Making Education Easy

11 August 2016, Sydney, Australia

This publication summarises a recent presentation delivered by Professor Martin Dreyling at a Janssen-sponsored educational event on 11 August 2016 in Sydney, Australia. Professor Dreyling is Professor of Medicine and the Head of the Lymphoma Programme in the Department of Medicine III, University Hospital Großhadern, Ludwig Maximilians-University in Munich. His talk addressed the ways in which bendamustine [Ribomustin®] is changing the treatment paradigm for patients with indolent non-Hodgkin's lymphoma (iNHL) and mantle cell lymphoma (MCL).

Professor Martin Dreyling

Martin Dreyling is Professor of Medicine and the Head of the Lymphoma Programme in the Department of Medicine III, University Hospital Großhadern, Ludwig Maximilians-University in Munich. He studied at the Universities of Düsseldorf, Giessen, Tübingen and Würzburg, and completed his clinical training at the Universities of Bonn, Münster, Göttingen, and Munich. In addition, he was a visiting scientist at the University of Chicago from 1992 to 1995.

His scientific focus is on the molecular basis of malignant transformation, cell cycle dysregulation and secondary genetic alterations, as well as biological prognostic factors in malignant lymphoma. Professor Dreyling is also interested in innovative therapeutic approaches, including novel antibodies and molecular targeted approaches like inhibitors of the B-cell receptor pathway.

Professor Dreyling is the Coordinator of the European MCL Network and Assistant Coordinator of the German Low Grade Lymphoma Study Group (GLSG). He has co-authored numerous scientific papers, book chapters and abstracts in international peer-reviewed journals.

RESEARCH REVIEW™
The Australian Perspective — Since 2007

Indolent NHL subtypes

After chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL) is the second most common subtype of iNHL (38% vs 31%).[1] Of the other NHL subtypes, mucosa-associated lymphoid tissue (MALT) lymphoma and Waldenström macroglobulinaemia make up about 8% and 6%, respectively; the remaining entities include mantle cell lymphoma (MCL; 4%), hairy cell leukaemia (HCL; 3%), B-cell prolymphocytic leukaemia (B-PLL; 1%), unknown (4%), and other indolent lymphomas (5%).[1]

FL has a median age at diagnosis of 60–65 years, is usually characterised by an indolent clinical course, and has a median survival rate of 15–20 years. Most patients with FL present at an advanced stage (III/IV). In relapse, FL remains sensitive to chemotherapy.

The best therapeutic approach is the optimal strategy for the individual patient. An algorithmic approach to first-line treatment in FL is based on clinical risk factors (tumour stage, FLIPI 1/2, grade), the presence or absence of symptoms, and patient perspective as to goals of therapy (longer survival, long remission, better quality of life).[2]

Treatment substantially depends on the stage of disease:

- in asymptomatic cases, watch and wait
- for mild symptoms, antibody monotherapy (rituximab, radioimmunotherapy)
- for high tumour burden, first-line immunochemotherapy regimens include rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP), rituximab/cyclophosphamide/vincristine/prednisone (R-CVP), or bendamustine plus rituximab (BR).[2] In Germany, the BR regimen is much more frequently used than R-CVP.

Optimal induction regimen

Bendamustine hydrochloride was first synthesised in 1963 by Ozegowski and Krebs in East Germany.[3] Chemically, it is a bifunctional alkylating agent containing a nitrogen mustard moiety, a benzimidazole ring, and an alkane carboxylic acid side chain.[4-6] The benzimidazole ring may be responsible for the purine analogue activity of bendamustine, which might explain its high efficacy.[4-6] Preclinical investigations indicate that the therapeutic success of bendamustine might be due to its inhibition of mitotic checkpoints, and induction of mitotic catastrophe, which has been observed in cells lacking functional p53 or caspases.[7-9] However, as Professor Dreyling emphasised, although bendamustine does work independently of p53 in the preclinical setting, this agent is not encouraged in the clinical setting for CLL with p53 mutations, since the duration of responses is relatively short.

In a phase III noninferiority trial comparing BR with R-CHOP, median progression-free survival (PFS) was more than doubled with BR in patients with FL (after a median observation time of 45 months, the median value was 69.5 vs 31.2 months; HR 0.58; $p<0.0001$).[10] The between-group differences were even more pronounced in the Waldenström macroglobulinaemia cohort, with median PFS values of 69.5 months with BR and 28.1 months with R-CHOP ($p=0.0033$). Professor Dreyling's advice is that the more leukaemic the indolent disease, BR is more appropriate than CHOP-like regimens.

The noninferiority, global, phase III BRIGHT study demonstrated that complete response (CR) rates for the BR regimen were noninferior to R-CHOP but superior to R-CVP.[11] With regard to tolerability, BR was highly comparable to R-CVP and much better tolerated than R-CHOP in terms of haematotoxicity, with one exception; in the FL population, the BR regimen was associated with a significantly higher incidence of grade 3/4 reductions in lymphocyte count compared with R-CVP and R-CHOP (63% vs 28% and 33%; $p<0.0001$ for both comparisons).[11] Professor Dreyling suggests this might be one reason as to why opportunistic infections develop in some clinical situations. Nevertheless, he added that as this is such a rare occurrence, antimicrobial prophylaxis is not recommended as a general rule. Professor Dreyling summarised the BRIGHT study data as demonstrating that BR is as well tolerated as R-CVP and as effective as R-CHOP.

In the early years of its utilisation, bendamustine was not well accepted in Germany, because of its inclusion in third and fourth lines of chemotherapy in heavily pretreated patients, followed subsequently by dosing at 300 mg/m^2. Hence, bendamustine was associated with high rates of myelotoxicity. With accumulating therapeutic experience, bendamustine standard doses in first-line therapy have gradually reduced over the years, falling to 90–120 mg/m^2, depending on the indication. Data from two nationwide surveys conducted in Germany in 2006 and 2009 confirm an increase in use of first-line BR both in indolent lymphoma and CLL (from 4% in 2006 to 26% in 2009) and a corresponding decrease in use of R-CHOP (from 71% to 59%, respectively).[1] Currently, the majority of patients with indolent lymphoma in Germany are given first-line BR rather than R-CHOP. In other countries worldwide, bendamustine labelling for FL restricts its use in to relapsed disease only in first-line regimens. In Australia, bendamustine [Ribomustin®] is available on the Pharmaceutical Benefits Scheme (PBS) for first-line iNHL and MCL. Bendamustine has regulatory approval, but not PBS reimbursement, for first-line CLL and relapsed/refractory iNHL in Australia.

According to international consensus on the optimal use of front-line bendamustine in iNHL:

- BR should be given at the dose and schedule utilised in the StiL and BRIGHT trials (i.e. 90 mg/m^2 every 4 weeks for up to 6 cycles)
- re-treatment with bendamustine is feasible
- and is appropriate for unfit patients (i.e. renal insufficiency is not of concern with bendamustine)[12]

R-CHOP remains the preferred regimen for grade IIIa (formerly indolent) and grade IIIb (aggressive) FL.[13] Evidence shows that these types of lymphoma differ from grades 1 and 2 of FL by disease markers, genetic alterations, and by treatment outcomes. However, Professor Dreyling pointed out that it is extremely difficult to differentiate between grades IIIa and IIIb. He recommends that a diagnosis of FL grade IIIa that presents with significantly elevated lactate dehydrogenase (LDH) levels should be treated as aggressive disease (grade IIIb) with R-CHOP.

Rituximab maintenance data

The PRIMA trial assessed the potential benefit of 2 years of rituximab maintenance after first-line treatment in patients with FL receiving a rituximab plus CHOP, CVP, or fludarabine, cyclophosphamide, and mitoxantrone (FCM) chemotherapy regimen.[14] Patients with a high tumour burden and previously untreated FL received 1 of 3 non-randomised immunochemotherapy induction regimens. Patients achieving a complete or partial response were then randomly assigned to receive 2 years of rituximab maintenance therapy (375 mg/m^2 every 8 weeks) or observation. The study data demonstrate that at a median 36 months of follow-up, PFS was 74.9% in the rituximab maintenance group and 57.6% in the observation group. Professor Dreyling emphasised the importance of achieving a meaningful remission; rituximab maintenance treatment will not achieve the desired results in patients with large residual tumour bulk. A Cochrane analysis has demonstrated improved overall survival (OS) with rituximab maintenance treatment (pooled HR of death 0.76; 95% CI, 0.62 to 0.92) compared with patients in the no maintenance group.[15] However, this benefit was only seen in those patients with refractory or relapsed º(i.e. previously treated) FL treated with rituximab maintenance (pooled HR of death 0.72; 95% CI, 0.57 to 0.91); previously untreated patients had no survival benefit (pooled HR of death 0.86; 95% CI, 0.60 to 1.25).[15] According to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines on FL, rituximab maintenance for 2 years improves PFS and radioimmunotherapy consolidation prolongs PFS after chemotherapy only; these guidelines do not recommend myeloablative consolidation followed by ASCT in first-line therapy of responding patients.[2]

Early progression of disease

In an analysis of long-term outcomes of FL cases treated with first-line R-CHOP, 5-year OS was lower in patients experiencing early progression of disease (POD) within 2 years after diagnosis compared with those with no early POD (50% vs 90%).[16] European Group for Blood and Marrow Transplantation (EBMT)/ESMO consensus recommendations define indications for high-dose therapy with autologous stem cell rescue (HDT-ASCR) and for allogeneic transplantation in patients with FL in the rituximab era:[17]

- In patients in first relapse with chemosensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission.
- Remission consolidation with HDT-ASCR is an appropriate treatment option in first relapse in patients with a short response duration (<3 years) after rituximab-based immunochemotherapy.

It is possible to identify those patients with FL receiving first-line immunochemotherapy (R-CHOP) who are at highest risk of treatment failure. A novel clinicogenetic risk algorithm (termed m7-FLIPI) has been developed that includes the mutation status of seven genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, and *CARD11*), the Follicular Lymphoma International Prognostic Index (FLIPI), and Eastern Cooperative Oncology Group (ECOG) performance status.[18] In a GLSG discovery cohort of previously untreated patients with symptomatic, advanced-stage FL with a median follow-up of 7.7 years after R-CHOP, m7-FLIPI defined a high-risk group with a 5-year FFS of 38.29% versus 77.21% for the low-risk group (HR 4.14; 95% CI, 2.47 to 6.93; p<0.0001).[18] In a validation cohort of symptomatic FL considered ineligible for curative irradiation with a median 6.7-year follow-up after R-CVP plus maintenance treatment, m7-FLIPI again defined a high-risk group with a 5-year FFS of 25.00% versus 68.24% in the low-risk group (HR 3.58; 95% CI, 2.00 to 6.42; p<0.0001).[18] Professor Dreyling believes that this easy-to-use prognostic model will be easy to introduce into clinical routine.

The end of chemotherapy?

Is it possible to avoid chemotherapy altogether for the 80% of patients with indolent FL disease?[19] Philosophies differ on the treatment of FL. The European practice favours attempting to achieve a CR and have a long duration of CR, starting with BR/R-CHOP, followed by salvage rituximab-based chemotherapy plus autologous transplant in relapsed disease, and finally biologics. An alternate approach favours avoiding chemotherapy for as long as possible. Long-term data from a phase II study indicate support for rituximab induction monotherapy for low-tumour-burden FL.[20] After 7 years of follow-up, the median PFS for CR patients was ~4.5 years. However, the majority of patients had low or intermediate FLIPI scores (0–2) at study entry; only a few were of high-risk FLIPI status (3–5). This 'watch and wait' patient population differs from those in current conventional treatment studies, where the majority of participants are of high-risk (~50%) and intermediate FLIPI status (~30%).

Anti-CD20 monoclonal antibody therapy

Targeting the CD20 receptor with an anti-CD20 antibody, such as rituximab, has greatly improved survival in FL, although newer anti-CD20 antibodies with enhanced functional activity may result in superior efficacy. Obinutuzumab (GA101) is a novel glycoengineered anti-CD20 targeted monoclonal antibody recognising a unique CD20 type II epitope that induces higher antitumour activity and lower complement dependent cytotoxicity (CDC) activity in human lymphoma xenograft models as compared with rituximab.[21] In rituximab-refractory iNHL, the phase III GADOLIN trial demonstrated an improved median PFS for patients treated with obinutuzumab plus bendamustine versus bendamustine alone.[22]

Professor Dreyling noted that the updated ESMO Clinical Practice Guidelines have deliberately emphasised the division between therapeutic algorithms for first relapse and later relapse in FL.[2] The reasoning is that with second and later relapse, patient quality of life is more important. An additional treatment option is the phosphatidylinositol 3-kinase delta (PI3Kδ) inhibitor idelalisib, which is registered for double-refractory FL.[2] Idelalisib targets multiple pathways,[23] which may explain its 57% response rate in a clinical trial of relapsed iNHL.[24]

iNHL: a general summary

Large-scale, global clinical trials have revealed good efficacy and tolerability with the use of BR as first-line immunochemotherapy for iNHL. In patients with FL, BR regimens have been associated with prolonged PFS as compared with R-CHOP and with superior CR rates as compared with R-CVP. In regard to haematotoxicity, BR has proven to be as well tolerated as R-CVP and much better tolerated than R-CHOP.

MCL: molecular pathogenesis

Diagnosis of mantle cell lymphoma (MCL) is challenging on the basis of histopathological criteria. Clinicopathological evidence has revealed not only the cytological subtypes of classical, small cell, pleomorphic and blastic, but also pleomorphic subgroups with mixtures of cells (classical + pleomorphic type) or transitions (classical/pleomorphic type).[25] Cyclin D1 positivity, a reliable diagnostic marker for MCL, or identification of the t(11;14) translocation, is needed to establish an unequivocal diagnosis of MCL. Moreover, an MCL gene expression signature provides a precise measurement of tumour cell proliferation and identifies patient subsets that differ by more than 5 years in median survival.[26] The Ki-67 index provides additional prognostic impact; a high Ki-67 proliferation index (dichotomised at the validated 30% cut-off) in neoplastic cells is associated with significantly poorer survival in MCL, independently of ASCT, with or without radioimmunotherapy, conventional treatment, with or without maintenance therapy, or biologics.[27] The MCL-specific prognostic index, the Mantle Cell Lymphoma International Prognostic Index (MIPI) score, is another independent prognostic factor, integrating age, performance status, lactate dehydrogenase (LDH) level, and leukocyte count, determining PFS and OS.[28] The modified, simplified combination of the Ki-67 index and MIPI (MIPI-c) demonstrates a refined risk stratification, both in patients younger than 65 years and 65 years and older.[27] The MIPI-c identifies patients with survival >90%, even in the elderly.[27] With such tools available, Professor Dreyling believes it is appropriate to individually tailor treatment strategies for MCL.

Furthermore, prognosis is unfavourable in younger MCL patients (median age, 56 years) treated first-line with immunochemotherapy and ASCT, with or without high-dose cytarabine, who present with deletions of *CDKN2A* (p16) and *TP53*; simultaneous deletions of these genes are reflected by dismal outcomes (median OS, 1.8 years) compared with single deletions (median OS, 4.3 and 5.1 years) or without these deletions (median OS, 7 years).[29] The additive prognostic effects of CDKN2A and TP53 deletions were independent of the Ki-67 index.[29]

MCL has been described as "a spectrum of disease", exhibiting either an indolent disease course (15%), classical MCL involvement (80%), or transformed MCL (5%).[30] Indolent MCL is characterised by normal serum LDH level, splenomegaly, bone marrow and blood involvement, but without major adenopathy, whereas classical MCL follows an aggressive clinical course associated with complex karyotypes, high proliferation and rapid progression, resulting in blastoid features (transformed MCL).[30]

MCL: chemotherapy standards in first-line

Conventional regimens (single agent, combination chemotherapy with or without anthracyclines) are associated with very poor PFS in stage III and IV MCL.[31] Nowadays, standard care for younger patients (≤65 years) consists of dose-intensified, immunochemotherapy (R-CHOP and R plus high-dose cytarabine, alternating or sequential, followed by ASCT).[2]

A meta-analysis has proven the benefit of ASCT in first-line regimens for younger patients with advanced-stage MCL, independent of the application of rituximab.[32] If omitted from first-line treatment, ASCT has much less effect upon survival when applied in relapsed disease, noted Professor Dreyling. Data from the European MCL Network reveal that in patients aged <65 years, immunochemotherapy containing high-dose cytarabine followed by ASCT resulted in significantly higher rates of minimal residual disease (MRD) after induction compared with MRD rates in the R-CHOP treatment arm.[33] Substituting R-CHOP with 3 cycles of R-DHAP (rituximab plus dexamethasone, high-dose cytarabine, and cisplatin) increased the bone marrow MRD-negative rate from 37% to 70%.[33] This outcome translated into an ongoing treatment benefit of around 25–30% in PFS and a significantly longer time to treatment failure in the R-DHAP group versus the R-CHOP group.[33]

Even among responders to initial treatment for MCL, disease relapse inevitably occurs. The majority of patients are elderly and cannot tolerate dose intensification. A European MCL Network study compared the rates of response among patients aged ≥60 years with stage II–IV MCL randomised to an induction regimen consisting of fludarabine, cyclophosphamide, and rituximab (R-FC) or an induction regimen with R-CHOP.[34] OS was significantly shorter with R-FC than with R-CHOP (4-year survival rate, 47% vs 62%; p=0.005), and haematological toxic effects occurred more frequently with R-FC than with R-CHOP.[34] Clinical study data suggest the BR regimen is a preferred first-line treatment approach to R-CHOP because of increased PFS (OS is identical), however, patients continue to relapse.[10] Moreover, BR appears to be noninferior to standard R-CHOP with regard to clinical response in treatment-naïve MCL.[11] An improved treatment approach is needed.

According to treatment advice issued by the most recent Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) MCL guidelines:[35]

- For young, fit patients, R-immunochemotherapy induction followed by autologous peripheral blood stem cell transplantation (autoPBSCT)
- BR becomes more important with increasing ECOG status and older age (>65 years)

Clinical studies have investigated the efficacy of three compounds that are registered for MCL: bortezomib, temsirolimus and lenalidomide.

- Bortezomib: A phase III trial evaluated whether replacing vincristine with bortezomib in R-CHOP improves outcomes in newly diagnosed MCL patients ineligible for bone marrow transplantation (BMT).[36] Compared with R-CHOP, first-line bortezomib (VR-CAP) significantly prolonged PFS and duration of remission. However, VR-CAP was associated with significant haematological side effects.
- Temsirolimus: Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR), a molecule implicated in multiple tumour-promoting intracellular signalling pathways.[37] In a phase III trial that randomised patients with R/R MCL to monotherapy with either temsirolimus or ibrutinib, results strongly favoured treatment with ibrutinib.[38] Overall response rates were 71.9% with ibrutinib and 40.4% with temsirolimus (p<0.001).
- Lenalidomide: The MCL-002 (SPRINT) phase II study evaluated monotherapy with lenalidomide versus best investigator's choice of single-agent chemotherapy (rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine) in R/R MCL.[39] The study deliberately enrolled medically non-fit patients. An early fall in survival with lenalidomide suggests that this therapy is not the answer. However, lenalidomide provided constant therapeutic benefit, with significantly improved PFS compared with investigator's choice at a median 15.9 months' follow-up (PFS: median 8.7 months vs 5.2 months; HR 0.61; 95% CI, 0.44 to 0.84; p=0.004).

Ibrutinib

Clinical experience supports the fact that ibrutinib is a well-tolerated agent, with much better tolerability than chemotherapy. The MCL3001 (RAY) phase III study compared the efficacy and safety of ibrutinib with that of temsirolimus in R/R MCL.[38] At a 2-year landmark, PFS rates were 41% for ibrutinib and 7% for temsirolimus (p<0.0001).

In a phase II trial that assessed the efficacy and safety of ibrutinib in R/R MCL, the most frequently reported (>15% of patients) grade ≥3 haematological adverse events were neutropenia (17%), thrombocytopenia (13%) and anaemia (11%).[40] An unusual side effect associated with ibrutinib is cutaneous bleeding, which affects around one-third of patients receiving ibrutinib for R/R MCL. This bleeding event is more of a cosmetic concern, advises Professor Dreyling. It becomes a critical concern in patients on oral anticoagulation; anticoagulants are contraindicated with ibrutinib in the European registration. Nevertheless, Professor Dreyling uses ibrutinib when no other therapeutic option exists for those patients with MCL requiring direct oral anticoagulants. The Australian registration states that ibrutinib should be used with caution in patients taking anticoagulants or medications that inhibit platelet function; ibrutinib is not contraindicated in these patient populations.

The earliest clinical experience with ibrutinib in MCL was in heavily pretreated patients, some of whom initially responded, before progressing rapidly (within ~3 months). Typically, these patients had very high Ki-67 (~90%). A recent meta-analysis of ibrutinib treatment lines in relapsed MCL found significant improvement in OS in those patients who received subsequent treatment upon relapse compared with those who did not, and very few heavily pretreated patients with very high Ki-67.[41]

In the current era of combination therapy, physicians need to consider the optimal combination for patients, based on the clinical evidence.

MCL: a general summary

As a first-line treatment in MCL, clinical study data indicate that the BR regimen is preferred over R-CHOP due to the improvement in PFS associated with BR. Moreover, the most recent DGHO MCL guidelines highlight the therapeutic value of BR over R-immunochemotherapy regimens, when seeking therapeutic options for increasing ECOG status and older age. Much has been learnt about MCL with the maturation of clinical data over the last 20 years. Professor Dreyling and colleagues remain committed to exploring new findings and therapeutic possibilities in both MCL and iNHL.

References

1. Schmidt C, et al. Changes in the diagnosis and treatment of patients with low grade lymphoma in Germany: years 2006–2009. Leuk Lymphoma. 2015;56(3):694–702.
2. Dreyling M, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii76–82.
3. Ozegowski W, Krebs D. w-[bis-(chlorethyl)-amino-benzimidazolyl-(2)]-propionic or butyric acids as potential cytostatic agents. J Prakt Chem. 1963;20(3-4):178–86.
4. Balfour JA, Goa KL. Bendamustine. Drugs. 2001;61(5):631–8.
5. Niemeyer CC, et al. SDX-105 (bendamustine) is a clinically active chemotherapeutic agent with a distinct mechanism of action. Am Assoc Cancer Res. 2004;45:(abstract 1129).
6. Rummel MJ, et al. Bendamustine and rituximab act synergistically in vitro and are effective in the treatment of relapsed or refractory indolent and mantle cell lymphomas. J Clin Oncol. 2005;23(16S):6565.
7. Leoni LM, et al. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanistic features compared with other alkylating agents. Clin Cancer Res. 2008;14(1):309–17.
8. Niemeyer, C, et al. Mitotic catastrophe induced in cells treated with SDX-105 (Treanda™). Proc Am Assoc Cancer Res. 2005;46:(abstract 2291).
9. Castedo M, et al. Mitotic catastrophe constitutes a special case of apoptosis whose suppression entails aneuploidy. Oncogene. 2004;23(25):4362–70.
10. Rummel MJ, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203–10.
11. Flinn IW, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944–52.
12. Cheson BD, et al. Optimal use of bendamustine in hematologic disorders: Treatment recommendations from an international consensus panel - an update. Leuk Lymphoma. 2016;57(4):766–82.
13. Wahlin BE, et al. Clinical significance of the WHO grades of follicular lymphoma in a population-based cohort of 505 patients with long follow-up times. Br J Haematol. 2012;156(2):225–33.
14. Salles G, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet Oncol. 2011;377(9759):42–51.
15. Vidal L, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. J Natl Cancer Inst. 2011;103(23):1799–806.
16. Casulo C, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516–22.
17. Montoto S, et al. Indications for hematopoietic stem cell tran2splantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party.
18. Pastore A, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol. 2015;16(9):1111–22.
19. Cheson BD. CLL and NHL: the end of chemotherapy? Blood. 2014;123(22):3368–70.
20. Colombat P, et al. Rituximab induction immunotherapy for first-line low-tumor-burden follicular lymphoma: survival analyses with 7-year follow-up. Ann Oncol. 2012;23(9):2380–5.
21. Mössner E, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell–mediated B-cell cytotoxicity. Blood. 2010;115(22):4393–402.
22. Sehn LH, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016;17(8):1081–93.
23. Coutré SE, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma. 2015;56(10):2779–86.
24. Gopal AK, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370(11):1008–18.
25. Tiemann M, et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol. 2005;131(1):29–38.
26. Rosenwald A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell. 2003;3(2):185–97.
27. Hoster E, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: Results from randomized trials of the European Mantle Cell Lymphoma Network. J Clin Oncol. 2016;34(12):1386–94.
28. Hoster E, et al. Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. J Clin Oncol. 2014;32(13):1338–46.
29. Delfau-Larue MH, et al. High-dose cytarabine does not overcome the adverse prognostic value of *CDKN2A* and *TP53* deletions in mantle cell lymphoma. Blood. 2015;126:604–11.
30. Dreyling M, on behalf of the European MCL Network. Mantle cell lymphoma: Biology, clinical presentation, and therapeutic approaches. ASCO 2014 Educational Book.
31. Dreyling MH, Hiddemann W, for the European MCL Study Group. Prognostic factors in mantle cell lymphoma: Clinical characteristics, pathology and cell proliferation. 35th Meeting of the American Society of Clinical Oncology, Atlanta. J Clin Oncol (Proceedings of the ASCO) 18: 3a (Vortrag), 1999.
32. Hoster E, et al. Autologous stem cell transplantation and addition of rituximab independently prolong response duration in advanced stage mantle cell lymphoma. Blood. 2009;114(22):880.
33. Hermine O, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. Lancet. 2016;388(10044):565–75.
34. Kluin-Nelemans HC, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520–31.
35. Dreyling M, et al. Onkopedia guidelines. Mantle cell lymphoma. https://www.onkopedia-guidelines.info/de/onkopedia/guidelines/mantelzell-lymphom/@@view/html/index.html
36. Cavalli F, et al. Randomized phase 3 study of rituximab, cyclophosphamide, doxorubicin, and prednisone plus vincristine (R-CHOP) or bortezomib (VR-CAP) in newly diagnosed mantle cell lymphoma (MCL) patients (pts) ineligible for bone marrow transplantation (BMT). J Clin Oncol. 2014;32:5s (suppl; abstr 8500).
37. Rini BI. Temsirolimus, an inhibitor of mammalian target of rapamycin. Clin Cancer Res. 2008;14(5):1286–90.
38. Dreyling M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016;387(10020):770–8.
39. Trněný M, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol. 2016;17(3):319–31.
40. Wang ML, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507–16.
41. Martin P, et al. Post-ibrutinib outcomes in patients with mantle cell lymphoma. Blood. 2016;127(12):1559–63.

Professor Dreyling has received research support from Celgene, Janssen, Mundipharma, Pfizer, and Roche. He has also received speaking honoraria from Celgene, Gilead, Janssen, Mundipharma, Pfizer, and Roche. Professor Dreyling has served on Scientific Advisory Boards for Bayer, Celgene, Gilead, Janssen, and Pfizer.

This publication was sponsored by Janssen-Cilag Pty Ltd (Janssen) Australia. Janssen has no control over the editorial content. The views expressed in this publication may be those of Professor Dreyling and do not necessarily reflect the views of Janssen Pharmaceutical Companies of Johnson & Johnson. Products mentioned in this presentation are prescription medicines and detailed prescribing information is available at http://www.tga.gov.au. Please consult the full Product Information or Data Sheet for licensed instructions on all medicines discussed in this meeting. Treatment decisions based on these data are the full responsibility of the prescribing physician.

