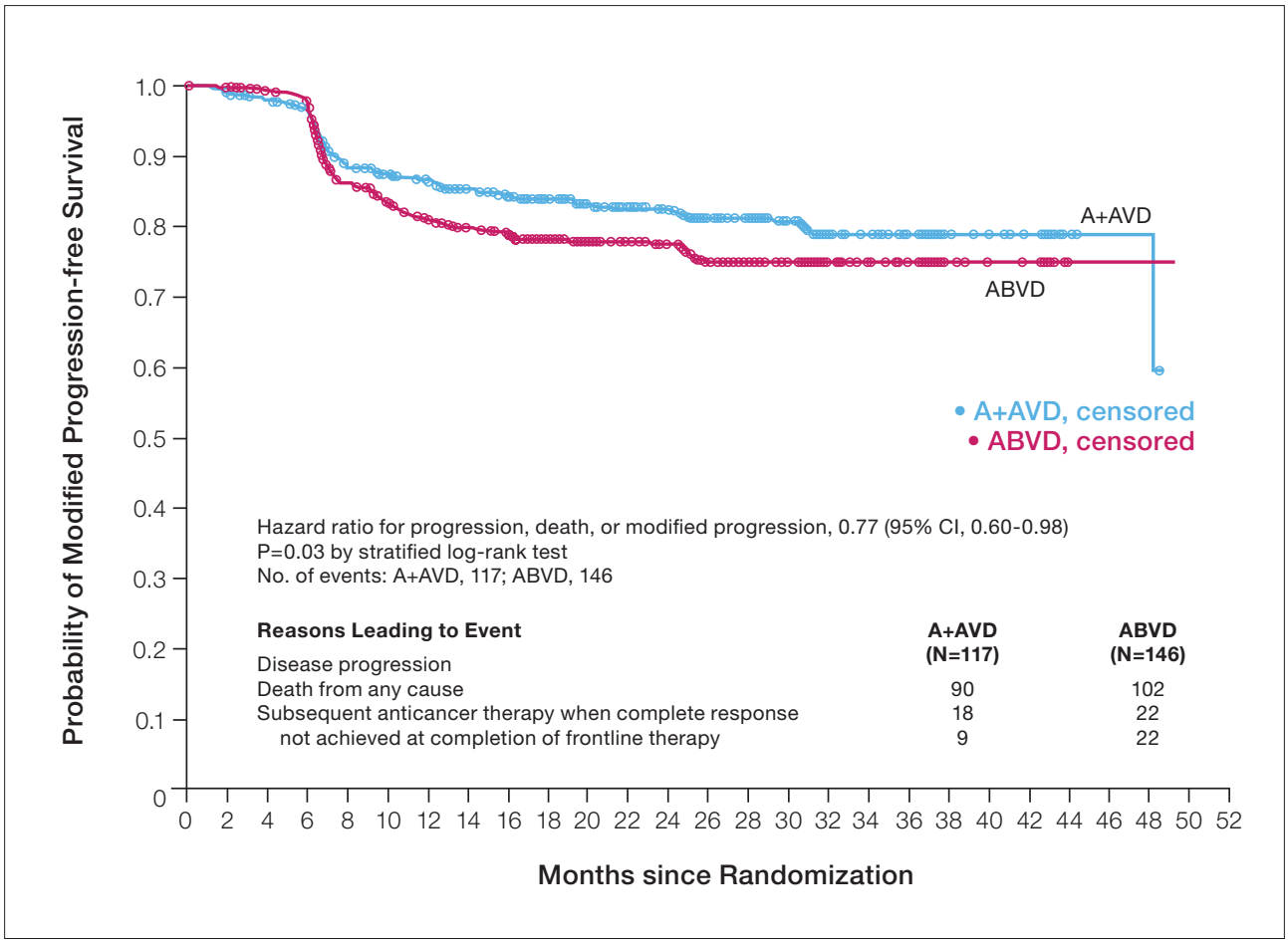

FIGURE 1. Modified progression-free survival as assessed by independent review committee in the phase III ECHELON-1 study.[4]

a >50% more likelihood of platelet response and a 74% reduction in TTP-related death, recurrence of TTP or major thromboembolic event.[9] There was a higher likelihood of relapse observed in patients with <10% ADAMTS13 activity at time of stopping the treatment, suggesting that treatment should be continued until complete resolution of the underlying disease. The safety profile of CAP was favorable with mucocutaneous bleeding as the most frequently reported adverse event. CAP is a new treatment option for patients with acquired TTP. Of note, the laboratory producing CAP is Belgian (Ablynx NV, Zwijnaarde, Belgium).

NEW KIT INHIBITOR IN SYSTEMIC MASTOCYTOSIS

Advanced systemic mastocytosis (advSM), including aggressive systemic mastocytosis, mastocytosis associated with hematological neoplasms and mast cell leukemia, is characterized by KIT^{D816V} driving mutations. *DeAngelo et al.* reported the results of an ongoing phase 1 trial with BLU-285, a highly potent and specific oral KIT inhibitor.[10] Patients also received specific antineoplastic therapies for the associated hematological malignancies. BLU-285 as a single daily dose demonstrated significant clinical activity (reduction of spleen volume, reduction of urticaria pigmentosa, less malabsorption, weight gain) with rapid and durable reductions in mast cell (MC) burden and D816V mutant allele fraction in 28/30 patients included in the study. The most common adverse event was periorbital edema, occurring in 43% of cases (7% grade ≥3). Activity was also noted in patients who were refractory to midostaurin.[10] Taken together, these data warrant further clinical testing of BLU-285 in systemic mastocytosis.

MECHANISMS OF DISEASE

TPO-INTERFERON GAMMA INTERACTION IN CHRONIC INFLAMMATION

Thrombopoietin (TPO) is a main regulator of hematopoietic stem cell and progenitor self-renewal and survival. Chronic inflammation is characterized by bone marrow suppression but paradoxically, levels of TPO are markedly increased. In this elegant study, *Alvarado et al.* showed that interferon

gamma (IFN gamma) forms heterodimers with TPO, hence reducing its binding affinity for the TPO receptor.[11] The beneficial effect of eltrombopag in severe aplastic anemia on trilinear hematopoiesis can be explained by its binding to the transmembrane part of the TPO receptor leading to evasion of the IFNgamma-mediated inhibition (*Figure 2*).[11]

NGS INTO PRACTICE

NGS FOR MRD DETECTION IN AML

MRD was assessed by NGS in acute myeloid leukemia (AML) patients achieving a morphological complete remission (CR) after 2 courses of standard induction chemotherapy.[12] NGS was performed to detect mutations in 54 genes (Illumina) known to be frequently mutated in AML. Driver mutations were present in 89.2% at diagnosis and persisted in 51.4% of patients achieving a morphological CR. Persistent mutations in *DNMT3A*, *TET2* and *ASXL1* (DTA mutations) (also known to be associated with clonal hematopoiesis of indeterminate potential or CHIP mutations) were frequently occurring in 78.7%, 54.2% and 51.6%, respectively and were not associated with an increased risk of relapse, unless they were associated with any other non-DTA mutation. In these cases, the 5-years cumulative incidence of relapse was 58.3% *vs.* 33.9% (*Figure 3*). In a multivariate analysis, NGS MRD was an independent risk factor for relapse and survival.[12]

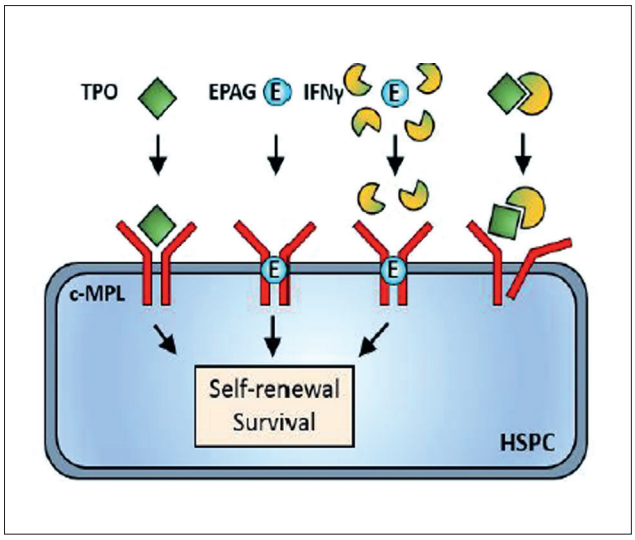

FIGURE 2. The beneficial effect of eltrombopag (EPAG) in severe aplastic anemia on trilinear hematopoiesis can be explained by its binding to the transmembrane part of the TPO receptor, hence evading the IFNgamma-mediated inhibition.[11]

NGS FOR NEW GENE DISCOVERIES IN BLEEDING DISORDERS

Lentaigne et al. performed high throughput sequencing (HTS) on samples provided by many different laboratories in

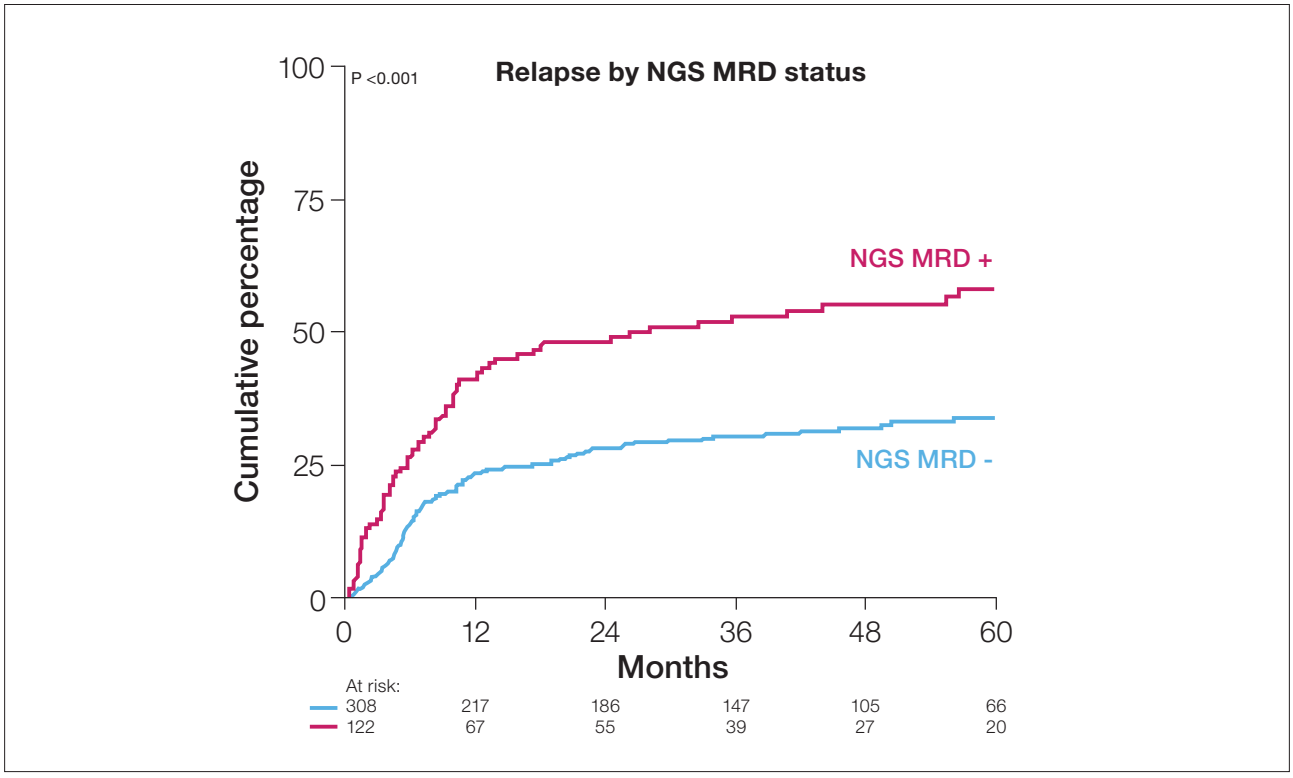

FIGURE 3. Targeted NGS MRD detection is established as a powerful and independent predictor for relapse and survival in adults with newly diagnosed AML.[12]

KEY MESSAGES FOR CLINICAL PRACTICE

1. **The venetoclax plus ibrutinib combination in B-CLL and the daratumumab-VMP schedule in eldery MM patients are likely to become standard of care first-line therapies in the near future.**
2. **CAR T-cells can be provided from a central manufacturing site to many hospital sites and produce high and high-quality response rates in DLBCL and in MM. The optimal management of severe side effects and the durability of responses require further clinical investigation.**
3. **Caplacizumab is a good treatment option for acquired TTP and the duration of treatment must be based on ADAMTS13 levels.**
4. **NGS for some, but not all, recurrent mutations is useful for MRD detection in AML patients with a morphological CR after induction chemotherapy.**

many different countries. Samples were obtained from 3,449 patients with undiagnosed bleeding and platelet disorders (BPD) and were analyzed by a 79-gene panel testing for mutations known to occur in these disorders. In addition to this, whole exome sequencing (WGS) was performed on all samples. NGS results were interpreted in combination with standardized patient information allowing for laboratory and clinical phenotyping. As such, mutations could be assigned as pathogenic, likely pathogenic and of unknown significance. The study led to the identification of hundreds of novel variants of known pathogenic mutations in BPD, and to 23 novel BPD genes in patients with thus far unknown but suspected inherited BPD.[13] As such, NGS is a powerful tool to diagnose bleeding and platelet disorders and allows to detect new mechanisms of disease.

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