

90 Y-ibritumomab tiuxetan: a nearly forgotten opportunity

Patrizia Mondello^{1,2,3}, Salvatore Cuzzocrea², Michele Navarra² and Michael Mian^{4,5}

¹ Department of Human Pathology, University of Messina, Messina, Italy

² Department of Biological and Environmental Sciences, University of Messina, Messina, Italy

³ Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁴ Department of Hematology, Hospital S. Maurizio, Bolzano/Bozen, Italy

⁵ Department of Internal Medicine V, Hematology and Oncology, Medical University Innsbruck, Innsbruck, Austria

Correspondence to: Patrizia Mondello, **email:** patriziamondello@hotmail.it

Keywords: radioimmunotherapy, Y-ibritumomab tiuxetan, follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma

Received: September 11, 2015

Accepted: November 26, 2015

Published: December 09, 2015

ABSTRACT

Y-ibritumomab tiuxetan (90Y-IT) combines the benefits of a monoclonal antibody with the efficacy of radiation in the treatment of B-cell non-Hodgkin lymphoma (NHL), a remarkably radiosensitive hematologic malignancy. 90Y-IT activity has been well established in the indolent setting, being approved in front-line treatment of follicular lymphoma (FL) patients as well as salvage therapy. However, no advantage in OS was observed with respect to standard treatment. Promising data are available also for aggressive B-cell lymphoma. In particular, the addition of RIT to short-course first line chemotherapy enables reduction of chemotherapy while maintaining cure rates in elderly, untreated diffuse large B-cell lymphoma (DLBCL) patients. Furthermore, 90Y-IT improves response rate and outcomes of relapsed/refractory DLBCL patients, eligible and ineligible for autologous stem cell transplantation (ASCT). Clinical results have shown a role of 90Y-IT even in mantle cell lymphoma (MCL). RIT might improve responses and treat minimal residual disease when used as consolidation after first-line chemotherapy in MCL. Moreover, 90Y-IT has demonstrated its efficacy in combination with high-dose chemotherapies as conditioning regimen for ASCT, with evidence suggesting the ability to overcome chemotherapy resistance. Herein, we review the available evidence for this approved drug and examine the recently published and ongoing trials for potential novel indication in aggressive B-cell NHL.

INTRODUCTION

More than a decade ago, monoclonal antigens targeting B-cell specific antigens to treat B-cell non-Hodgkin lymphomas (NHL) entered clinical routine. [1-3] Nevertheless, in some patients, B-cell lymphomas were a priori resistant to such drugs [4] or developed resistance during therapy. An alternative approach to achieve an additional cytotoxic effect and to overcome some resistance mechanisms was to conjugate monoclonal antibodies to a radioisotope since most lymphomas are highly radiosensitive. In detail, the radiolabeled antibody binds to a specific antigen present on cancer cells, bringing the radioactive substance close to the neoplastic cell. This leads not only to death of the bound cancer cell, but also to that of the surrounding cells ("crossfire effect"). (Figure

1) Moreover, radioimmunotherapy (RIT) also induces remodeling of the tumor vasculature favouring neoplasia eradication [4], probably by migration of immune cells towards the malignant lesions [5].

Because CD20 is a transmembrane phosphoprotein expressed in more than 90% of B-cell NHL, in mature B-cells and pre-B cells, but not in plasma cells or stem cells, it represents an attractive target in lymphoma. [6] Currently, there are two approved RIT agents for use in B cell lymphoma: 131 I-tositumomab (Bexxar[®]; GSK) and 90 Y-ibritumomab tiuxetan (90Y-IT) Zevalin[®]; Spectrum pharmaceuticals), both targeting CD20. [7, 8] These agents utilize radionuclides that decay by releasing beta particles (high-energy electrons) exerting their lethal effects by causing double-strand DNA breaks in tumor cells.

Bexxar[®] consists of Iodine-131, a radiation-emitting

form of iodine, conjugated to the monoclonal antibody tositumomab, which binds to CD20. Iodine-131 emits beta and gamma radiation. Beta radiation is responsible for most of the tumor killing effect while gamma radiation allows gamma camera scans to evaluate the distribution and clearance of radiation from the patient's body. Iodine-131 is eliminated from the body mainly through the urine and by the natural decay of Iodine-131.

Instead, Zevalin® consists of indium-111 or yttrium-90 conjugated to ibritumomab which targets CD20. Indium-111 is a gamma emitter used for imaging studies. In November 2011, the FDA considered the biodistribution scan no longer necessary since five prospective trials demonstrated that a true altered biodistribution occurs in approximately only 1% of patients, which is why it is no longer used. [9] Instead, the yttrium-90 radioisotope is a pure beta emitter able to damage and kill the targeted cancer cells as well as nearby cells independently of their CD20 expression. Because of the pure beta emission from yttrium-90 radioisotope, patients do not need any special safety precautions. [10] The situation regarding the special care of patients varies from country to country according to local radio protection laws. For example, Germany and Austria require isolation in a nuclear medicine ward for patients undergoing 90Y-IT treatment. If administered correctly, the mean effective half-life of this drug in blood is 27 hours (range 14-44 h) [11]. Urinary excretion is the primary clearance mechanism, and it accounts for the elimination of almost 10% of unbound 90Y within the first 12 to 24 hours, while the remaining 90% decay. Dosing of 90Y-IT is based on the patient's weight and platelet count. For patients with a platelet count greater than 150,000/ μ L, the prescribed dose is 0.4 mCi/kg up to

a maximum of 32 mCi. For patients with a platelet count between 100,000 to 150,000/ μ L, the dose is 0.3 mCi/kg, again up to a maximum of 32 mCi. The most common toxicity for both radioisotopes is myelosuppression with thrombocytopenia and neutropenia usually begins two to three weeks following the therapeutic dose, remaining low for several weeks and baseline levels being recovered after two to three months. [12] Therefore, the majority of trials investigating RIT activity in B-cell NHL had an inclusion limit of 25% bone marrow infiltration to avoid excessive hematotoxicity. Non-haematological toxicities are uncommon and usually minor.

Both agents are currently indicated for the treatment of relapsed or refractory CD20-positive lymphomas, but Bexxar® was withdrawn from the market in October 2013 for commercial reasons. 90Y-IT has an additional treatment indication as consolidation therapy in previously untreated FL patients who achieve a complete response (CR) or a partial response (PR) to first-line chemotherapy.

FOLLICULAR LYMPHOMA

Front-line setting

Although FL is characterized by a high overall response rate (ORR) to a single-agent or multidrug immunochemotherapy, relapses are frequent and tend to be less responsive to the next line treatment, which is why advanced stage FL is still considered as incurable with the current standard of care [13]. Moreover, after the first relapse, the time to next recurrence is shorter leading to a median overall survival of 4-5 years. For these reasons,

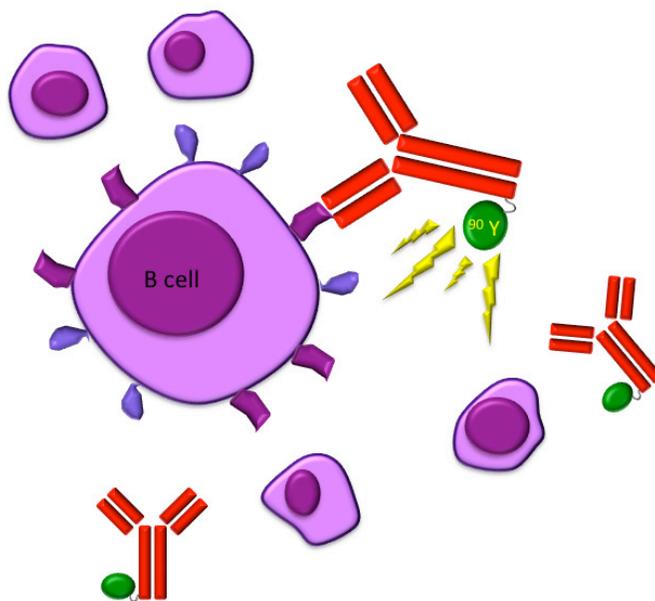


Figure 1:The radio-labeled antibody 90 Y-ibritumomab tiuxetan (Zevalin) binds to cells with CD20 receptors producing a crossfire effect.

Table 1: 90Y-ibritumomab tiuxetan treatment in follicular lymphoma

Trial design	Disease	No of patients	Response rate	Response duration
After induction therapy [15]	Chemonaïve FL	208	CR 87%	mPFS 49 months (all responder) 92 months (in CR) 30 months (in PR)
After 3cycles of R-CHOP/R-CVP [16]	Chemonaïve FL	41	CR 72%	5-year PFS 64% 5-year OS 96%
After 3 cycles of R-CHOP [17]	Chemonaïve FL	60	CR 96%	2-year PFS 78% 2-year OS 100%
After 4 cycles of R-FND [18]	Chemonaïve FL	47	CR 91%	5-year PFS 74% 5-year OS 93%
After 4 cycles of FM [19]	Chemonaïve FL and MZL	22	ORR 100% CR 79% PR 21%	mPFS 47.2 months mOS not reached
After 4 cycles of R-FM [20]	Chemonaïve FL	55	ORR 96% CR 89%	3-year PFS 81% 3-year OS 100%
Monotherapy [23]	Chemonaïve FL	59	ORR 87% CR 56% PR 31%	mPFS 25.9 months
Monotherapy [26]	Chemonaïve FL	74	ORR 96% CR 69%	3-year PFS 58% 3-year OS 95%
Monotherapy [27]	R/R FL	54	ORR 74% CR 50%	mTTP 6.8 months
Monotherapy [28]	R/R FL	143	ORR 80% CR 20%	mTTP 12.6 months
Monotherapy [29]	R/R FL	211	ORR eR 86% IR 72% CR eR 51% IR 28%	mTTP eR 15.4 months IR 9.2 months

Abbreviations: FL follicular lymphoma; CR complete response; PR partial response; mPFS median progression-free survival; OS overall survival; ORR overall response rate; mTTP median time to progression; R/R relapsed/refractory; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP rituximab, cyclophosphamide, vincristine and prednisone; R-FND rituximab, fludarabine, mitoxantrone, dexamethasone; FM fludarabine, mitoxantrone; eR early relapse; IR late relapse.

achieving CR or even elimination of minimal residual disease (MRD), is more advisable in first line than with the following treatment lines. Several authors investigated the administration of 90Y-IT either as consolidation treatment after immunochemotherapy or as monotherapy in first line Table 1.

RIT as consolidation after induction therapy

In FL, as in other hematologic neoplasias, MRD is becoming always more important since it significantly improves the outcome [14]. Therefore, RIT as consolidation after induction immunochemotherapy could induce a more profound response, postponing an eventual relapse or even lead to cure of the disease. Indeed, the FIT randomized phase III trial [15] proved a benefit for 90Y-IT as consolidation in previously untreated FL patients. After completing induction therapy

of investigators's choice, patients were randomized to receive either standard dose of 90Y-ibritumomab tiuxetan ($n = 208$) or no further treatment ($n = 206$). The regimens used were cyclophosphamide, vincristine and prednisone (CVP/COP) ($n = 106$), anthracyclin-based regimens ($n = 183$), fludarabine-based therapies ($n = 22$), chlorambucil ($n = 39$) and rituximab in association with chemotherapy ($n = 59$). After (immuno-)chemotherapy, the CR rate was similar in both arms (53% in the observation arm and 52% in the 90Y-IT arm). After RIT almost three-quarters of patients in PR converted to CR, leading to CR rate of 87%. This response improvement led to a significant PFS prolongation of more than 2 years in the RIT-consolidation arm as compared to the control arm. In detail, PFS was 49 vs 15 months in all responders, 30 vs 6 months for partial responders and 92 vs 32 months in complete responders, suggesting that 90Y-IT improves

PFS regardless of response to therapy. Moreover, 90Y-IT was able to prolong median time to next treatment (TTNT) for more than 5-years in comparison to the control group. However, there was no statistical significant difference in OS, probably due to the usually indolent clinical course of FL. Despite these promising results, their value for current clinical routine is limited since almost all patients nowadays receive rituximab in first line, while in the FIT trial approximately only 14% underwent immunochemotherapy. This because at the time the study was designed rituximab was not yet a standard agent for front-line therapy in some countries involved in the trial. Due to the small number of rituximab-treated patients, the subgroup analysis including only those patients was insufficiently powered to detect a difference in final CR rates (93% for the 90Y-IT arm vs 71% for the observation arm) or in rates of conversion from PR to CR (71% vs 42%, respectively) despite promising results.

The use of RIT as first line consolidation might also allow for the reduction of the number of immunochemotherapy cycles. Five studies investigated 90Y-IT consolidation after abbreviated courses of rituximab-based induction regimens. Hainsworth et al. [16] conducted a phase II trial including 41 patients with previously untreated FL who received rituximab for 4 consecutive weeks, followed by 3 cycles of rituximab combined with either CHOP (88%) or CVP (12%) prior to 90Y-IT consolidation. 90Y-IT was able to increase the CR rate from 30% to 72%. After a median follow-up of 67 months, the estimated 5-year PFS and OS rates were 64% and 96% ($p = 0.3$), respectively. Another phase II trial [17] included 60 patients with stage II-IV symptomatic or bulky FL who received three cycles of R-CHOP followed by RIT and four additional weekly rituximab administrations. The percentage of CR assessed with positron emission tomography (PET), improved from 46% after induction therapy to 89% following 90Y-IT consolidation. The remaining three trials [18-20] investigated the efficacy of fludarabine-based immunochemotherapy regimens plus 4 or more cycles of rituximab followed by RIT consolidation, with or without adjuvant rituximab maintenance, in untreated and intermediate/high risk FL patients. The conversion rates from PR to CR after RIT varied from 13% to 95%, confirming that the addition of RIT consolidation to immunochemotherapy was able to improve the quality of responses as well as long-term outcomes, even for patients previously treated with rituximab. Therefore, 90Y-IT is an interesting treatment option for a subgroup of FL patients, for example those who are not eligible for rituximab maintenance. [21, 22]

RIT monotherapy in first-line treatment

90Y-IT has proved to be an efficient and feasible treatment option as front-line therapy of FL. Scholz et al. [23] evaluated the efficacy and safety of RIT in 59 chemo-naïve, fit FL patients. The ORR at 6 months after

RIT was 87%, with 41% of the patients achieving CR, 15% CR unconfirmed (CRu), and 31% PR. Median PFS was 25.9 months. Compared with the standard first line immunochemotherapies, the CR rates achieved with 90Y-IT are similar [24], while median PFS was below the reported values [24, 25]. However, patients in CR after RIT alone in first line achieved long-lasting remission with a PFS not reached after a follow-up of nearly 31 months. 90Y-IT might delay or even avoid the need for chemotherapy in first line for a considerable number of patients, leaving aggressive regimens an option for relapsed FL. Furthermore, 90Y-IT as first line treatment has achieved a superior ORR with respect to four courses of rituximab monotherapy in the same setting. [23] In all trials, RIT was safe with the most common adverse event being transient myelosuppression. Non-hematologic toxicities were unfrequent and never exceeded grade 2.

The favourable toxicity profile and the efficacy of 90Y-IT were also confirmed in a more recent phase II trial [26] evaluating a fractionated 90Y-IT administration (11.1MBq/kg given 8-12 weeks apart) in 74 untreated, fit FL patients. The ORR was 96% with 69% CR/CRu. After a median follow-up of 3.1 years, PFS was 58%, treatment-free survival 66%, and OS 95%. Noteworthy, in this study the patient cohort had a more unfavourable baseline characteristics profile with respect to the previous one [23] with almost twice as many high-risk FLIPI patients (44%), but displayed a superior median PFS (40.2 v 26 months). In addition, 3-year PFS of 85% (median not reached) for patients with CR was markedly improved compared with the 1- and 2-year PFS rates of 77% and 54% reported by Scholz [23]. No significant difference in PFS was observed for patients with or without bulky disease, suggesting that patients with large initial tumor bulks may benefit from fractionation of the therapy. Tumor regression after the initial 90Y-IT infusion may allow improved delivery to sites of bulk with the second fraction. [26] The median PFS of 40.2 months is in line with the one after non-anthracycline-based regimen (eg. R-CVP), but slightly inferior to R-CHOP and R-Bendamustine [24, 25]. However, fractionated RIT led to high response rates as initial treatment in a high-risk population with one third of patients achieving CR and durable remissions. Consequently, RIT might be an interesting strategy for a selected subpopulation, not eligible for chemotherapy.

Therefore, RIT has an important part in the front line setting, either as single agent or as consolidation following standard chemoimmunotherapy. RIT as single agent showed to be superior with respect to the immunotherapy, which is why it should be considered in patients who are not candidates for standard (immuno-)chemotherapy. 90Y-IT consolidation is superior to observation following standard immunochemotherapy, increasing the conversion of PR to CR, prolonging relapse free survival and improving OS.

Table 2: 90Y-ibritumomab tiuxetan treatment in diffuse large B cell lymphoma

Trial design	Disease	No of patients	Response rate	Response duration
After 6 cycles of CHOP [30]	Chemonaïve DLBCL	20	ORR 100% CR 95% PR 5%	2-year PFS 75% 2-year OS 95%
After 6 cycles of R-CHOP [31]	Chemonaïve, elderly DLBCL	63	ORR 88% CR/CRu 86% PR 2%	3.5-year PFS 75% 3.5-year OS 84%
After 4 cycles of R-CHOP [32]	Chemonaïve, elderly DLBCL	55	ORR 80% CR 73% PR 7%	2-year PFS 85% 2-year OS 86%
After either 4 or 6 cycles of R-CHOP [34]	Chemonaïve, early stage DLBCL	53	ORR 98% CR/CRu 79% PR 19%	5-year PFS 78% 5-year OS 94%
Monotherapy [37]	R/R DLBCL	104	ORR 44%	mPFS 1.6 - 5.9 months mOS 4.6 – 22.4 months
Monotherapy followed by 4 weekly doses of rituximab [39]	R/R DLBCL	25	ORR 31% CR 21% PR 13%	mEFS 2.5 months mOS 8.1 months 5-year OS 53% (all patients) 81% (long-term responders)
Z-BEAM [40]	R/R DLBCL	43	ORR 98% CR 98%	2-year PFS 59% 2-year OS 91%
Z-BEAM [41]	Transformed lymphoma	63	ORR 100%	2-year PFS 68% 2-year OS 90%
After 3 cycles of R-CHOP and in association with ASCT [42]	DLBCL patients in PR or CRu after first line treatment	37	ORR 100%	mPFS 5.1 years mDFS 4.3 years mOS 7.8 years

Abbreviations: DLBCL diffuse large B cell lymphoma; ORR overall response rate; CR complete response; PR partial response; mPFS median progression-free survival; mOS median overall survival; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R/R relapsed/refractory; mEFS median event free survival; BEAM carmustine, etoposide, cytarabine, and melphalan; ASCT autologous stem cell transplantation; mDFS median disease free survival.

Relapsed/refractory FL

Several studies have demonstrated that 90Y-IT is safe in patients who underwent more treatment lines with relapsed or refractory low-grade lymphoma (Table 1) [27-29]. Witzig et al. [27] administered 90Y-IT at a dose of 0.4 mCi/kg to 54 FL patients, refractory to rituximab, obtaining an ORR of 74% with 50% of CR, and median time to progression of nearly 7 months. Based on these results, Gordon et al. [28] randomized 143 rituximab-naïve patients with relapsed or refractory FL or transformed B-cell NHL to receive either 90Y-IT or rituximab alone. 90Y-IT proved to be more efficient in inducing a response than rituximab in this patient setting, leading to an ORR and a CR rate of 80 vs 56% ($p = 0.002$) and 30 vs 16% ($p = 0.04$), respectively. Although this study was not powered to detect differences in time dependent variables, there was a trend towards a longer median time to progression (TTP; 15 vs. 10.2 months; $p = 0.07$), duration of response (16.7 vs. 11.2 months; $p = 0.44$) and time to next therapy

(21.1 vs. 13.8 months; $P = 0.27$). Interestingly, in patients achieving a CR after 90Y-IT, the median TTP was longer, though it was not significant when compared to the control group (24.7 months v.s. 13.2 months; $p = 0.41$), suggesting a more profound disease eradication. As observed in other anticancer treatments, the administration of 90Y-IT in an earlier treatment line led to a better outcome [29]. Pooled data from four clinical trials including patients with relapsed FL demonstrated a significantly higher ORR (86% vs 72%; $p = 0.051$), CR rate (51% vs 28%; $p = 0.004$) and longer TTP (12.6 vs 7.9 months, $p = 0.038$) when 90Y-IT was administered in first relapses compared to a higher treatment line. Therefore, RIT represents a valid approach for relapsed or refractory FL patients as well, especially in elderly or unfit patients who can not undergo transplant or aggressive regimens.

DIFFUSE LARGE B-CELL LYMPHOMA

90Y-IT has been evaluated as consolidation after

first line therapy and in relapsed or refractory patients as part of transplantation setting (Table 2).

RIT as consolidation after induction therapy

RIT has been studied as consolidation after CHOP-based therapy in untreated elderly DLBCL patients [30-32]. Zinzani et al. [30] administered a 90Y-IT consolidation to 20 patients after 6 cycles of CHOP. Four out of 5 patients in PR after CHOP achieved a CR, leading to an overall CR rate of 95% and PR of 5%. The 2-year PFS was 75% with a 2-year OS of 95%. However, CHOP is not the standard first line therapy anymore [33] and the addition of 90Y-IT seems to have similar results with respect to R-CHOP. Since both drugs target CD20, the prior use of rituximab in induction treatment could hamper the efficacy of RIT after R-CHOP. Nevertheless, the patient group used was small and consequently it was not possible to draw a conclusion from this study.

In a phase II study 63 high-risk elderly, untreated DLBCL patients, who were ineligible for stem cell transplantation, underwent 6 cycles of R-CHOP and then those with responding or stable disease received 90Y-IT consolidation 6-9 weeks later. After completion of the induction treatment, 50 patients were eligible for 90Y-IT and 44 were ultimately treated. 90Y-IT was well tolerated and 86% of patients achieved a CR/CRu, 2% experienced a PR, while 12% did not respond. 90Y-IT improved response from PR to CR or CRu to CR in 16% of patients. At 42 months, the OS for 90Y-IT treated patients was 83.5% and the PFS was 74.5%. [31]

Based on these promising data, a phase II trial evaluated the possibility to administer a short-course R-CHOP chemotherapy followed by 90Y-IT in order to increase the global treatment efficacy along with a decreased exposure to cytotoxic drugs [32]. 55 high-risk elderly DLBCL patients received four courses of R-CHOP and 48 underwent RIT. 90Y-IT improved the remission status of 8/16 patients in PR after R-CHOP regimen leading to a ORR of 80% (CR 73%, PR 7%). The 2-year PFS was 85% with 2-year OS of 86%. These promising results provided the rationale for a randomized, phase III trial, which aims at evaluating the value of RIT after R-CHOP or R-CHOP-like therapy in a large cohort of elderly untreated, DLBCL patients (NCT01510184).

Recently, Witzig et al. [34] have evaluated the role of 90Y-IT in early stage DLBCL. Fifty-three patients underwent either four (21/53, 40%) or six (30/53, 57%) cycles of R-CHOP followed by RIT. After induction immunochemotherapy, the ORR was 98% (CR/CRu 79%, PR 19%). Forty-eight patients proceeded to RIT. Four of the five cases with CRu undergoing to RIT converted to CR. Of the 10 patients in PR, three achieved a CR, one a CRu while three did not change their status remission and one progressed during RIT. At 5-year follow-up, PFS was 78% and OS was 94%. Among 52 responders 84%

remained in remission after 5-years. 90Y-IT demonstrated to improve the ORR and reduce relapses in this setting. These results are comparable with the two Southwestern Oncology Group (SWOG) studies for early stage DLBCL. Treatment consists in the SWOG0014 [35] in 3 cycles of R-CHOP and involved field radiation therapy (IFRT) while in the SWOG0313 [36] in 3 cycles of CHOP followed by IFRT and then 90Y-IT. Unlike the SWOG studies, the ECOG3402 [34] demonstrated that adding RIT may enable reduction in chemotherapy for patients at least in PR at their interim restaging while maintaining cure rates. However, in the ECOG3402 trial, interim response was evaluated by computerized tomography (CT), while in clinical practice PET is preferred. For this reason, the SWOG S1001 phase II trial is currently evaluating a PET guided treatment approach in patients with limited-stage DLBCL. After 3 cycles of R-CHOP chemotherapy, all patients will be restaged by PET/CT. Patients with a CR will receive one additional cycle of R-CHOP, for a total of 4 cycles. Those with a PR will receive standard dose involved-field radiotherapy followed by a single infusion of 90Y-IT. (NCT01359592)

RIT might have a role as consolidation after induction therapy in elderly or unfit DLBCL patients, allowing for the reduction of the amount of chemotherapy and to maintain treatment efficacy. Results from the current clinical trial will help to clarify if the combination therapy is better than 6 full cycles of R-CHOP therapy and whether it would be advisable in selective setting of patients.

Relapsed/refractory DLBCL

RIT has demonstrated to be also an efficient and safe treatment option for relapsed or refractory DLBCL patients, achieving promising response rates and durable disease remissions. [27, 37-39] Morschhauser et al. [37] evaluated the efficacy of 90Y-IT in 104 DLBCL patients who were either refractory or relapsed after first line therapy associated or not with rituximab. The ORR was 44% and, as expected, it was higher in patients without a prior rituximab administration compared to those who underwent immunochemotherapy as primary treatment (53% versus 19%, respectively). The median PFS in three groups ranges from 1.6 to 5.9 months. Arnason et al. [39] confirmed the potential role of RIT in this poor risk subset. 90Y-IT was administered in 25 relapsed/refractory DLBCL patients, not candidates for transplant, followed by 4 weekly doses of rituximab. All non-progressing patients received 4 weekly doses of maintenance rituximab every 6 months for 4 cycles. The ORR was 31% (CR 21%, PR 13%). Median event free survival (mEFS) was 2.5 months. Median OS was 8.1 months. In addition, a study evaluating data from 4 clinical trials using 90Y-IT in recurring NHL demonstrated that RIT can produce durable responses and prolonged overall survival in a substantial number

Table 3: 90Y-ibritumomab tiuxetan treatment in mantle cell lymphoma

Trial design	Disease	No of patients	Response rate	Response duration
After 4 cycles of R-CHOP [48]	Chemo-naïve MCL	56	ORR 88% CR 67%	mTTF 34.3 months mPFS 31 months 2-years OS 90%
Z-BEAM [55]	R/R NHL	44	ORR 73%	3-year PFS 43% 3-year OS 60%
Z-BEAM [53]	R/R NHL	41	ORR 66%	2-year PFS 68% 2-year OS 85%
Z-BEAM or BEAC [56]	Chemo-naïve MCL	162	ORR 96% CR/CRu 91% PR 4%	4-year PFS 71%
Z-BEAM [57]	R/R MCL	46	ORR 100% CR 36% PR 64%	4-year PFS 41% 5-year OS 71%
After ASCT (unpublished data)	Chemo-naïve MCL	57	ORR 100% CR 100%	5-year PFS 79% 5-year OS 96%
Monotherapy [58]	R/R MCL	34	ORR 67% CR 15%	OS 21 months mEFS 6 months
Monotherapy [62]	R/R MCL	6	ORR 50% PR 33% SD 16%	mPFS 3.9 months
Combined with bortezomib [66]	R/R MCL	12	ORR 50% CR 42%	mPFS 6.4 months (all patients) 23 months (patients in CR) 4.4 months (patients in PR/SD)

Abbreviations: R/R relapsed/refractory; MCL mantle cell lymphoma; NHL non Hodgkin lymphoma; ORR overall response rate; CR complete response; PR partial response; mPFS median progression-free survival; OS overall survival; mTTF median time to treatment failure; mEFS median event-free survival; mDFS median disease free survival; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; BEAM carmustine, etoposide, cytarabine, and melphalan; ASCT autologous stem cell transplantation.

of patients in whom previous therapies have failed. The 5-year OS was 53% for all patients and 81% for long-term responders. Therefore, RIT might be considered as a valid therapeutic option for relapsed/refractory patients that refuse or can not tolerate chemotherapy. Indeed, RIT has response rate and survival similar to other chemotherapy regimens currently available. Furthermore, RIT is generally feasible and requires less time to complete the treatment.

90Y-IT in association with high-dose chemotherapy followed by ASCT proved to be efficient and safe in heavily pretreated patients as well. [40-42] A phase II trial randomized 43 relapsed/refractory DLBCL patients to receive high-dose chemotherapy consisting in carmustine, etoposide, cytarabine, and melphalan (BEAM) alone ($n = 21$) or combined to 90Y-IT (Z-BEAM, $n = 22$). Although the PFS difference between the two treatment arms was not statistically significant (59% and

37% after Z-BEAM and BEAM alone, respectively; $p = 0.2$), two-year OS was 91% and 62% after Z-BEAM and BEAM, respectively ($p = 0.05$). [40] Mei et al. reported encouraging results using the Z-BEAM conditioning regimen in 63 patients with transformed low grade lymphoma, which usually has a very poor prognosis [41]. Two-year PFS was 68%, and OS was 90%. A recent meta-analysis has shown that Z-BEAM improves PFS and OS at 2-years ($p < 0.05$ and $p < 0.01$) with respect to BEAM. In addition, 90Y-IT could overcome a poor pretransplant response rate without further toxicities. [43] Based on these promising results, a randomized phase II trial which compares R-BEAM with or without 90Y-IT in DLBCL patients eligible for transplantation is currently ongoing. (NCT00591630). This confirmatory trial will determine the real advantage of adding 90Y-IT to high-dose chemotherapy and may drive a change in the standard conditioning regimen to use in clinical practise.

The role of 90Y-IT as consolidation after early salvage transplant treatment was retrospectively evaluated. Thirty-seven patients with intermediate-high risk DLBCL not in CR assessed by PET after three cycles of R-CHOP switched to high dose chemotherapy followed by ASCT. Twenty patients underwent additional consolidation with ⁹⁰Y-IT. At the end of the treatment CR rate converted from 45% to 100%. PFS (5.1 years *versus* 2.7 years, $p = 0.007$) and DFS (4.3 years *versus* 2.0 years, $p = 0.001$) were significantly longer in the ⁹⁰Y-IT group. However, no difference in overall survival was observed, [42] but these are retrospective data. Currently there are no ongoing studies to confirm this finding and, therefore, this approach remains experimental.

MANTLE CELL LYMPHOMA

⁹⁰Y-IT has been investigated as consolidation after first line therapy, as part of transplantation setting and in relapsed or refractory patients (Table 3).

Front-line setting

RIT as consolidation after induction therapy

R-CHOP as initial therapy for untreated MCL yields a high response rate, but remissions are not durable [44, 45] Because MCL is predominantly a disease of patients older than 60 years, a valid approach to improve R-CHOP outcomes is to add a consolidation strategy. Because of the activity of RIT in MCL [46, 47], its favorable toxicity profile, and the need for a consolidation treatment applicable to all patients, including older and less-fit patients, the ECOG E1499 trial [48] investigated the efficacy of 4 cycles of R-CHOP chemotherapy followed by ⁹⁰Y-IT consolidation in 56 newly diagnosed stage II-IV MCL. The ORR was 88% at completion of all therapy, with a CR rate of only 13% after R-CHOP but 67% after ⁹⁰Y-IT. Time to treatment failure (TTF) was 34.2 months. This median TTF is better than that previously reported for six cycles of R-CHOP. [25, 44]. The 2-years OS rate was 90%, with an mPFS of 31 months. Alternative strategies to improve R-CHOP results include maintenance. Rituximab maintenance after R-CHOP regimen has demonstrated to prolong response duration, achieving a PFS from 37 to 56 months [49, 50]. An interesting question would be the comparison of RIT consolidation followed by rituximab maintenance, with rituximab maintenance alone.

Currently, in untreated MCL patients who cannot tolerate more-intensive regimens or clinical trials, R-CHOP for four cycles followed by ⁹⁰Y-IT could be a reasonable approach as initial therapy.

RIT-based stem cell transplant regimens for MCL

Another approach to improve outcomes after R-CHOP is to add consolidation therapy with high-dose

chemotherapy followed by ASCT. [51] Incorporating RIT into a transplant regimen might further enhance eradication of residual disease after induction therapy and ultimately prolong PFS and OS. [52-57]

A phase I dose-finding trial [55] of escalated dose RIT followed by high dose chemotherapy with BEAM and autologous stem cell reinfusion established the maximum-tolerated radiation-absorbed dose (RAD) to critical organs as 15Gy. In this cohort, seven out of 44 patients (16%) were affected by MCL. Among the 29 patients, (66%) with active disease at study entry, 11 achieved CR, and 6 achieved PR after protocol treatment. The estimated 3-year PFS and OS rates were 43% and 60%, respectively. There was no difference in PFS and OS between the different histologic subsets.

Based on these encouraging data, a phase II trial [53] associating ⁹⁰Y-IT with BEAM before ASCT was conducted in patients with refractory, relapsed or poor-risk NHL. The 2-year PFS and OS in the 13 patients included with MCL were 68% and 85%, respectively. In order to improve outcome for patients not in CR before ASCT the Nordic Lymphoma Group added ⁹⁰Y-IT to the high-dose induction chemotherapy. In the multicenter phase 2 trial MCL-3 study [56] patients in PR or CRu after first line treatment were randomized to receive ⁹⁰Y-IT in combination with BEAM or BEAC (C = cyclophosphamide) before ASCT. Although Z-BEAM followed by ASCT was feasible and without additional toxicity, it was not associated with improved PFS, probably because intensification with ⁹⁰Y-IT may be too late to improve the outcome in patients not in CR before transplant. Similarly, a recent retrospective study [57] has demonstrated that Z-BEAM followed by ASCT in relapsed or refractory MCL patients is not associated with significant survival improvement compared to the standard rituximab and BEAM (R-BEAM). The 5-year OS was 55% and 71% ($p = 0.2$) in the R-BEAM *vs* Z-BEAM groups, and the 4-year PFS was 32% and 41% ($p = 0.3$), respectively. Furthermore, we retrospectively assessed the role of ⁹⁰Y-IT as consolidation after ASCT in first line (data not yet published). Treatment intensification was well tolerated and led to a significantly longer response duration in comparison to the standard treatment (PFS was not reached *versus* 7 years, $p = 0.001$; OS was not reached *versus* 8.1 years, $p = 0.008$). The 5-year PFS was 79% in the ⁹⁰Y-IT group compared to 55% in the other one. The 5-year OS was superior in the ⁹⁰Y-IT group with respect to the other one as well (96% *versus* 81%). In contrast to the historical cohort, the addition of ⁹⁰Y-IT seemed to overcome important risk factors such as MIPI and bone marrow infiltration. Consolidation with ⁹⁰Y-IT after induction and ASCT seems not only able to significantly reduce the number of disease recurrences but also to delay relapse in newly diagnosed MCL patients with intermediate/high MIPI score.

The role of RIT as consolidation of high-dose

chemotherapy is unclear. Because of the contrasting results there is no reason to change the clinical practice. Currently, several trials evaluating RIT followed by autologous or allogenic stem cell transplant are ongoing (NCT00505232, NCT00695409, NCT00607854, NCT01434472) and will help to clarify this issue.

Relapsed/refractory MCL

Despite the intensification of first line treatment, relapses remain frequent [44, 45]. Wang et al. [58] reported a phase II trial using 90Y-IT as single agent in 34 refractory or relapsed MCL patients. All patients were heavily pretreated with a median of three prior chemotherapy regimens (range 1-6). ORR was 67% with 15% of CR rate. At median follow-up of 22 months, median OS was 21 months and mEFS was 6 months. This single-agent activity compared favorably with that of other single agents. [59-61] In particular, the remission rates and progression free survival duration obtained in patients who had previously received rituximab are similar to previous experiences with bortezomib and temsirolimus [59, 61]. In addition, 90Y-IT was more convenient due to the short time required to finish the treatment (1-2 weeks) rather than protracted duration. Moreover, 90Y-IT had fewer adverse effects than these agents. A similar study using 90Y-IT in relapsed/refractory MCL patients obtained comparable single-agent activity. [62] ORR was 50% with 33% of PR rate and 16% of SD. PFS was 3.9 months. However, these results are not really satisfactory. Based on preclinical data demonstrating synergy between proteasome inhibitor and radiation [63-65], a more recent phase I study evaluated the safety of 90 Y-IT combined with bortezomib in patients with relapsed or refractory MCL. The ORR was 50% with 42% of CR rate. [66] Given these promising results, a phase II trial is currently evaluating the efficacy of this novel combination in relapsed or refractory MCL. (NCT01497275)

CONCLUSIONS

90Y-IT is an effective and safe drug, which combines the benefits of a monoclonal antibody with the efficacy of radiation in the treatment of B-cell NHL, a remarkably radiosensitive hematologic malignancy. 90Y-IT activity has been well established in the indolent setting as supported by the FDA approval for treatment of chemo-naïve and relapsed/refractory FL patients. Nevertheless, no advantage in OS was reported with respect to the standard. The efficacy of RIT has been observed in aggressive NHL as well. However, future randomized, clinical trials are warranted to clarify the role of RIT in this setting and support its approval as alternative therapeutic approach.

ACKNOWLEDGMENTS

The authors thank Claire Oh for drawing Figure 1.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose that could be perceived as prejudicing the impartiality of the research reported.

GRANT SUPPORT

This article did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

REFERENCES

1. Kwak LW, Campbell MJ, Czerwinski DK, Hart S, Miller RA, Levy R. Induction of immune responses in patients with B-cell lymphoma against the surface-immunoglobulin idiotype expressed by their tumors. *N Engl J Med.* 1992; 327:1209-1215.
2. Nadler LM, Takvorian T, Botnick L, Bast RC, Finberg R, Hellman S, Canellos GP, Schlossman SF. Anti-B1 monoclonal antibody and complement treatment in autologous bone-marrow transplantation for relapsed B-cell non-Hodgkin's lymphoma. *Lancet.* 1984; 2:427-431.
3. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, Heyman MR, Bence-Bruckler I, White CA, Cabanillas F, Jain V, Ho AD, Lister J, et al.. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol.* 1998; 16:2825-2833.
4. Ganss R, Ryschich E, Klar E, Arnold B, and Hammerling GJ. Combination of T-cell therapy and trigger of inflammation induces remodeling of the vasculature and tumor eradication, *Cancer Res.* 2002; 62:1462-1470.
5. Tartour E, Pere H, Maillere B, Terme M, Merillon N, Taieb J, Sandoval F, Quintin-Colonna F, Lacerda K, Karadimou A, Badoual C, Tedgui A, Fridman WH, et al. Angiogenesis and immunity: a bidirectional link potentially relevant for the monitoring of antiangiogenic therapy and the development of novel therapeutic combination with immunotherapy. *Cancer Metastasis Rev.* 2011;30:83-95.
6. Grossbard ML, Press OW, Appelbaum FR, Bernstein ID, Nadler LM. Monoclonal antibody-based therapies of leukemia and lymphoma. *Blood.* 1992; 80:863-878.
7. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Pohlman BL, Bartlett NL, Wiseman GA, Padre N, Grillo-López AJ, Multani P, White CA. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus

- rituximab immunotherapy for patients with relapsed or refractory lowgrade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2002; 20:2453-2463.
8. Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, Lister TA, Stagg RJ, Tidmarsh GF, Kroll S, Wahl RL, Knox SJ, Vose JM. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol.* 2001; 19:3918-3928.
 9. Kylstra JW, Witzig TE, Huang M, Emmanouilides E, Hagenbeek A, Tidmarsh GF. Discriminatory power of the 111-indium scan (111-In) in the prediction of altered biodistribution of radio-immunoconjugate in the 90-yttrium ibritumomab tiuxetan therapeutic regimen: meta-analysis of five clinical trials and 9 years of post-approval safety data. *J Clin Oncol.* 2011;29 (15 suppl):8048. Abstract.
 10. Wagner HN Jr, Wiseman GA, Marcus CS, Nabi HA, Nagle CE, Fink-Bennett DM, Lamonica DM, Conti PS. Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with (90)Y labeled anti-CD20 monoclonal antibody. *J Nucl Med.* 2002;43:267-272.
 11. Chinn PC, Leonard JE, Rosenberg J, Hanna N, Anderson DR. Preclinical evaluation of 90Y-labeled anti-CD20 monoclonal antibody for treatment of non-Hodgkin's lymphoma. *Int J Oncol.* 1999; 15:1017-1025.
 12. Kaminski MS, Fig LM, Zasadny KR, Koral KF, DelRosario RB, Francis IR, Hanson CA, Normolle DP, Mudgett E, Liu CP, Moon S, Scoot P, Miller RA, et al. Imaging, dosimetry, and radioimmunotherapy with iodine 131-labeled anti-CD37 antibody in B-cell lymphoma. *J Clin Oncol.* 1992; 10:1696-1711.
 13. Fuks Z, Glatstein E and Kaplan HS. Patterns of presentation and relapse in the non-Hodgkin's lymphomata. *Br J Cancer.* 1975; Suppl 2:286-297.
 14. Ferrero S, Drandi D, Mantoan B, Ghione P, Omedè P, Ladetto M. Minimal residual disease detection in lymphoma and multiple myeloma: impact on therapeutic paradigms. *Hematol Oncol.* 2011; 29:167-176.
 15. Morschhauser F, Radford J, Van Hoof A, Vitolo U, Soubeyran P, Tilly H, Huijgens PC, Kolstad A, d'Amore F, Gonzalez Diaz M, Petrini M, Sebban C, Zinzani PL, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol.* 2008; 26:5156-5164.
 16. Hainsworth JD, Spigel DR, Markus TM, Shipley D, Thompson D, Rotman R, Dannaher C, Greco FA. Rituximab plus short-duration chemotherapy followed by Yttrium-90 Ibritumomab tiuxetan as first-line treatment for patients with follicular non-Hodgkin lymphoma: a phase II trial of the Sarah Cannon Oncology Research Consortium. *Clin Lymphoma Myeloma.* 2009; 9:223-228.
 17. Jacobs SA, Swerdlow SH, Kant J, Foon KA, Jankowitz R, Land SR, DeMonaco N, Joyce J, Osborn JL, Evans TL, Schaefer PM, Luong TM. Phase II trial of short-course CHOP-R followed by 90Y-ibritumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. *Clin Cancer Res.* 2008; 14:7088-7094.
 18. Fowler NH, Neelapu SS, Fanale MA, Rodriguez MA, Pro B, Hagemester FB, Younes A, Shah JJ, Kwak LW, Diana Rodriguez DR and McLaughlin P. Phase II Study with R-FND Followed by 90-Y Ibritumomab Tiuxetan Radioimmunotherapy and Rituximab Maintenance for Untreated High-Risk Follicular Lymphoma. *Blood (ASH Annual Meeting Abstracts).* 2011; 118:99.
 19. Karmali R, Kassar M, Jimenez A, Venugopal P, Shammo JM, Fung HC, Bayer R, O'Brien T and Gregory S. Update on a prospective study evaluating the safety and efficacy of combination therapy with fludarabine, mitoxantrone and C rituximab followed by yttrium-90 ibritumomab tiuxetan and maintenance rituximab as front line therapy for patients with indolent lymphomas. *Blood (ASH Annual Meeting Abstracts).* 2010; 116:3946.
 20. Zinzani PL, Tani M, Pulsoni A, De Renzo A, Stefoni V, Broccoli A, Montini GC, Fina M, Pellegrini C, Gandolfi L, Cavalieri E, Torelli F, Scopinaro F, et al. A phase II trial of short course fludarabine, mitoxantrone, rituximab followed by 90Y-ibritumomab tiuxetan in untreated intermediate/high-risk follicular lymphoma. *Ann Oncol.* 2012; 23:415-420.
 21. Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, Caballero D, Haioun C, Pedersen LM, 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.* 2011; 377:42-51.
 22. Chen Q, Ayer T, Nastoupil LJ, Rose AC, Flowers CR. Comparing the cost-effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma. *Value Health.* 2015; 18:189-197.
 23. Scholz CW, Pinto A, Linkesch W, Lindén O, Viardot A, Keller U, Hess G, Lastoria S, Lerch K, Frigeri F, Arcamone M, Stroux A, Frericks B, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. *J Clin Oncol.* 2013; 31:308-313.
 24. Federico M, Luminari S, Dondi A, Tucci A, Vitolo U, Rigacci L, Di Raimondo F, Carella AM, Pulsoni A, Merli F, Arcaini L, Angrilli F, Stelitano C, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. *J Clin Oncol.* 2013; 31:1506-1513.
 25. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C, Kofahl-Krause D, Heil G, Welslau M, Balser C, Kaiser U, Weidmann E, Dürk H, 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; 381:1203-1210.
26. Illidge TM, Mayes S, Pettengell R, Bates AT, Bayne M, Radford JA, Ryder WD, Le Gouill S, Jardin F, Tipping J, Zivanovic M, Kraeber-Bodere F, Bardies M, et al. Fractionated 90Y-ibritumomab tiuxetan radioimmunotherapy as an initial therapy of follicular lymphoma: an international phase II study in patients requiring treatment according to GELF/BNLI criteria. *J Clin Oncol*. 2014; 32:212-218.
 27. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, Pohlman BL, Bartlett NL, Wiseman GA, Padre N, Grillo-López AJ, Multani P, White CA. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory lowgrade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 ; 20:2453-2463.
 28. Gordon LI, Witzig T, Molina A, Czuczman M, Emmanouilides C, Joyce R, Vo K, Theuer C, Pohlman B, Bartlett N, Wiseman G, Darif M, White C. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. *Clin Lymphoma*. 2004; 5:98-101.
 29. Emmanouilides C, Witzig TE, Gordon LI, Vo K, Wiseman GA, Flinn IW, Darif M, Schilder RJ, Molina A. Treatment with yttrium 90 ibritumomab tiuxetan at early relapse is safe and effective in patients with previously treated B-cell non-Hodgkin's lymphoma. *Leuk Lymphoma*. 2006; 47:629-636.
 30. Zinzani PL, Tani M, Fanti S, Stefoni V, Musuraca G, Castellucci P, Marchi E, Farsad M, Fina M, Pellegrini C, Alinari L, Derenzini E, de Vivo A, et al. A phase II trial of CHOP chemotherapy followed by yttrium 90 ibritumomab tiuxetan (Zevalin) for previously untreated elderly diffuse large B-cell lymphoma patients. *Ann Oncol*. 2008; 19:769-773.
 31. Hamlin PA, Rodriguez MA, Noy A, Portlock CS, Straus D, McLaughlin P, Pro B, Fayad L, Hagemester FB, Wegner B, Dumitrescu O, Tasker NP, Moskowitz CH, et al. Final results of a phase II study of sequential R-CHOP and Yttrium-90 Ibritumomab Tiuxetan (RIT) for elderly high risk patients with untreated diffuse large B-cell lymphoma (DLBCL). *Blood (ASH Annual Meeting Abstracts)*. 2010; 116:1793.
 32. Zinzani PL, Rossi G, Franceschetti S, Botto B, Di Rocco A, Cabras MG, Petti MC, Stefoni V, Broccoli A, Fanti S, Pellegrini C, Montini GC, Gandolfi L, et al. Phase II trial of short-course R-CHOP followed by 90Y-ibritumomab tiuxetan in previously untreated high-risk elderly diffuse large B-cell lymphoma patients. *Clin Cancer Res*. 2010; 16:3998-4004.
 33. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002; 346:235-242.
 34. Witzig TE, Hong F, Micallef IN, Gascoyne RD, Dogan A, Wagner H Jr, Kahl BS, Advani RH, Horning SJ. A phase II trial of RCHOP followed by radioimmunotherapy for early stage (stages I/II) diffuse large B-cell non-Hodgkin lymphoma: ECOG3402. *Br J Haematol*. 2015; 170:679-686.
 35. Persky DO, Unger JM, Spier CM, Stea B, LeBlanc M, McCarty MJ, Rimsza LM, Fisher RI, Miller TP; Southwest Oncology Group. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol*. 2008; 26:2258-2263.
 36. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, LeBlanc M, Carlin S, Chase E, Fisher RI. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1998; 339:21-26.
 37. Morschhauser F, Illidge T, Huglo D, Martinelli G, Paganelli G, Zinzani PL, Rule S, Liberati AM, Milpied N, Hess G, Stein H, Kalmus J, Marcus R. Efficacy and safety of yttrium-90 ibritumomab tiuxetan in patients with relapsed or refractory diffuse large B-cell lymphoma not appropriate for autologous stem-cell transplantation. *Blood*. 2007; 110:54-58.
 38. Witzig TE, Molina A, Gordon LI, Emmanouilides C, Schilder RJ, Flinn IW, Darif M, Macklis R, Vo K, Wiseman GA. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer*. 2007; 109:1804-1810.
 39. Arnason JE, Luptakova K, Rosenblatt J, Zwicker J, Levine JD, Boussiotis V, Kim M, Avigan D, Joyce R. Long-term survival with 90yttrium ibritumomab tiuxetan and rituximab as treatment for relapsed or refractory diffuse large B-cell lymphoma. *J Clin Oncol (ASCO Meeting Abstracts)*. 2013 (suppl 15): 8558.
 40. Shimoni A, Avivi I, Rowe JM, Yeshurun M, Levi I, Or R, Patachenko P, Avigdor A, Zwas T, Nagler A. A randomized study comparing yttrium-90 ibritumomabtiuxetan (Zevalin) and high-dose BEAM chemotherapy versus BEAM alone as the conditioning regimen before autologous stem cell transplantation in patients with aggressive lymphoma. *Cancer*. 2012; 118:4706-4714.
 41. Mei M, Wondergem MJ, Palmer JM, Shimoni A, Hasenkamp J, Tsai NC, Simpson J, Nademane A, Raubitschek A, Forman SJ, Krishnan AY. Autologous transplantation for transformed non-Hodgkin lymphoma using an yttrium-90 ibritumomab tiuxetan conditioning regimen. *Biol Blood Marrow Transplant*. 2014; 20:2072-2075.
 42. Mondello P, Pitini V, Arrigo C, Derenzini E, Mian M.

- 90Y-Ibritumomab Tiuxetan consolidation after autologous stem cell transplantation improves survival of patients with intermediate-/high-risk diffuse large B-cell lymphoma not responding adequately to first-line treatment. *Anticancer Res.* 2014; 34:5121-5125.
43. Auger-Quittet S, Duny Y, Daures JP, Quittet P. Outcomes after (90) Yttrium-ibritumomab tiuxetan-BEAM in diffuse large B-cell lymphoma: a meta-analysis. *Cancer Med.* 2014; 3: 927-938.
 44. Howard OM, Gribben JG, Neuberg DS, Grossbard M, Poor C, Janicek MJ, Shipp MA. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: Molecular complete responses are not predictive of progressionfree survival. *J Clin Oncol.* 2002; 20:1288-1294.
 45. Lenz G, Dreyling M, Hoster E, Wörmann B, Dührsen U, Metzner B, Eimermacher H, Neubauer A, Wandt H, Steinhauer H, Martin S, Heidemann E, Aldaoud A, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). *J Clin Oncol.* 2005; 23:1984-1992.
 46. Wang M, Oki Y, Pro B, Romaguera JE, Rodriguez MA, Samaniego F, McLaughlin P, Hagemester F, Neelapu S, Copeland A, Samuels BI, Loyer EM, Ji Y, Younes A. Phase II study of yttrium-90-ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2009; 27:5213-5218.
 47. Zelenetz AD, Noy A, Pandit-Taskar N, Scordo m, Rijo i, Zhou Y, O'Donoghue JA and Divgi C. Sequential radioimmunotherapy with tositumomab/iodine I131 tositumomab followed by CHOP for mantle cell lymphoma demonstrates RIT can induce molecular remissions. *J Clin Oncol (ASCO Meeting Abstracts).* 2006; 24 (18 suppl):7560.
 48. Smith M, Chen L, Gordon LI, Gascoyne RD, Paietta E, Forero-Torres A, Kahl BS, Advani R, Hong F, Horning SJ. Phase II study of R-CHOP and 90Y-ibritumomab tiuxetan in patients with previously untreated mantle cell lymphoma (E1499). *J Clin Oncol.* 2012; 30: 3119-3126.
 49. Kluin-Nelemans JC, Hoster E, Walewski J, Stilgenbauer S, Geisler CH, Gisselbrecht C, Vehling-Kaiser U, Doorduijn JK, Trneny M, Coiffier B, Forstpointner R, Tilly H, Kanz L, et al. R-CHOP versus R-FC followed by maintenance with rituximab versus interferon-alfa: Outcome of the first randomized trial for elderly patients with mantle cell lymphoma. *Blood (ASH Annual Meeting Abstracts).* 2011; 118:439.
 50. Kahl B, Longo WL, Eickhoff, JC, Zehnder J, Jones C, Blank J, McFarland T, Bottner W, Rezazadeh H, Wernldi J, Bailey HH; Wisconsin Oncology Network. Maintenance rituximab following induction chemoimmunotherapy may prolong progression-free survival in mantle cell lymphoma: A pilot study from the Wisconsin Oncology Network. *Ann Oncol.* 2006; 17:1418-1423.
 51. Dreyling M, Lenz G, Hoster E, Van Hoof A, Gisselbrecht C, Schmits R, Metzner B, Truemper L, Reiser M, Steinhauer H, Boiron JM, Boogaerts MA, Aldaoud A, et al.: Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progressionfree survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European MCL Network. *Blood.* 2005; 105:2677-2684.
 52. Kang BW, Kim WS, Kim C, Jang G, Lee SS, Choi YH, Lee DH, Kim SW, Kim S, Ryu JS, Huh J, Lee JS, Suh C. Yttrium-90-ibritumomab tiuxetan in combination with intravenous busulfan, cyclophosphamide, and etoposide followed by autologous stem cell transplantation in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. *Invest New Drugs.* 2010; 28:516-522.
 53. Krishnan A, Nademanee A, Fung HC, Raubitschek AA, Molina A, Yamauchi D, Rodriguez R, Spielberger RT, Falk P, Palmer JM, Forman SJ. Phase II trial of a transplantation regimen of yttrium-90 ibritumomab tiuxetan and high-dose chemotherapy in patients with non-Hodgkin's lymphoma. *J Clin Oncol.* 2008; 26:90-95.
 54. Nademanee A, Forman S, Molina A, Fung H, Smith D, Daxis A, Kwok C, Yamauchi D, Anderson AL, Falk P, Krishnan A, Kirschbaum M, Kogut N, et al. A phase 1/2 trial of high-dose yttrium-90-ibritumomab tiuxetan in combination with high-dose etoposide and cyclophosphamide followed by autologous stem cell transplantation in patients with poor-risk or relapsed non-Hodgkin lymphoma. *Blood.* 2005; 106:2896-2902.
 55. Winter JN, Inwards DJ, Spies S, Wiseman G, Patton D, Erwin W, Rademaker AW, Weitner BB, Williams SF, Tallman MS, Micallef I, Mehta J, Singhal S, et al. Yttrium-90 ibritumomab tiuxetan doses calculated to deliver up to 15 Gy to critical organs may be safely combined with high-dose BEAM and autologous transplantation in relapsed or refractory B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 2009 ; 27:1653-1659.
 56. Kolstad A, Laurell A, Jerkeman M, Grønabæk K, Elonen E, Rätty R, Pedersen LB, Loft A, Bogsrud TV, Kimby E, Hansen PB, Fagerli UM, Nilsson-Ehle H, et al. Nordic MCL3 study: 90Y-ibritumomab-tiuxetan added to BEAM/C in non-CR patients before transplant in mantle cell lymphoma. *Blood.* 2014; 123:2953-2959.
 57. Berger MD, Branger G, Klaeser B, Taleghani BM, Novak U, Banz Y, Mueller BU, Pabst T. Zevalin and BEAM (Z-BEAM) versus rituximab and BEAM (R-BEAM) conditioning chemotherapy prior to autologous stem cell transplantation in patients with mantle cell lymphoma. *Hematol Oncol.* 2015 [Epub ahead of print]. PMID: 25689832.
 58. Wang M, Oki Y, Pro B, Romaguera JE, Rodriguez MA,

- Samaniego F, McLaughlin P, Hagemeister F, Neelapu S, Copeland A, Samuels BI, Loyer EM, Ji Y, et al. Phase II study of yttrium-90-ibritumomab tiuxetan in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2009; 27:5213-5218.
59. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, Johnson P, Lister A, Feuring-Buske M, Radford JA, Capdeville R, Diehl V, Reyes F. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: A multicenter phase II study. *Blood.* 1998; 92:1927-1932.
 60. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, Leonard JP, Lonial S, Stadtmauer EA, O'Connor OA, Shi H, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2006; 24 : 4867-4874.
 61. Witzig TE, Geyer SM, Ghobrial I, Inwards DJ, Fonseca R, Kurtin P, Ansell SM, Luyun R, Flynn PJ, Morton RF, Dakhil SR, Gross H, Kaufmann SH. Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma. *J Clin Oncol.* 2005; 23:5347-5356.
 62. Weigert O, von Schilling C, Rummel MJ, Pezzuto A, Unterhalt M, Hiddemann W, Dreyling M. Efficacy and safety of a single-course of yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin(R)) in patients with relapsed or refractory mantle cell lymphoma (MCL) after/not appropriate for autologous stem cell transplantation (ASCT) - A phase II trial of the European MCL Network. *Blood (ASH Annual Meeting Abstracts).* 2005; 106:4786.
 63. Kurland JF, Meyn RE. Protease inhibitors restore radiation-induced apoptosis to Bcl-2-expressing lymphoma cells. *Int J Cancer.* 2001; 96:327-333.
 64. Delic J, Masdehors P, Omura S, Cosset JM, Dumont J, Binet JL, Magdelénat H. The proteasome inhibitor lactacystin induces apoptosis and sensitizes chemo- and radioresistant human chronic lymphocytic leukaemia lymphocytes to TNF- α -initiated apoptosis. *Br J Cancer.* 1998; 77:1103-1107.
 65. Pervan MI, Calimlim J, Matso D, Said JW, McBride WH, and de Vos S. Active combination therapy of bortezomib and ibritumomab tiuxetan in an in vivo diffuse large B-cell lymphoma model. *Blood (ASH Annual Meeting Abstracts).* 2005;106:2406.
 66. Beaven AW, Shea TC, Moore DT, Feldman T, Ivanova A, Ferraro M, Ford P, Smith J, Goy A. A phase I study evaluating ibritumomab tiuxetan (Zevalin®) in combination with bortezomib (Velcade®) in relapsed/refractory mantle cell and low grade B-cell non-Hodgkin lymphoma. *Leuk Lymphoma.* 2012; 53:254-258.