Best of ASH 2018

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Hundreds of oral- and poster presentations were communicated during the 60th Annual Meeting of ASH in San Diego. Of course, it is impossible to cover all topics and give detailed highlights. In this presentation, I will give you my 'favorites', sometimes in a historical perspective. For a more complete overview of congress highlights, I refer to the other articles in this special issue of the BJH.

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LYMPHOMA

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): FIRST-LINE, 6 OR 8 COURSES OF R-CHOP: 6 IS ENOUGH

The standard of care for previously untreated patients with DLBCL consists of rituximab plus CHOP (R-CHOP). In daily practice, we often have the discussion on the number of R-CHOP courses: 6 or 8 with 3-weekly interval. The RICOVER study showed that 6 courses of R-CHOP are enough when administered at 2-weekly intervals. The GOYA study showed that no additional progression-free survival (PFS) benefit was observed with 8 cycles of R-CHOP every 3 weeks compared with 6 cycles of R-CHOP+ 2R every 3 weeks while the incidence of grade 3-5 adverse events was significantly higher in patients receiving 8 courses. Therefore, 6 courses of R-CHOP+2R should be considered standard of care for newly diagnosed patients with DLBCL.[1]

DLBCL: VERY FAVORABLE DISEASE: 4 COURSES OF R-CHOP+2R IS ENOUGH

Several studies have shown that addition of R to CHOP significantly improves the survival in patients with untreated DLBCL, especially in the subgroup with favorable non-bulky disease and an age-adjusted IPI of 0. The phase III FLYER trial demonstrated non-inferiority of R-CHOP x 4 cycles + 2R versus standard R-CHOP x 6 cycles in younger patients with DLBCL and a favourable prognosis (36-months event free survival [EFS] rate 89 *vs.* 89%, overall survival [OS] rate 99 *vs.* 98%) (*Figure 1*). Both arms exhibited comparable relapse patterns and rates. Non-hematologic adverse events (AEs) were reduced by approximately one third with R-CHOP x4. In conclusion, chemotherapy can be spared without compromising prognosis in young patients with newly diagnosis of non-bulky DLBCL and age-adjusted IPI of 0.[2]

CAR T CELL THERAPY FOR RELAPSED/ REFRACTORY DLBCL

Patients with relapsed/refractory (R/R) DLBCL after ASCT or for whom ASCT is not an option will not be cured with conventional chemotherapy and will die as a result of their disease. Conventional chemotherapy contributes to significant toxicities and decreases the quality of life of patients. These patients should be considered for novel therapies and clinical trials. Results with novel therapeutics should be compared with the best "standard of care in the setting at hand". In the context of DLBCL, the SCHOLAR-1 study is not ideal but the best we have to compare with. This study retrospectively evaluates outcomes in patients with refractory DLBCL

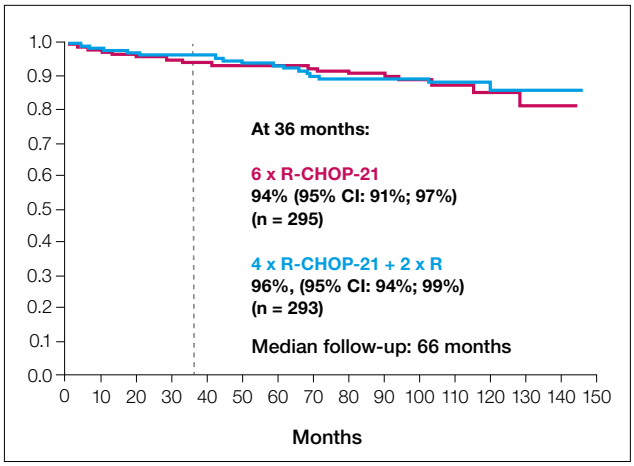

FIGURE 1. Comparable PFS with 6x R-CHOP and 4x R-CHOP + 2x rituximab in localized, favorable DLBCL.[6]

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

TABLE 1. Overview of CAR T cell data in DLBCL.[3-9]

	ZUMA-1 [3]	ZUMA-1 update [4]	JULIET [5]	JULIET update [6]	Real-world Nastoupil [7]	Real-world Jacobson [8]	Elderly [9]
Patients apharesed	111		38 (21 DLBCL)	165	211	73	
Patients infused	101 (91%)	108	28 (74%)	113 (68%)	16 (78%) + 23 pending	62 (85%)	20
ORR	82%	82%	50% (DLBCL)	52%	79%	64%	94%
CR rate	54%	53%	43%	40%	50%	41%	71%
Sustained response	42% (median 15 months)	42%		65% at 12 months	59% (0f 39 pts at day 100)	TBD	
Grade 3/4 CRS	12%		18%	22%	7%	17%	15%
Grade 3/4 neurotoxicty	31%		11%	12%	31%	38%	45%
					40% of patients did not meet ZUMA-1 eligibility criteria		

and pooled data from 2 phase 3 clinical trials and two observational cohorts. The objective response rate (ORR) was 26%, with a complete response (CR) rate of only 7%. The median OS in SCHOLAR-1 was 6.3 months with 20% of patients being alive at 2 years. However, keep in mind that the refractory DLBCL population contains a wide spectrum of patients who are not all represented in prospective studies. Patients with less favourable features are included in retrospective analyses, but not in prospective trials (for example due to symptomatic disease that requires expedited treatment, abnormal laboratory values that deem patients ineligible for clinical trials). Therefore, prospective trials conducted in refractory DLBCL patients should be interpreted cautiously in comparison with retrospective data and the results in a clinical trial setting may not reflect the situation in 'daily practice'.

Infusion of CAR T cells is a very promising cellular therapy for patients with R/R DLBCL. Several updates and new studies were presented and are summarized in *Table 1*.[3-9] My conclusions are as follows:

1. The previously reported high CR rates in the pivotal CAR T cell studies (around 40%) are durable with longer follow up and seem to result in long-term remissions for 40% of patients with R/R DLBCL.
2. Patients who do not achieve a CR experience a rapid progression,
3. Significant cytokine release (12-22%) and neurological toxicities (11-45%) complicate treatment course
4. "Real world" experience confirm these promising results even in elderly patients >65 years.[5-7]
5. There is a significant selection bias in CAR T cell studies. For example, in the JULIET trial 238 patients were screened, 71 were excluded, 165 were enrolled, 50 discontinued study before infusion, and 12 could not have CAR T cells manufactured. This leaves 111 patients that actually received CAR T cells.[4]
6. CAR T cell infusion induces significantly financial toxicity.

In conclusion, CAR T is one of the most promising new therapies in hematology, but it is not an 'off-the-shell' product. It requires patients to wait for apheresis and manufacturing. Some patients cannot wait and need immediate therapy. CAR T also requires a performance status that is adequate to tolerate potential toxicities. In addition 60% of patients will not obtain a prolonged remission. For all these reasons, other treatment modalities are still needed.

Several studies were also presented with non-cellular therapies in patients with R/R DLBCL, including BTK inhibitors, new monoclonal antibodies, iMIDS, with or without chemotherapy (*Table 2*). The ORR ranged from 37-58%, CR rates ranged from 21 to 36% with durable response rates from <9 to more than 12 months. Some of these products could be

TABLE 2. Overview of clinical trial results with targeted agents in R/R DLBCL.

	Phase	N	Median PFS	ORR	CR	Median DoR	≥ gr 3 tox	Median OS
Ibrutinib, lenalidomide, rituximab [12]	II	55	5 mos	55%	30%	9 mos	85%	
CD79b-MMAE, bendamustine, rituximab-obinutuzumab [14]	1b/II	67	5-8 mos	43%	36%	10-28 mos		11 mos
MOR208 (anti CD19), lenalidomide [10]	II	81	16 mos	58%	33%	>12 mos	35%	>12 mos
Blinatumomab (anti CD19 anti CD3) [13]	II	41	9 mos	37%			59%	
Mosunetuzumab (anti CD20, anti CD3) [11]	I	28		50%			52%	
RG606 (CD20-Tcb) [15]	I	64		38%			22%	

OS: overall survival; DoR: duration of response; CR: complete response; ORR: objective response rate; PFS: progression-free survival; mos: months; tox: toxicity

an alternative for patients who may not be ideal candidate for therapy with CAR T cells.[10-15]

In conclusion, CAR T CD19 cellular therapy induce a high CR rate and is a promising therapy for patients with a stable performance status who can wait several weeks in the setting of R/R disease. However, there is still a need for alternative new treatment modalities, especially given the 60% failure rate after CAR T cell therapy.

PERIPHERAL T-CELL LYMPHOMA

Peripheral T-cell lymphoma (PTCL) is a heterogenous group of rare and aggressive diseases including PTCL, not otherwise specified (NOS), angio-immunoblastic PTCL, ALK-positive and negative PTCL. These lymphomas are treated similarly with CHOP or CHOP-like regimens with low CR rates, poor PFS and a poor OS. CD30 expression is variable in PTCL, NOS but universally expressed in ALK-PTCL. The double-blind randomized, placebo-controlled ECHELON-2 study showed significant improvements in PFS and OS with brentuximab vedotin and CHP (BV-CHP) as compared to CHOP in the frontline treatment of PTCL. A-CHP reduced the death risk with 34% compared with CHOP. The safety profile was manageable.[16] These results are practice-changing and reimbursement in Belgian is sought.

HODGKIN LYMPHOMA: HOPE FOR PATIENTS WITH R/R HL

Although BV showed a high ORR of 75% with a CR in 34% of patients with R/R HL, only 9% of patients remain in remission without additional therapy after 5 years of follow up in the pivotal study with BV. PD-1 blockade with nivolumab or pembrolizumab also showed a high ORR around 75% in patients with R/R HL, but only about 15% of patients obtain a CR with this treatment. Thus, R/R HL remains a significant clinical challenge. The addition of BV to PD-1 blockade is a logical next step to try to increase the CR rate. Two abstracts were extremely promising, the first with combination therapy, the second abstract with a newly designed PD-1 blocker.[17,18]

In the first study (phase I) ipilimumab and nivolumab activate the immune cells in the tumor microenvironment with concurrently targeting the HL cells with BV. For the full population, the ORR was 82%, with a CR rate of 68%. For patients treated with at least 3 cycles of therapy who were evaluable for response, the ORR was even higher (95% with a CR rate of 79%)![17]

Tislelizumab (a humanized IgG4 monoclonal antibody with a high affinity/specificity for PD-1) was specifically engineered to minimize binding to FcR on macrophages, thereby abrogating antibody-dependent phagocytosis which is a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy. Seventy patients with R/R HL were enrolled. The ORR was 85.7 % with 43 patients (61.4%) achieving a CR. The safety profile was generally consistent with other PD-1 inhibitors.[18]

COMBATTING SICKLE CELL DISEASE

Sickle cell disease (SCD) was given a special place during this ASH symposium. SCD is an inherited disease by a mutation in the β globulin gene and was first described more than 100 years ago. Over the last twenty years, there was a steady increase in the understanding of the pathophysiology and new treatment modalities became available

TABLE 3. Venetoclax + hypomethylating agents (HMAs) in untreated AML.[20]

Outcome	Venetoclax 400 mg + AZA (N=84)	Venetoclax 400 mg + DEC (N=31)
CR	44	55
CRi	27	19
Median time to CR, months (range)	1.2 (0.7-5.5)	1.9 (0.9-4.6)
Median treatment cycles in patients with CR, N (range)	6 (1-32)	6 (1-29)
Median DoR, after CR/CRi, months (95% CI) • 12-month EFS in patients with CR/CRi, % (95% CI)	21.2 (14.4-30.2) 69 (52-80)	15.0 (5.0-22.5) 57 (32-76)
12-month overall EFS, % (95% CI) • 12-month EFS in patients with CR/CRi, % (95% CI) • 12-month EFS in patients with no CR/CRi, % (95% CI)	57 (46-67) 72 (58-81) 19 (6-37)	61 (42-76) 74 (51-87) 25 (4-56)
Median overall OS, months (95% CI) • Median OS in patients with CR/CRi, months (95% CI) • Median OS in patients with no CR/CRi, months (95% CI)	16.9 (11.3-NR) 40.3 (16.9-NR) 4.5 (2.4-8.9)	16.2 (9.1-27.8) 18.2 (12.3-42.7) 4.8 (0.7-17.0)
MRD negativity n/N (%)	29/60 (48)	9/23 (39)

in the Western World. Thirty years ago, it was first shown that hydroxyurea (HU) induces fetal hemoglobin production and ameliorates chronic organ damage, decreases acute vaso-occlusive events and prolonged survival in the Western World population of SCD patients. However, the incidence in sub-Saharan Africa is much higher compared to the USA and other Western countries. More than 300.000 babies with SCD are born annually. It was unclear whether HU is also safe, effective and feasible in the African setting. One of the highlights of this 60th annual meeting was the presentation of the REACH trial during the plenary scientific session. REACH is a prospective multinational trial evaluating HU for SCD in sub-Saharan Africa (simultaneously published in the N Engl J Med).[19]

A total of 635 children were enrolled of whom 606 children completed screening and began receiving HU. As compared with the pre-treatment period, the rates of clinical adverse events decreased with HU, including lower rates of vaso-occlusive pain (98.4 *vs.* 44.6 events per 100 patient years), malaria infection, transfusion and death. HU treatment was shown to be feasible, safe and had both laboratory and clinical benefits when compared with pre-treatment rates.[19]

PROGRESS IN ACUTE MYELOID LEUKEMIA

Classical cytotoxic induction chemotherapy has been employed since the 70s and is still considered standard of care for most patients with acute myeloid leukemia (AML). New treatments have become available over the last years and soon more novel agents that target molecular mutations will enter the treatment arsenal, probably in combination with classical chemotherapy. In elderly patients, who often have adverse-risk karyotypes, significant comorbidities and a poor performance status, physicians are faced with the choice between cytotoxic therapy or less intensive treatment strategies. Hypomethylating agents (HMAs) with either azacitidine or decitabine might strike a balance between efficacy and intensity. However, for this particular group of elderly AML patients, survival remains dismal.

Antiapoptotic proteins, such as BCL-2, are overexpressed in AML and AML stem cells. Venetoclax is an oral inhibitor of BCL-2 and showed promising activity in elderly AML patients. One very hopeful approach is the combination of venetoclax and a HMA. *Pollyea et al.* presented the results of a study evaluating venetoclax 400 mg in combination with azacitidine (N=84) and decitabine (N=31) in 115 patients with previously untreated AML who were unfit for intensive therapy because of comorbidities or age (*Table 3*). The combination resulted in a rate of CR/CRi of 70% and 74% with venetoclax + azacytidine and venetoclax + decitabine, respectively. The 12-month duration of response (DoR) was 69% *vs.* 57% and the median OS was 16.9 *vs.* 16.2 months. Baseline genetic mutations and cytogenetics had little effect

TABLE 4. Treatment responses to brand-name and generic imatinib in an observational study.[22]

Efficacy outcome	Brand Name Imatinib (N=285)	Generic Imatinib (N=160)	P Value
CCyR, n/N (%)	67/74 (90.5)	93/100 (93)	0.58
BCR/ABL < 10% at 3 months, n/N (%)	142/197 (72)	77/112 (69)	0.60
BCR/ABL < 1% at 6 months, n/N (%)	**139/193 (72)**	**34/113 (30)**	**< 0.0001**
ELN 2013 response at 3 months, % • Optimal • Warning • Failure	 **71** 22 **7**	 **60** 24 **16**	 **0.30** 0.732 **0.004**
ELN 2013 response at 6 months, % • Optimal • Warning • Failure	 **70** **18** 12	 **55** **30** 15	 **0.006** **0.012** 0.395

on CR/CRi rates. Common serious AEs were febrile neutropenia (31 *vs.* 45%) and pneumonia (23 *vs.* 29%).[20] These promising results with the combination of venetoclax and a HMA led to accelerated approval in November 2018 by FDA for newly diagnosed AML in patients ≥75 years or who have comorbidities preventing the use of intensive induction chemotherapy.

MYELODYSPLASTIC SYNDROMES: HOPE FOR A SUBCATEGORY OF PATIENTS WITH RING SIDEROBLASTS

Myelodysplastic syndromes (MDS) are a group of clonal disorders characterized by dysplastic features in blood and bone marrow, a variable degree of cytopenias and a potential progression into AML. The clinical manifestation of the disease varies among patients from mild symptomatic cytopenias to aggressive disease, profound cytopenias and AML transformation leading to death in the majority of patients. Another, clinical disappointing characteristic of MDS is the lack of new FDA- and EMA-approved therapies for patients. Patients with the WHO 2016 subcategory ring sideroblasts (RS) (3-11% of all MDS cases) belong to the group with mild (a)symptomatic cytopenia(s). The presenting symptoms are usually related to anemia and progressive iron load. Supportive care with transfusions and iron chelation is the main intervention. Treatment with erythropoietin (if available) in anemic lower-risk patients with low level of endogenous erythropoietin should be considered before transfusion-dependence is established, because the probability to respond is higher for early treated, transfusion-independent patients. Transforming growth factor β activation contributes to impairment of erythropoiesis. A pre-liminary strategy of blocking this pathway with, for example luspatercept, confirms the importance of this pathway. Promising data from the MEDALIST trial in MDS-RS were presented.[21] MEDALIST is a phase 3, randomized, double-blind, placebo-controlled study of Luspatercept to treat anemia in patients with very low-, low-, or intermediate-risk MDS with RS who require red blood cell (RBC) transfusion. In this trial, a significantly greater proportion of patients treated with luspatercept achieved the primary endpoint of RBC transfusion independency after 12 weeks: 37.9% *vs.* 13.2 % for luspatercept and placebo, respectively. In addition, a reduction of transfusion need (≥4 RBC units/8 week) was reported in 48.6% *vs.* 14.3%, while an increase in Hb (≥1.5 g/dL) was seen in 69.6% *vs.* 5% with luspatercept and placebo, respectively. Treatment-emergent AEs were consistent with previously reported phase 2 data and were generally well tolerated.[21] A randomized study comparing luspatercept and erythropoietin is to be expected.

CHRONIC MYELOID LEUKEMIA

GENERIC' VERSUS 'BRAND-NAME' IMATINIB

Generic formulations of imatinib recently became available as a more cost-effective treatment option. However, there are few studies that have prospectively evaluated the efficacy and safety of these generic drugs. *Pagnano et al.* presented the results of a multicenter observational study evaluating the efficacy and safety of generic imatinib compared to Glivec in 445 patients with chronic phase CML.[22] The group

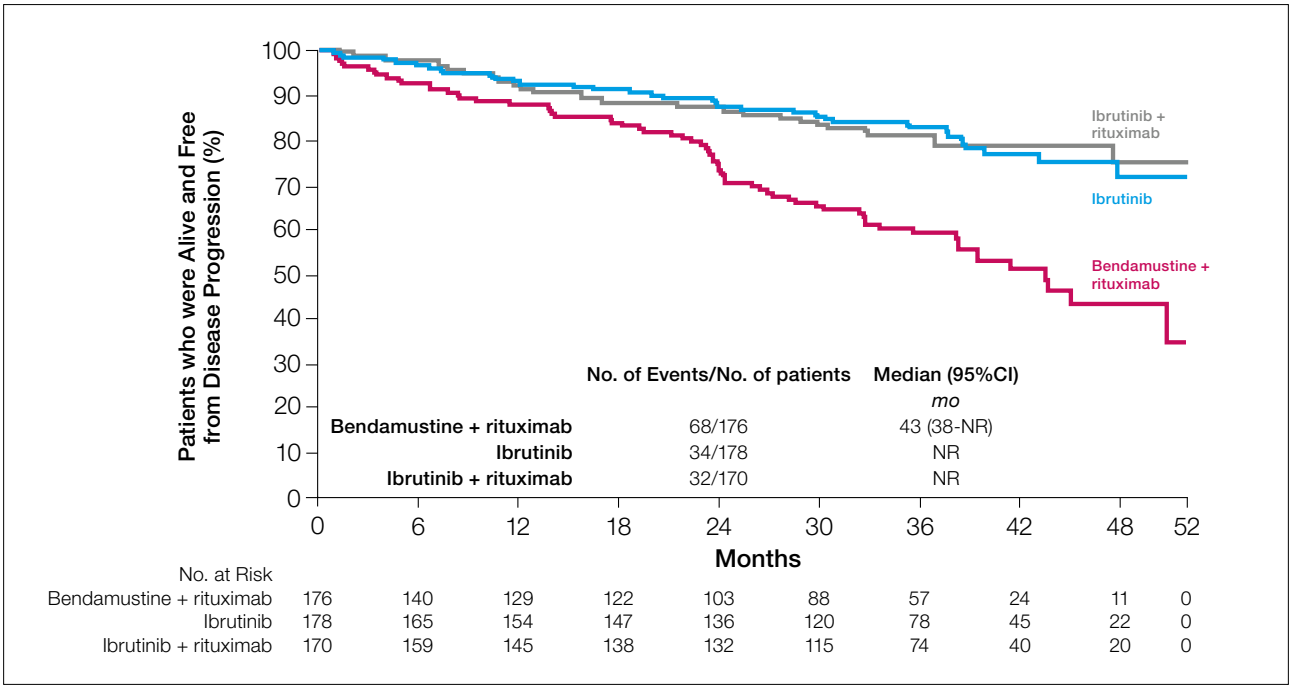

FIGURE 2. PFS with ibrutinib, ibrutinib-rituximab and BR in untreated elderly CLL patients.[24]

treated with generic imatinib presented higher rates of treatment failures at 3 months (*Table 4*) and lower rates of OS, PFS and EFS at 24 months. There were no differences in the safety profile. Study limitations include a higher rate of younger patients, a higher rate of patients with a high-risk Sokal score and a longer median time from diagnosis to imatinib use in the generic cohort. A randomized study between generic *vs.* brand-name imatinib to solve the disadvantages of this observational study would be ideal but will never come. Caution in use of generic imatinib is the message of this study.

TO STOP OR NOT TO STOP

TKI discontinuation has become a critical goal of CML management in many patients. Several studies have demonstrated the feasibility of stopping imatinib safely but failed to identify robust and reproducible predictive factors allowing a better selection of candidate patients for successful treatment free remission (TFR). *Nicolini et al.* presented results of the STIM2 trial demonstrating that residual disease by digital PCR, and TKI duration are critical predictive factors for molecular recurrence after stopping imatinib first-line in chronic phase CML patients. In this study, patients were enrolled with newly diagnosed CML, chronic phase in sustained MR$^{4.5}$ (=2 years on at least 5 consecutive points) according to ELN criteria. The molecular recurrence free survival was 50% at 24 months. Two significant predictive factors were identified to predict TFR: duration of imatinib therapy (=74.8 months) and the residual leukemic cell load as determined by digital droplet quantitative PCR for *BCR-ABL1* (=0.0023% IS). These data might help to select patients for whom therapy with TKI can be stopped safely.[22]

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): FROM AN INDOLENT BUT FATAL LEUKEMIA TO A CHRONIC DISEASE?

The treatment of CLL has undergone a remarkable evolution in recent years. Important advances in the understanding of CLL biology, driven by technological progress, combined assessment of clinical, biological and genetic information to predict outcome and design of clinical trials suggests that this disease slowly transforms from an indolent, but often fatal disease to a more chronic condition. The Ham-Wasserman lecture, *"On the architecture of translational research designed to control chronic lymphocytic leukemia, given by Michael Hallek*, was one of the highlights of this meeting. Highly-recommended literature for anyone who is interested in CLL!

Two abstracts in CLL drew my special attention. *Woyach et al.* presented data of a phase III trial comparing ibrutinib alone or in combination with rituximab to bendamustine-rituximab (BR) in untreated older patients with CLL.[24] For older patients with CLL, chlorambucil in combination with obinutuzumab or BR are considered to be the standard of care. Ibrutinib has not been compared head to head with standard immunochemotherapy. The median PFS (primary endpoint) was not reached with ibrutinib monotherapy and

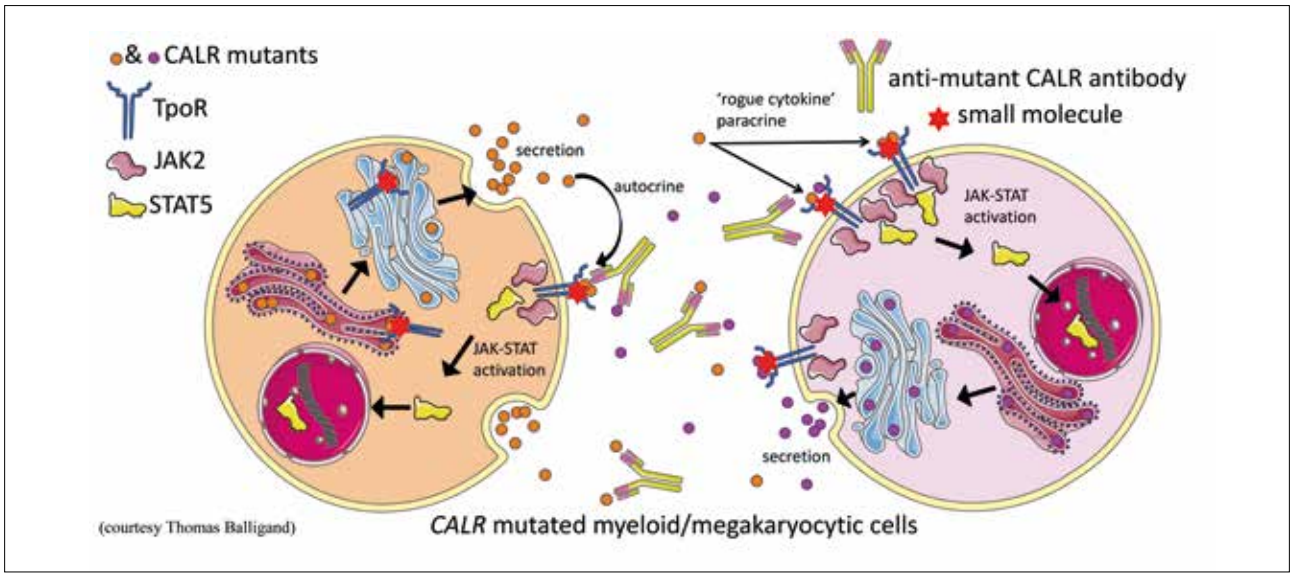

FIGURE 3. CALR mutated cells secrte mutant CALR that acts in an autocrine and a 'rogue cytokine' fashion.[27]

with ibrutinib-rituximab and was 43 months with BR. The 2-year PFS rate was 87% with ibrutinib, 88% with ibrutinib + rituximab and 74% with BR (*Figure 2*) Ibrutinib was associated with important toxicities in this older cohort, and investigators recommend close monitoring with ibrutinib in this setting. Significantly higher rates of hypertension ($p<0.001$), and atrial fibrillation ($p=0.05$) were reported with ibrutinib-based therapy. In contrast, BR exhibited significantly higher rates of hematologic AEs ($p<0.001$) and febrile neutropenia ($p<0.0001$). Identification of discontinuation strategies for ibrutinib is of significant interest.

The second abstract was presented at the late-breaking abstracts session and focused on ibrutinib *vs*. FCR in young patients with treatment-naïve CLL.[25] FCR is the current standard of care for the frontline treatment of younger (<65-70 years) CLL patients. The ECOG-E1912 study randomized untreated, young CLL between ibrutinib (N=354, median age 58 years) and FCR (N=175, median age 57 years). After a median follow up of 33.4 months, the HR for PFS favored ibrutinib-rituximab over FCR (HR[95%CI]: 0.352[0.223-0.558]; $p<0.0001$) This reflects a 65% reduction in the risk of disease progression or death with ibrutinib-rituximab compared with FCR. There was also an OS advantage with ibrutinib-rituximab (secondary endpoint). Grade 3-5 treatment-related AEs with ibrutinib included significantly higher rates of atrial fibrillation and hypertension, but significantly lower rates of myelosuppression, infections or neutropenic fever were seen with ibrutinib-rituximab than with FCR.[25] The authors concluded that ibrutinib-based therapy is the most effective treatment for untreated young CLL patients with reduced sight effects. This study also raised questions about the pharmaco-economics ('financial toxicity') of long-term targeted therapy with ibrutinib, instead of a 6-months course of chemotherapy.

MULTIPLE MYELOMA: A NEW STANDARD OF CARE IN PATIENTS WHO ARE NO CANDIDATE FOR HIGH-DOSE CHEMOTHERAPY

Facon et al. demonstrated that the addition of daratumumab to lenalidomide and dexamethasone reduced the risk of progression or death by 44% in patients with ASCT-ineligible newly diagnosed myeloma. Also the depth of response was significantly improved with the addition of daratumumab. They concluded that this triple should become the new standard of care in this particular group of myeloma patients.

MYELOPROLIFERATIVE NEOPLASMS: PERSPECTIVES FOR NEW THERAPIES BY STUDYING SECRETED MUTANT CALRETICULINS

The presentation of *Thomas Balligand (Ludwig Institute for Cancer Research, Brussels)* during the Plenary scientific Session was one of the absolute highlights of the symposium. The presented abstract was entitled: "Secreted mutant calreticulins as rogue cytokines trigger thrombopoietin receptor activation specifically in CALR mutated cells." The aim of this impressive research was to assess the direct TpoR-mutant CALR interactions both when expressed in the same or in different cells and to determine whether mutant CALRs are secreted and can act as extracellular cytokines. *Balligand et al.* demonstrated that CALR mutant proteins are

secreted from *CALR* mutated cells and are detectable in the blood of patients. Exogenous CALR mutant proteins are able to bind and activate cell-surface bound TpoR on the same cell or on neighboring *CALR* mutated cells. Only *CALR* mutated cells are sensitive to exogenous CALR mutant concentrations as detected in patients and paracrine and autocrine actions of secreted mutant CALR enhance pathologic signaling in the MPN clone (*Figure 3*). Based on these findings, antibodies and small molecules that specifically target the mutant *CALR* MPN clone could hypothetically represent a new therapy for *CALR*-mutant MPN patients.[27]

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