ASCO 2017 meeting summary: updates to practice-changing studies in untreated non-Hodgkin lymphoma

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ABSTRACT

The 2017 annual meeting of the American Society of Clinical Oncology took place in Chicago, Illinois, 2–6 June. At the meeting, results from key studies in the first-line treatment of indolent non-Hodgkin lymphoma (iNHL) were presented. Of those studies, two were selected for oral presentations: 9-year follow-up data from the stil NHL.1 trial, which compared the efficacy and safety of bendamustine plus rituximab (BR) with those of rituximab plus cyclophosphamide–vincristine–prednisone–doxorubicin (r-chop); and 5-year follow-up data from the bright study, which compared BR with r-chop and r-cvp (rituximab plus cyclophosphamide–vincristine–prednisone) combined. Our meeting report describes the foregoing studies and includes interviews with key investigators, plus commentaries from three Quebec hematologists on the potential effects for Canadian practice.

Key Words Indolent non-Hodgkin lymphoma, untreated; front-line treatment; first-line treatment

BACKGROUND

The current standard of care in Canada for the first-line treatment of indolent non-Hodgkin lymphoma (iNHL) is bendamustine in combination with rituximab (BR), followed by rituximab maintenance1. Before the acceptance of BR as the standard regimen in this setting, rituximab with either cyclophosphamide–vincristine–prednisone–doxorubicin (r-chop) or cyclophosphamide–vincristine–prednisone (r-cvp) was given as first-line therapy. Because of the potential cardiotoxicity associated with doxorubicin, r-cvp was used in preference to r-chop in most centres in Canada. And given that patients are likely to be exposed to additional treatments over time, it was deemed preferable to save anthracyclines for later in the disease course, especially in light of the relatively high incidence of transformation to more aggressive disease. In contrast, r-chop was given in preference to r-cvp elsewhere in the world, especially once the results of a study by Federico et al.2 demonstrated superior 3-year progression-free survival (PFS) for r-chop compared with r-cvp (p < 0.05).

The shift in treatment from r-chop or r-cvp to BR was based largely on initial results from the phase III Study Group Indolent Lymphomas (STIL) NHL.1 trial, published in 2013, which, in comparing BR with r-chop, demonstrated an improvement in PFS with BR3. The safety profile was also improved with BR, with lower rates of alopecia, hematologic toxicities, and infections than occurred with r-chop; however, rates of skin reactions were increased (p < 0.05). Results from STIL NHL.1 were subsequently confirmed by the BRIGHT study, which showed that the complete response (CR) rate with BR was statistically noninferior (p = 0.0225) to that with r-chop or r-cvp4. However, given that the BRIGHT study used response rates as the primary outcome, which is less appropriate than PFS in this setting, changes in practice were based primarily on PFS data from the STIL NHL.1 trial.

After publication of the STIL NHL.1 results, funding for BR was approved in most provinces in Canada, with the exception of Quebec. More recently, BR has become available throughout Quebec as well, but its adoption as first-line treatment there has been slower than in the rest of Canada.

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METHODS

Founded in 1964, the American Society of Clinical Oncology is the world’s leading professional organization for physicians and oncology professionals caring for people with cancer. The Society’s annual meeting is the largest oncology congress in the world, bringing together more than 30,000 professionals to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field. The meeting is held each year in Chicago, Illinois, with the 2017 meeting having taken place 2–6 June. This year, the congress attracted a total of 39,300 attendees. Overall, 5040 abstracts were accepted for publication at the meeting, of which 262 were chosen for oral presentations because of the high quality of their design and their potential effect on practice.

The summary presented here specifically focuses on the first-line treatment of inHL. In choosing the abstracts with the most impact, we included only those selected by the American Society of Clinical Oncology for oral presentations. Two studies met that criterion: results from a 9-year follow-up of stil NHL1, presented by Dr. Mathias Rummel; and 5-year follow-up data from the bright study, presented by Dr. Ian Flinn.

The subsections that follow summarize the two studies, including interviews with Dr. Rummel and Dr. David MacDonald, key investigators from the stil NHL1 and bright studies respectively. After the summaries, commentaries from three Quebec hematologists provide a Canadian perspective on the data and the potential impact on clinical practice in the country, with a specific focus on Quebec.

STUDIES OF FIRST-LINE TREATMENT IN INHL

Bendamustine Plus Rituximab (B-R) Versus CHOP Plus Rituximab (CHOP-R) As First-Line Treatment in Patients with Indolent Lymphomas: Nine-Year Updated Results from the Stil NHL1 study (Abstract 7501)1

Objectives: To present updated results, after a median of 113 months’ follow-up, for overall survival (os), time-to-next-treatment (ttnt), and secondary neoplasms (npl) in patients with inHL.

Methods: The prospective multicentre randomized open-label noninferiority stil NHL1 trial involved patients from 81 centres across Germany. Patients 18 years of age and older with a World Health Organization performance status of 2 or less were eligible if they had newly diagnosed stage ii or iv inHL or mantle-cell lymphoma (mcl). Patients were stratified by histologic subtype and were then randomly assigned according to a pre-specified randomization list to receive either intravenous bendamustine (90 mg/m² on days 1 and 2 of a 4-week cycle) or chop (cycles every 3 weeks of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² on day 1, and prednisone 100 mg daily for 5 days). Patients in both groups received rituximab 375 mg/m² on day 1 of each cycle (Figure 1). During the study, 420 patients with inHL received either br (n = 215) or r-chop (n = 205) for a maximum of 6 cycles. The primary endpoint of the study was pfs, with secondary endpoints including os, ttnt, and snpl. For the 113-month follow-up analysis, os, ttnt, and snpl were reassessed.

Results: Patient characteristics were well-balanced between the arms, with the median age being 64 years. After a median follow-up of 117 months, median ttnt was not yet reached in the br group [95% confidence interval (ci): 124.9 months to not reached]; it was 56 months in the r-chop group (95% ci: 39.1 to 82.0 months; Figure 2). The ttnt was significantly prolonged with br [hazard ratio (hr) compared with r-chop: 0.55; 95% ci: 0.41 to 0.73; p < 0.0001]. Compared with patients receiving r-chop, those treated initially with br needed fewer second-line treatments because of disease progression (77 patients in the br group received salvage treatment compared with 109 patients in the r-chop group). In br patients, r-chop was used as second-line therapy 27 times; br was used in the second line 52 times for patients initially treated with r-chop.

The difference in os between the two treatment arms was not statistically significant, with 62 deaths in the br group compared with 71 deaths in the r-chop group (hr: 0.82; 95% ci: 0.59 to 1.16; p = 0.2665). The estimated 10-year survival rates were 70% for the br group and 66% for the r-chop group. In responding patients (complete or partial response), the 10-year survival rates were 74% for those receiving br and 70% for those receiving r-chop (hr: 0.81; 95% ci: 0.55 to 1.17; p = 0.2630). Compared with patients having elevated lactate dehydrogenase (ldh > 240 U/L), those with normal ldh (≤ 240 U/L) experienced a significantly longer os duration (not reached vs. 127 months, p < 0.0001). Patients with normal ldh taking br also experienced a borderline significant improvement in os (hr compared with r-chop: 0.61; 95% ci: 0.37 to 1.00; p = 0.0499; Figure 3). Compared with patients having a Follicular Lymphoma International Prognostic Index score of 3–5, those with a score of 0–2 also experienced a significant improvement in os (hr: 0.33; 95% ci: 0.22 to 0.54; p < 0.0001). However, no significant difference in os was evident between the treatment groups when stratified by Follicular Lymphoma International Prognostic Index category.

The median age at study entry of patients who later died was 68 years, compared with a median age of 62 years in the entire study population. Secondary neoplasms were observed in 37 patients in the br group and in 40 patients in the r-chop group. The npl in each group included 2 cases of myelodysplastic syndrome; the r-chop group had 1 case of acute myeloid leukemia.

Author Conclusions: In patients with previously untreated inHL, br demonstrates a pfs and ttnt benefit over r-chop, with fewer salvage treatments needed.

Investigator Q&A

Dr. Mathias Rummel, head of the Department for Hematology, Clinic for Hematology and Medical Oncology, Justus-Liebig University Hospital, Giessen, Germany, spoke with us about the stil NHL1 trial.

Q Please describe the rationale of the trial.

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When the **STiL** NHL1 study was first designed 14 years ago, **R-CHOP** was the standard of care worldwide for the treatment of **IHN**L. However, bendamustine has been used in Germany for more than 30 years as a treatment option for hematologic diseases. This experience with bendamustine was formally justified based on results from the phase ii study by our group, which was later confirmed by Robinson et al., showing that the bendamustine–rituximab combination was an effective and well-tolerated treatment option for **IHN**L patients with relapsed or refractory disease. After the positive phase ii results, our phase iii **STiL** NHL1 trial used a randomized noninferiority design to examine the efficacy and safety of bendamustine–rituximab in the front-line setting. The **STiL** NHL1 trial did not include rituximab maintenance for any patients, because it was not a standard at the time. The trial therefore had a clean and straightforward design to compare the two treatment regimens, because it was not influenced by rituximab maintenance or consolidating transplantation.

Initial results of the **STiL** NHL1 trial, which were published after a 4-year median follow-up, showed bendamustine–rituximab to be superior to **R-CHOP** in terms of efficacy, with an improved safety profile. We now have almost 10 years of follow-up, and we are able to look at the long-term efficacy and safety of bendamustine–rituximab compared with **R-CHOP**. For our initial analysis, progression-free survival (PFS) was the primary outcome; however, given the subjectivity surrounding measurement of progression, we used time to next treatment (TTNT) rather than PFS as the primary outcome in the follow-up analysis. In our study and in past studies, a perfect correlation was shown between TTNT and PFS, and given that TTNT is not open to interpretation, we felt that it was a cleaner endpoint. In addition, one cannot expect patients to attend further follow-up control imaging with computed tomography (CT) when they are in ongoing remission without disease symptoms for 5 years or longer. Given the missing CT imaging, we cannot provide an exact measurement of PFS; however, TTNT can be used as a good surrogate marker.

Please describe the efficacy outcomes from the **STiL** NHL1 trial follow-up.

The long-term follow-up analysis from **STiL** NHL1 confirms the superior TTNT for **BR** over **R-CHOP** (not yet reached vs. 56 months, \( p < 0.0001 \)), with a sustained separation in the curves. At this point, some patients with a CR are potentially cured of their disease and might die of factors unrelated to their lymphoma. We might reanalyze the
data in another 5 years to determine whether even longer responses have occurred. Furthermore, the greater number of salvage therapies given after r-CHOP (109 vs. 77) confirms the superior efficacy of BR. We will also look at patients who were re-treated with BR to determine response duration after salvage therapy.

The OS analysis by LDH status shows interesting results. In patients with normal LDH (≤240 U/L), who might have a “true” low-grade lymphoma and more accurately represent the target iNHL population, we found an OS difference of borderline significance (p = 0.0499) between the treatment groups, favouring the patient group treated with BR.

**Q** Please describe the secondary malignancies reported in each treatment group.

**A** In the stiil NHL1 trial, we found no difference in the number of patients with a second malignancy in each group (37 for BR vs. 40 for r-CHOP). Moreover, there was no signal to suggest a greater number of non-melanoma skin cancers in the BR group. In the update of the BRiGHT trial, the number of second malignancies was greater for BR than for the combined r-CHOP and CVPI group; however, removing the non-melanoma skin cancers, the difference between the groups was no longer significant. It is important to note that no OS difference was evident between the BR and r-CHOP groups in our trial (visually, the OS curve with BR lies above the r-CHOP curve), and thus there was no reduction in OS in the BR group as a result of secondary cancers. In Germany, where we have many years of experience using bendamustine, there is no official warning to suggest an increased risk of second malignancies. Ultimately, we have to weigh the safety of the two regimens, and it is clear from our trial that BR has an improved safety profile compared with r-CHOP.

**Q** Based on the results of the stiil NHL1 trial, how would you treat patients with iNHL in the first-line setting?

**A** Overall, the longer follow-up from our trial confirms the use of BR as first-line treatment for iNHL, which is also supported by the updated results of the BRiGHT trial. It remains to be seen which patients should also receive rituximab maintenance; however, it appears that BR is an excellent treatment, and it therefore has to be demonstrated (for example, by our stiil NHL7 trial) whether rituximab maintenance therapy can further improve the outcomes seen with BR. For the patients, having an end to treatment is important, because it provides a longer treatment-free interval and the ability to focus on other aspects of their lives. If patients do eventually relapse, we have a number of effective treatment options to offer as salvage therapy. Therefore, given the results of both our stiil NHL1 study and the BRiGHT study, I would give BR to all patients.

**First-Line Treatment of iNHL or MCL Patients with BR or R-CHOP/R-CVP: Results of the BRiGHT 5-Year Follow-Up Study (Abstract 7500)**

**Objectives:** To present updated results after a follow-up of at least 5 years in each patient for PFS, event-free survival, duration of response (DOR), and OS.

**Methods:** The phase III open-label noninferiority BRiGHT study compared BR with r-CHOP or r-CVP (combined) for efficacy and safety in treatment-naive patients with iNHL or MCL. Investigators preassigned the standard treatment regimen that they considered most appropriate for each patient. The primary endpoint of the study was CR; however, in the follow-up analysis, time-to-event variables including PFS, event-free survival, DOR, and OS were assessed. Patients were randomized to receive BR (n = 224) or standard therapy (r-CHOP/r-CVP, n = 223) for 6 cycles; 2 additional cycles were permitted, but not mandated (Figure 4). Rituximab maintenance was allowed at the investigator’s discretion and was given in 43% and 45% of patients in the BR and r-CHOP/r-CVP groups respectively. The follow-up analysis included 419 patients with median follow-up durations of 65.0 months (BR) and 64.1 months (r-CHOP/r-CVP).

**Results:** The 5-year PFS rate was significantly improved in the BR group (65.5%; 95% CI: 58.5% to 71.6%) compared with the r-CHOP group (55.8%; 95% CI: 48.4% to 62.5%; HR: 0.61; p = 0.0025). In the iNHL subgroup specifically, a trend for improved PFS (that did not reach significance) was evident for the BR group compared with the r-CHOP/r-CVP group (HR: 0.7; p = 0.0582; Figure 5). In an unplanned sub-analysis, a significant improvement in PFS was observed for BR compared with r-CHOP/r-CVP in patients treated with any preassigned treatment or histology; a trend that did not reach significance was observed for patients preassigned to r-CVP (Figure 6).

The 5-year DOR rate in the full study population was significantly superior for the BR group compared with the r-CHOP/r-CVP group (65.5% vs. 56.9%, p = 0.00134). The difference did not remain significant for patients in the iNHL subgroup specifically (70.5% vs. 62.4%, p = 0.1051), but a trend toward the superiority of BR compared with r-CHOP/r-CVP was evident in all time-to-event analysis subgroups (Figure 7). No significant difference in OS was observed between the treatment groups in the full study population or in the iNHL subgroup specifically.

Second-line treatment was given more frequently to patients initially treated with r-CHOP/r-CVP (34%) than to those treated with BR (22%). Of the patients originally treated with BR, 8% were subsequently given r-CHOP/r-CVP, and of those originally treated with r-CHOP/r-CVP, 12% were subsequently given a bendamustine-containing regimen. A significantly greater number of patients in the BR group than in the r-CHOP/r-CVP group experienced new cancers (19% [n = 42] vs. 11% [n = 24], p = 0.022). However, when non-melanoma skin cancers were removed, the difference between the groups was no longer significant (10% vs. 6%, p = 0.133).

**Author Conclusions:** The long-term follow-up of the BRiGHT study confirms the superior PFS, event-free survival, and DOR of BR compared with r-CHOP/r-CVP, with no statistically significant difference in OS.

**Investigator Q&A**

Dr. David MacDonald, assistant professor in the Division of Hematology, Dalhousie University, and QEII Health Sciences Centre, Halifax, Nova Scotia, spoke with us about the BRiGHT trial.
Q How is the design of the BRIGHT study relevant to the management of iNHL in Canada?

A The BRIGHT trial was designed to demonstrate non-inferiority in response rates after treatment with BR or with rituximab plus chemotherapy (R-chemo). At the time, R-CHOP was the regimen most commonly used worldwide. However, R-CVP was also considered a standard treatment regimen in Canada, and it was chosen over R-CHOP for most patients. Given that the BRIGHT study included a large number of Canadian centres, patients given R-CVP constituted a large proportion of the study population.

The study by Federico et al.² demonstrated statistically superior efficacy for R-CHOP compared with R-CVP, but at the expense of increased grade 3 or 4 neutropenia (50% vs. 28%, \( p < 0.001 \)). Results of the stil NHLI trial³ clearly showed an efficacy and safety advantage of BR over R-CHOP, but had not included R-CVP as a treatment option. The contribution of R-CVP as a treatment option in the BRIGHT trial is therefore interesting, having resulted in a better safety profile in the R-chemo arm than might have been seen with R-CHOP alone. However, a limitation of the BRIGHT trial design is that the choice of R-CHOP or R-CVP was at the investigator’s discretion, which might have introduced selection bias, given that R-CVP could have been reserved for older patients or those with greater comorbidities.

Q Please describe the design and measurement of outcomes in the 5-year follow-up.
A In the original design of the BRIGHT trial, the primary outcome was response rate, with less attention given to time-to-event outcomes. An annual follow-up was included in the protocol, but CT imaging was not mandatory. After a regulatory request for more in-depth monitoring, the protocol was amended to increase the frequency of monitoring measurements to every 6 months. At that point, CT imaging was recommended, but again was not required, introducing a level of subjectivity into the progression outcomes. Although that limitation is important to keep in mind, the design was randomized and would presumably not influence differences in outcomes between treatment arms.

Q Please describe the differences in efficacy between treatment groups in the BRIGHT trial.

A After 5 years of follow-up, the PFS benefit of br over r-chemo was maintained, with no reduction in the difference between groups over time (65.5% vs. 55.8%, p = 0.0025). Moreover, in iNHL specifically, the difference between treatment groups trended toward significance (70.3% vs. 62.0%, p = 0.0582). The reason for the lack of statistical significance in the iNHL subgroup might simply be a result of inadequate power because of the smaller numbers of patients in the sub-analysis. It is also important to consider the possible selection bias discussed earlier and the fact that PFS was not a primary outcome of the study. Moreover, the greater use of second-line treatments in the r-chemo group (34% vs. 22%), supports the superior efficacy results for br over r-chemo. In our trial, rituximab maintenance was given at the investigator’s discretion, but maintenance was equally distributed between the br and r-chemo groups, at 43% and 45% respectively. Unfortunately, no subgroup analysis examined PFS outcomes in patients who did and did not receive rituximab maintenance; however, it is likely that the numbers in each group would have been too small to effectively assess that outcome.

Q Please comment on the rate of secondary malignancies reported in the follow-up analysis from the BRIGHT trial.

A The greater rate of secondary malignancies reported for br compared with r-chemo in the BRIGHT trial (19% vs. 11%, p = 0.022) warrants further consideration. It is unclear why that finding was more strongly demonstrated for non-melanoma skin cancers, and why it was not confirmed in the sti. NHL follow-up. It will be important to look at safety results with br over time to see whether secondary malignancies affect OS rates. Further follow-up should provide a better understanding of the effect of secondary malignancies on survival within each treatment group. In the sti. NHL trial, which has a longer 10-year follow-up, a trend toward improved OS was evident in the br group, which, importantly, shows that second malignancies did not affect OS in that study.

Q Do the follow-up data from both BRIGHT and sti. NHL confirm br as the standard first-line treatment for iNHL?

A The longer follow-up results for both studies support the continued use of br over r-chemo as the standard of care for the treatment of iNHL in most patients. However, given the possible signal for secondary malignancies with br and an increasing median os in iNHL overall, I might consider using r-chemo over br in a small subgroup of young, good-prognosis patients who also have an increased risk of second cancers. Furthermore, in elderly patients who might not receive the long-term benefits of br, I might consider giving r-CVP as a treatment alternative.

Clinical Impact in Canada: Q&A About Perspectives from Quebec

With Drs. Pierre Laneuville (PL), Jean-Francois Larouche (JFL), and Axel Tosikyan (AT)

Q How are the designs of the sti. NHL and BRIGHT studies relevant to the management of iNHL in Canada?

A (AT) The sti. NHL and BRIGHT studies each provide valuable data concerning the efficacy and safety of br as the standard of care for the treatment of iNHL in Canada.

FIGURE 6 Subgroup analysis for progression-free survival. BR = bendamustine–rituximab; R-CHOP = rituximab plus cyclophosphamide–prednisone–vincristine–doxorubicin; R-CVP = rituximab plus cyclophosphamide–prednisone–vincristine; iNHL = indolent non-Hodgkin lymphoma; MCL = mantle cell lymphoma; CI = confidence interval.

The *stil NHL1* trial is widely accepted as the landmark study in this setting, and it was very well designed, with a long follow-up time of 10 years. The *bright* study is important as a confirmatory trial and is relevant for Canada given that it included patients treated with r-cvp, which was the most widely used treatment in the country at the time. In Quebec, more than 90% of patients were treated with r-cvp and were subsequently given rituximab maintenance at the time of the study. Given that the *bright* study included patients treated with r-cvp and that approximately 45% of patients were treated with rituximab maintenance, results are largely generalizable to a real-world patient population in Quebec. However, the primary endpoint of the *bright* study was cr, which is a key limitation of its design compared with the *stil NHL1* trial, which used pfs as its primary endpoint.

**A (PL)** In Quebec, br was not available for a long period because the Institut national d’ excellence en santé et en services sociaux would not review the application after Health Canada’s approval of bendamustine as monotherapy, even after publication of the initial *stil NHL1* results. In contrast, in the rest of Canada, br was quickly adopted as the standard of care after the *stil NHL1* publication. In Quebec during that period, r-cvp was the preferred regimen for the front-line treatment of inhl. The Guides du Comité de l’évolution de la pratique en oncologie eventually published a guideline supporting the use of br in that setting, and many hospitals—although not all—have since allowed its use despite the lack of approval by Institut national d’ excellence en santé et en services sociaux.

Both the *stil NHL1* and *bright* studies provided important data to support br as the standard of care for the treatment of inhl. The design of the *stil NHL1* trial is clean and provides a clear comparison between br and r-chop without the influence of maintenance therapy or use of other rituximab chemotherapy. The *bright* study, while confirmatory, is limited by the fact that the choice of r-cvp or r-chop was left to the investigator’s discretion, which makes it difficult to interpret the data from sub-analyses comparing br with either r-cvp or r-chop alone. However, the combined r-chop/-cvp group compared with the br group is a valid comparison and aids in confirming the results of the *stil NHL1* trial.

**A (FJL)** The *bright* trial is limited by the fact that, by including both r-chop and r-cvp in the comparator arm, the study is more difficult to analyze. In addition, the follow-up analysis included pfs; however, pfs was not the primary endpoint of the study, and the way in which it was measured is unclear given that only yearly assessment was planned. On the other hand, the *stil NHL1* study design was robust, with long follow-up. At our centre, we use br without rituximab maintenance, and so the results of both studies are relevant to our patient population.

**Summary** The design of the *stil NHL1* trial was robust, and *stil NHL1* should be considered the landmark study in the upfront setting for inhl. The *bright* study, while having some design limitations, can be thought of as confirmatory within a separate patient population.

**Q** Do the outcomes of the *bright* and *stil NHL1* trials support the continued recommendation of br as standard treatment for inhl?

**A (AT)** In the *stil NHL1* and *bright* trials, br was demonstrated to have a significant and sustained advantage over r-chop and r-cvp, respectively, ttn and pfs. In the *bright* trial, the sub-analysis comparing br with r-chop showed a numerical improvement in pfs duration with br, but that difference did not reach statistical significance. The lack of a significant difference between br and r-chop in the *bright* trial could have been attributable to a lack of power, given that pfs was not a primary endpoint and the sub-analysis was not preplanned. In addition, ct imaging was not mandated, and so progressions might potentially have been missed. Importantly, the sub-analysis comparing br with r-cvp in the *bright* trial significantly favoured br. That comparison is more relevant for Canada than the comparison with r-chop, because r-cvp was the preferred treatment in the province. Moreover, in both trials, a greater number of salvage treatments were needed for patients initially given r-chop/-cvp than for those initially given br. Taken together, those results show a clear benefit of br over r-chop/-cvp and support the continued use of br as the standard of care in Quebec and throughout Canada.

**A (PL)** Both the *stil NHL1* and *bright* follow-up analyses demonstrated the superior efficacy of br compared with r-chop/-cvp in treatment-naïve patients with inhl. Although it is appropriate to specifically compare br with r-chop in the *stil NHL1* trial, the sub-analysis examining the same comparison in the *bright* trial is not appropriate, given that the decision to give one regimen over the other was at the investigator’s discretion and might therefore introduce bias. The *bright* trial does, however, confirm the superior efficacy of br compared with r-chop and r-cvp as a combined group. When comparing the results of the two trials, the difference in outcomes might be explained in part by the partial use of rituximab maintenance in the *bright* study, given that rituximab maintenance is known to improve pfs and os for cvp and chop in inhl; however, the benefit of rituximab after br remains uncertain.

Despite the limitations of the *bright* trial, the results of both studies suggest that br is more effective and less toxic than r-chop and that br should therefore remain the standard of care. An additional advantage of br is that rituximab maintenance might not be needed afterward, as shown by the long ttn in the *stil NHL1* study. The effect of eliminating rituximab maintenance from treatment might include a reduced cost of treatment and increased time off treatment for patients, thus improving their quality of life.

**A (FJL)** The results of both the *stil NHL1* and *bright* trials support the use of br as the standard of care for the first-line treatment of inhl. However, the results of the *bright* trial should be taken with an element of caution, considering that it is unclear how pfs was measured and that questions remain about how progression was determined. In addition, there was a difference between the two studies in terms of efficacy outcomes; comparing their results is difficult considering the different designs involved. It is
important to consider that the STRIL NHL1 trial was designed as a noninferiority study, and therefore a look at whether BR was superior to R-CHOP was not preplanned. In addition, the R-CHOP arm in the STRIL NHL1 study did less well than had been shown in earlier trials, and no clear OS benefit of BR was demonstrated. I am therefore not convinced that BR is more effective than R-CHOP; however, it is clear that BR is at least as effective as R-CHOP, with less hematologic toxicity. I would therefore suggest that BR should remain the standard of care in this setting—not because it is more effective than R-CHOP, but because it is at least as effective while being less toxic.

Summary The results of the STRIL NHL1 trial suggest that BR is at least as effective, if not more effective, than R-CHOP, while being less toxic. Results of the BRIGHT trial—while limited by the fact that PFS was not the primary outcome, and affected by a lack of clarity concerning how progression was measured—do support the results from the STRIL NHL1 trial. Overall, when considering the results of both trials taken together, it is clear that BR should remain the standard of care in the setting of the initial treatment of NHL.

Q Please comment on the secondary malignancies reported in the STRIL NHL1 and BRIGHT trials.

A (AT) It was surprising to see a greater number of second malignancies reported for BR compared with R-CHOP and R-CVP in the BRIGHT trial, especially considering that a similar pattern was not shown in the STRIL NHL1 study, which has longer follow-up. Given that the STRIL NHL1 trial is the landmark study in this setting and has a more robust design, with longer follow-up, I would place more weight on the STRIL NHL1 data. However, it would be interesting to pool the results from both studies for a closer look at this outcome. Overall, I am not convinced that an increase in second malignancies is a real signal in the BRIGHT study, given that earlier studies, including the STRIL NHL1 trial, have not shown that outcome. I would therefore continue to monitor second cancers in these and other studies, but I would not change my practice based on the BRIGHT results.

A (PL) More second malignancies occurred in the BRIGHT trial because of a higher incidence of skin cancers, but those findings were not confirmed by the STRIL NHL1 results, which, if anything, showed a numerically higher occurrence of second malignancies in the R-CHOP group. It is possible that geographic location played a role in those findings: compared with the STRIL NHL1 trial, which was based in Germany, the BRIGHT trial included countries with more exposure to the sun. Because there is a relationship between ultraviolet light exposure and skin cancers, location might explain the greater number of non-melanoma skin cancers seen in the BRIGHT trial. What is most important, however, is that no increase was observed in the rates of more serious cancers such as acute myeloid leukemia or myelodysplastic syndrome in the BRIGHT trial. I would therefore not change my practice based on those results, but would continue to monitor this outcome within clinical trials.

A (JFL) Although a greater number of second malignancies were reported for BR in the BRIGHT trial, I do believe that it is important to remove less serious cancers such as non-melanoma skin cancers from the analysis. Once the affected patients are removed, only a small difference in second cancers is evident between the groups, which could be explained by chance. We therefore cannot make any firm conclusions regarding this potential signal, and it should therefore not affect our clinical practice. However, it would be interesting to look at the patients receiving rituximab maintenance after BR to determine whether the rate of second malignancies is higher in that group than in the group not receiving rituximab maintenance. It will also be interesting to see long-term data about second malignancies from the PRIMA and GALLIUM trials, because those studies also included patients given BR.

Summary Overall, the greater number of second malignancies reported for BR in the BRIGHT trial is not confirmed by prior studies, including the STRIL NHL1 trial, which has longer follow-up. Moreover, it is unclear whether any difference in second cancers remains once non-melanoma skin cancers are removed from the analysis. At the present time, there is therefore no reason to change clinical practice based on the rate of second cancers reported from the BRIGHT trial. It is reasonable to continue to monitor for that outcome within the context of clinical trials.

Q Please describe how INHL is treated in Quebec and the potential effects of the results from the BRIGHT and STRIL NHL1 trials.

A (AT) At this point, BR is the preferred treatment for INHL in the upfront setting throughout Quebec and Canada, which is supported by the long-term results from both trials. Overall, there are no patients to whom I would not give BR; however, the unanswered question is whether to give rituximab maintenance. At our centre, we do not give maintenance, but approximately 50% of physicians in Quebec currently give maintenance after BR induction therapy.

A (PL) The results of both trials support the continued use of BR as the preferred first-line therapy for INHL. I give BR to most patients unless they are so old or frail that they should be given only rituximab monotherapy. There are also some very immunocompromised patients who could be lymphopenic after prior therapy and therefore be at increased risk of opportunistic infections. For those patients, less-immunosuppressive treatment with rituximab monotherapy, R-CVP, or even R-CHOP might be advisable. Some recent data show that, in MCL, rituximab maintenance might not improve PFS after treatment with BR. Although data about the benefit of rituximab maintenance after BR in INHL have not yet been reported, I do not think that rituximab maintenance is essential in this setting. Removing maintenance has the advantage of reducing treatment costs and increasing the treatment-free interval for patients.

A (JFL) At our centre, BR is given to most treatment-naive patients with INHL. We will, however, give R-CHOP if we believe that there is a strong possibility of transformation,
even if not proven by biopsy. In addition, if a patient is immunosuppressed for some reason other than their disease, I might give r-cvp or r-chop because of the types of opportunistic infections seen with BR.

Summary Results from both the stiil NHL1 and BRIGHT trials support the continued use of BR as the standard of care for the treatment of iNHL in the front-line setting. In most cases, then, BR should be used. The exceptions are very frail or immunocompromised patients or patients in whom the risk of transformation is high. Although rituximab maintenance is still used at many centres in Quebec, it might not add sufficiently to the efficacy of treatment. Removing rituximab maintenance has the benefit of reducing treatment costs and increasing the treatment-free interval for patients.

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