LymphomaHub

CLL/SLL, FL, MCL, MZL, WM

ASCO 2017 | iNHL and MCL: 5-year updated results of the BRIGHT study and 9-year updated results of the StiL NHL1 study

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At the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting, an oral abstract session took place that was jointly chaired by John M. Pagel, MD, PhD, of the Swedish Cancer Institute, Seattle, WA, USA, and Ranjana H. Advani, MD, from the Stanford Cancer Institute, Stanford, CA, USA.

Two key oral abstracts were presented on indolent Non-Hodgkin Lymphoma (iNHL): one on 5-year follow-up of the BRIGHT study and the other on 9-year follow-up of the StiL NHL1 study; both comparing BR with R-CHOP (or R-CVP) in patients with iNHL and MCL.

- Both studies found no difference between BR and R-CHOP/R-CVP in terms of OS
- In BRIGHT, the incidence of secondary malignancies was higher with BR; however, no increased of secondary malignancies was found between BR and R-CHOP in the NHL1 study

Abstract 7500

The first abstract of the session was on 5-year follow-up results of the BRIGHT study (NCT00877006), which aimed to compare BR with R-CVP/R-CHOP as first-line therapy for patient with advanced iNHL and MCL, and was presented by Ian Flinn, MD, PhD, from Tennessee Oncology, Nashville, TN, USA.

BRIGHT, a phase III, open-label, non-inferiority study, randomized patients with newly diagnosed FL (grade 1 or 2), WM, MZL, or MCL to 6–8 cycles of BR or R-CHOP/R-CVP who then underwent complete assessments at end of treatment, then were monitored regularly.

In the initial analysis, published in Blood in 2014, CR was non-inferior with BR (31%) vs. R-CHOP/R-CVP (25%; $P = 0.0225$ for NI [0.88 margin]). Increased hypersensitivity, vomiting, nausea, and lymphocytopenia was observed with BR; but increased peripheral neuropathy, alopecia, and neutropenia were seen with R-CHOP/R-CVP.

Of the 447 randomized patients, 224 were administered BR, 104 R-CHOP, and 119 R-CVP; 419 entered the follow-up. Patients were monitored for ≥5 years in order to evaluate the overall effect of BR or R-CHOP/R-CVP in a controlled clinical setting. This abstract presented the time-to-event variables (PFS, EFS, DoR, and OS) of the 5-year follow-up study.

	BR	R-CHOP/R-CVP

Randomized (ITT)	224	223
Treated (safety population)	221	215
Evaluable (primary endpoint)	213	206
Completed ≥6 cycles	203	196
Received rituximab maintenance	43%	45%

The median follow-up time for patients administered BR was 65.0 months and for R-CHOP/R-CVP was 64.1 months. 5-year PFS for those who received BR was 65.5% (95% CI, 58.5–71.6) compared to 55.8% (95% CI, 48.4–62.5); HR = 0.61 (95% CI, 0.45–0.85; *P* = 0.0025). When stratified by lymphoma type, 5-year PFS in patients with iNHL treated with BR compared to R-CHOP was 70.3% vs. 62.0% (HR, 0.70; 95% CI, 0.49–1.01; *P* = 0.0582). In patients with MCL, 5-year PFS for BR and R-CHOP/R-CVP was 39.7% vs. 14.2% (HR, 0.40; 95% CI, 0.21–0.75; *P* = 0.0035).

5-year OS in patients treated with BR and R-CHOP/R-CVP was 81.6% (95% CI, 75.7–86.3) compared to 85.0% (95% CI, 79.2–89.2); HR = 1.15 (95% CI, 0.72–1.84; *P* = 0.5461). In patients with iNHL, 5-year OS in patients treated with BR was 86.1% (95% CI, 80.0–90.5) compared to 89.1% (83.3–93.0) in patients treated with R-CHOP/R-CVP. In MCL patients, 5-year OS was 59.4% (95% CI, 41.2–73.6) and 62.6% (95% CI, 43.5–76.8) in patients who received BR vs. R-CHOP/R-CVP; HR = 0.86 (95% CI, 0.40–1.83; *P* = 0.6894).

Causes of patient mortality in patients treated with BR (all causes, n=40) compared to R-CHOP/R-CVP (all causes, n=32) were: disease progression (16 vs. 17), complications of stem cell transplant and reason not reported (3 vs. 6), cardiovascular (7 vs. 2), respiratory (3 vs. 1), infection (6 vs. 3), and secondary malignancy excluding transformed NHL (5 vs. 3).

Secondary malignancy	**BR (n=221)**	**R-CHOP/R-CVP (n=215)**	***P* value**
Transformed NHL/DLBCL	5	7	
Basal cell carcinoma	9	4	
Squamous cell carcinoma of the skin	12	2	
Melanoma	2	1	

MDS	1	1	
Other solid malignancy	19	11	
Patients with secondary malignancy	42 (19%)	24 (11%)	*P* = 0.022
Excluding NHL and non-melanoma skin cancer	22 (10%)	13 (6%)	*P* = 0.133

Ian Flinn concluded this abstract presentation by stating that PFS, EFS, and DoR significantly favored BR compared to R-CHOP/R-CVP. The greatest benefit was observed compared to R-CVP, and in MCL patients. No difference between the regimens in terms of OS was observed. The safety profiles of the regimens were comparable and mostly in agreement with what has been previously reported; however, the incidence of secondary malignancies was found to be higher with BR than previously thought.

Abstract 7501

Mathias J. Rummel, MD, PhD, from Justus-Liebig Universität, Gießen, Germany, presented the next oral abstract on 9-year updated results of the StiL NHL1 study (NCT00991211).

StiL NHL1 was a phase III, randomized, multicenter trial aiming to compare front-line BR (274, 261 were assessed) and R-CHOP (275, 253 assessed) in iNHL (FL grade 1 and 2, WM, MZL, SLL) and MCL patients; the rationale behind this study is that BR has a more favorable toxicity profile compared to R-CHOP and so if it can be shown to have non-inferior efficacy, then BR could improve not only the prognosis but the QoL of patients.

In the analysis published in The Lancet in 2013, the median follow-up duration was 45 months (IQR, 25–57). It was reported that BR achieved a significantly longer median PFS of 69.5 months (26.1–not reached) compared to 31.2 months (15.2–65.7) with R-CHOP (HR, 0.58; 95% CI, 0.44–0.74; $P < 0.0001$). Time to Next Treatment (TTNT) for patients treated with BR vs. R-CHOP was not yet reached compared to 42.3 months (HR, 0.52; 95% CI, 0.39–0.69; $P < 0.0001$). As expected, BR demonstrated a more tolerable safety profile compared to R-CHOP, achieving lower rates of alopecia (0% vs. 100%), hematological toxicity (30% vs. 68%), infections (37% vs. 50%), peripheral neuropathy (7% vs. 29%), and stomatitis (6% vs. 19%). However, erythematous skin reactions were more frequent in patients treated with BR compared to those administered R-CHOP (16% vs. 9%).

In the updated analyses presented by Prof. Rummel, the median follow-up duration was 117 months.

		BR	**R-CHOP**	**Age (median)**
Total	n	215	205	62

FL	66%	139	140	60
MZL	16%	37	30	66
WM	10%	22	19	64
SLL	5%	10	11	68
Unclassifiable	3%	7	5	69

Updated TTNT for BR and R-CHOP patients was not yet reached vs. 56.0 months. Seventy-seven salvage events took place in the BR group compared to 109 in the R-CHOP group. The salvage regimens used in patients who failed initial therapy with BR compared to R-CHOP included BR (16 vs. 52), R-CHOP (27 vs. 2), rituximab monotherapy (5 in each arm), fludarabine-based regimens (4 vs. 9), APBSCT (3 vs. 11), radiotherapy (7 vs. 8), ibritumomab tiuxetan (1 vs. 4), various/unknown (14 vs. 18).

The estimated 10-year OS for patients treated with BR was 70.3% (62 deaths) compared to 66.3% (71 deaths) in R-CHOP treated patients (HR, 0.82; 95% CI, 0.59–1.16; $P = 0.2665$). The estimated 10-year OS in responding patients (those who had achieved CR or PR) was 73.9% (51 deaths) and 70.0% (58 deaths) in BR and R-CHOP treated patients, respectively (HR, 0.81; 95% CI, 0.55–1.17; $P = 0.2630$).

Of the total group (n=420), 386 patients achieve CR or PR (ORR = 91.9%). Thirty-four patients achieved SD or primary refractoriness (8.1%). Overall, there were 133 deaths (31.7%); the death rate in SD/refractory patients was 71% (n=24) and in CR/PR patients was 28% (n=109). Nearly two-thirds (65%; n=86) died due to relapsed lymphoma. Approximately one-third (35%; n=47) died while in first complete remission, and 40% (n=19) of these had a secondary malignancy.

	BR (n=215)	**R-CHOP (n=205)**
Patients with secondary malignancies	37	40
Number of secondary malignancies	39	47
Prostate	3	7
Colon/gastric	6	6

Bronchial	2	5
Kidney/urothelial	4	5
Pancreatic	-	1
Breast	4	4
Other carcinoma	18	16
MDS	2	2
AML	-	1

Professor Rummel concluded the talk by stating that a prolonged TTNT was observed with BR, and no difference in OS was observed between BR and R-CHOP. The estimated 10-year OS rate with the longer follow-up is now 70% in patients administered 6 cycles of BR without maintenance with rituximab. Moreover, fewer salvage therapies were needed after first-line BR and no increased rate of secondary malignancies was observed between BR and R-CHOP. Lastly, it was reported than patients who achieved CR had a longer OS, and patients with initial low LDH trended towards a longer OS.

References:

1. Flinn I. *et al.* First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: Results of the BRIGHT 5-year follow-up study. J Clin Oncol 35, 2017 (suppl; abstr 7500). 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 June 2–6; Chicago, IL, USA.
2. Rummel M.J. *et al.* 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. J Clin Oncol 35, 2017 (suppl; abstr 7501). 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 June 2–6; Chicago, IL, USA.