

Radioimmunotherapy-based treatment of cancer

Shokrollah Farrokhi^{1,2,5}, Mohammad Reza Ravanbod²,
Shahram Amiri^{1,2}, Iraj Nabipour⁴, Majid Assadi⁵

¹Department of Immunology and Allergy, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

²Department of Immunology and Allergy, The Persian Gulf Tropical and Infectious Diseases Research Centre, Bushehr University of Medical Sciences, Bushehr, Iran

³Department of Oncology, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

⁴Department of Endocrine and Metabolic Diseases, The Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran.

⁵The Persian Gulf Nuclear Medicine Research Centre, Bushehr University of Medical Sciences, Bushehr, Iran

(Received 16 May 2012, Revised 27 June 2012, Accepted 22 July 2012)

ABSTRACT

The principle of cancer immunotherapy includes various methods of manipulations to influence immune responses against tumors in both humans and animals. This advanced technology of hybridoma production provided the necessary skills to efficiently produce highly specific monoclonal antibodies (mAb). Radioactively-tagged antibodies which are applied in radioimmunotherapy (RIT), can target adjacent cells and may not require immune function. This study highlights the mechanism and the effect of action of radioimmunotherapeutic agents, especially two applied agents including ⁹⁰Y-ibritumomab tiuxetan and ¹³¹I-tositumomab that are approved by Food and Drug Administration (FDA) for treatment of some cancers.

Key words: Radioimmunotherapy (RIT), Monoclonal antibodies (mAb), Cancer, ⁹⁰Y-Ibritumomab tiuxetan, ¹³¹I-Tositumomab.

Iran J Nucl Med 2012;20(1):45-53

Corresponding author: Dr Shokrollah Farrokhi, Department of Immunology and Allergy, Medical College, Bushehr University of Medical Sciences, Moallem St, Bushehr 3631, Iran. E-mail: farrokhi_sh@yahoo.com

INTRODUCTION

Cancer is one of the most important causes of death in the world today. For decades, primary cancer therapy including chemotherapy and radiotherapy eliminate the bulk of tumor mass or metastatic cells. In history, the first successful cancer immunotherapy was carried out by William Coley in the 1890 using toxins derived from *Streptococcus erysipelatis* and *Bacillus prodigiosus*. The opening principle of cancer immunotherapy has been profoundly influenced by Paul Ehrlich's 'magic bullet', and confirmed by the development of antibiotics [1].

The principle of cancer immunotherapy including various methods of manipulations to hassle immune responses against tumors in both humans and animals [2, 3]. Therefore, the advent of the advanced technology of hybridoma production provided the necessary skills to efficiently produce highly specific

monoclonal antibodies (mAb) [4-6]. A variety of immunoglobulin-derived molecules were utilized in RAIT (Fig. 1) [7].

Monoclonal antibodies (mAb) may mediate its anti-tumor effects by using one of effector mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, and inducing or blocking intracellular signals, but the exact mechanisms of action of many of these clinically active antibodies remain unknown [8]. Antibodies targeting cell surface receptors that alter intracellular signaling pathways like as Rituximab bind to CD20, particularly when cross-linked, initiates a cascade of intracellular signals, many quite similar to signaling through the B cell receptor. The result of stimulation of these complex signaling pathways is cell cycle arrest or apoptosis [9].

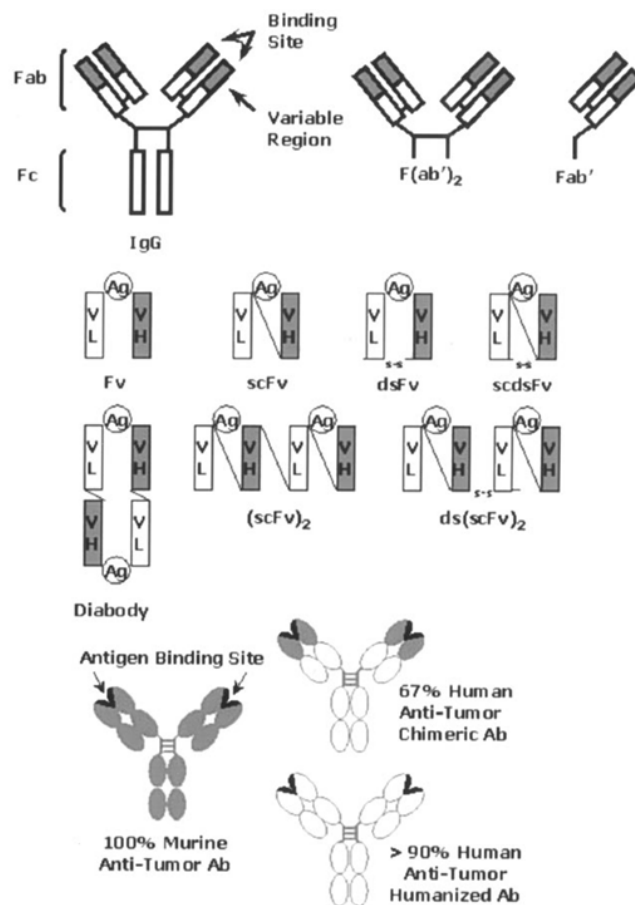


Fig 1. Schematic illustration of various antibody-derived targeting molecules being investigated in radioimmunotherapy (RIT). (Reprinted by permission of the Society of Nuclear Medicine from [7]).

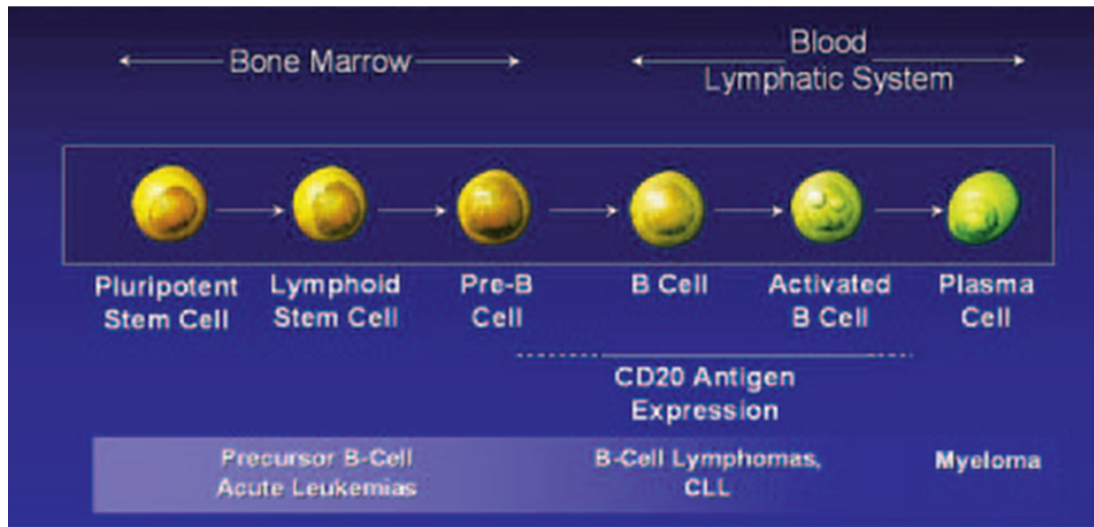


Fig 2. CD 20 antigen expression. (Reprinted by permission of the Society of Nuclear Medicine from [18]).

Unlabeled antibodies may not reach to all cancer cells to kill them. Therefore, using antibody–drug conjugates may overcome low antigen density and lack of necessary local immune cells. Accordingly, radioactively-tagged antibodies or radioimmunotherapy (RIT) can target adjacent cells and may not require immune functions [8]. This study reviews the mechanism and the effect of action of radioimmunotherapeutic agents, ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab approved by Food and Drug Administration (FDA) effective in treatment of in some cancers.

DISCUSSION

General features of radioimmunotherapy

Advances in cancer diagnosis and therapy require improvements in the agents used to image and treat disease [10]. RIT has the potential to deliver radiation therapy to tumor or metastatic cells throughout the body while maintaining a high therapeutic index [11]. On the other hand, RIT represents a novel therapeutic approach that combines the tumor-targeting attributes of lymphocyte-specific monoclonal antibodies with therapeutic radioisotopes [12]. Therefore, RIT has been used to consolidate remissions after chemotherapy with good results in future [13, 14].

There are a number of radiopharmaceuticals are used in RIT e.g ^{67}Cu -21T-BAT-Lym-1 for Non-Hodgkin's Lymphoma(NHL) [15], ^{131}I -Labeled Chimeric Monoclonal Antibody MOv18 in patients with ovarian cancer [16] and solid tumors [17]. The most extensively studied, Yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®) and Iodine-131 (^{131}I)-

tositumomab (Bexxar®) are both directed against CD20 [12] which is found on the surface of pre–B lymphocytes, mature B lymphocytes and more than 90% of B-cell NHL (Fig. 2) [18-24]. Both radioimmunotherapeutic agents recognize epitopes in the extracellular domain of the CD20 antigen, and formation of the antibody–antigen complex induces apoptosis, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity [25, 26]. The radioisotopes also contribute to the mechanism of action of the drugs by emitting β -particles, which deposit enough energy in the tumor to result in cell death [27-29].

Although no comparative clinical trial has been performed between ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab, published results suggest that the two compounds achieve similar response rates and response durations [12, 30-32]. Also, RIT utility may be improved by re-treatment, radiosensitizing agents and pre-targeting [33-35]. For example, RIT responses in rituximab-refractory patients suggest a different mechanism of action, i.e. targeted radiation therapy, rather than antibody-dependent killing [8]. The efficacy of RIT is usually assessed with positron emission tomography (PET) scan [36]. It should be mentioned that subsequent chemotherapy following RIT in NHL is tolerable [36-38].

Clinical using of radioimmunotherapy in the treatment of cancers

The FDA approved radioimmunotherapeutic agents (Zevalin and Bexxar) are recommended for the treatment of patients with follicular and transformed NHL who failed to respond to or relapsed after prior

therapies, including rituximab and standard chemotherapy [39, 40]. Initial interesting data were confirmed this application in a phase II trial by multicenter studies [41]. The efficacies reported thus far for therapeutic regimens containing ^{90}Y -ibritumomab tiuxetan and ^{131}I -tositumomab are similar in patients with previously treated and chemotherapy-refractory low-grade relapsed NHL, with overall response rates in the 60%–83% range and complete response rates ranging from 15% to 52% (M4, 8–15). ^{131}I -tositumomab has a higher overall response rate (95%) and complete response rate (75%) when applied as initial therapy for follicular NHL [42]. In total, the safety of both agents is confirmed. The most common adverse events for these radioimmunotherapies in patients previously treated with chemotherapy are serious cytopenias, which are experienced by most patients receiving either ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab [21].

In untreated patients with advanced-stage Follicular Lymphoma (FL), the second most common histological subtype of NHL, ^{131}I -tositumomab showed an overall response rate of 95%, with a rate of complete remission of 74%. In this study, the 5-y progression-free survival was 59%, the toxicity was moderate myelosuppression, and no cases of myelodysplastic syndrome or acute leukemia had been observed at the time of the report [42]. Some other studies reported that ^{90}Y -ibritumomab tiuxetan has been effective in relapsed or refractory patients with CD20-positive FL [29, 43, 44]. Also, providing low-dose radiation to enhance the expression of CD20 in B-cell malignancies, together with its geographically selective cytotoxic effects, warrant further exploration of the use of focal low doses of radiation and CD20-targeted radioimmunotherapy in patients with CD20-positive B cell malignancies [45]. According to the same studies, ^{90}Y -ibritumomab tiuxetan has been approved for consolidation treatment as a part of first-line therapy in both Europe and now the United States [39]. Overall, about 60% of oncologist believed that ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab as a suitable second- or first-line treatment for patients with NHL. As it seems, the future growth of RIT with ^{131}I -tositumomab or ^{90}Y -ibritumomab tiuxetan was judged to be positive by most oncologist [39].

Another research field utilizes RIT prior to stem cell transplant [46, 47]. There is a strong rationale for using RIT as a part of preconditioning treatment for stem cell transplantation (SCT). This is especially pertinent because the majority of patients with relapsed or refractory B-cell NHL are more than 60 years old, and yet are often denied potentially curative high-dose chemotherapy and/or total-body irradiation because of the risk for excessive treatment

related morbidity and mortality [48, 49]. In contrast to total-body irradiation, and by virtue of its targeted activity, RIT (conventional and high dose) can be used in elderly patients with comorbidities undergoing SCT, making it appropriate as a pretransplant regimen for a wider patient population [50]. In two studies, ^{90}Y ibritumomab tiuxetan was used to treat patients with NHL who were not eligible for high-dose chemotherapy and/or total-body irradiation containing therapies prior to SCT.

Data demonstrated better disease control in relapsed and refractory FL and transformed B-cell NHL with no unexpected additional toxicities [32, 51]. Because RIT delivers targeted radiation, it is feasible that any additional therapeutic benefit would be delivered without adding to the high-dose chemotherapy associated toxicity, which could increase the treatment options for older and frailer patients [52].

Also, ^{90}Y -ibritumomab tiuxetan has been used in phase II trials in relapsed and refractory mantle cell lymphoma (MCL). Overall response rates were about 30%, but with only moderate event-free survival of 6 months (median) in relapsed MCL [53]. However, the efficacy of RIT as a member of multimodal strategies might be more efficient. RIT may be applied as part of the induction therapy, consolidation therapy or part of high-dose regimen followed by autologous transplantation [54]. Accordingly, this study suggest that consolidating RIT results in impressively improved complete response rates (from 13% to 55%) and a prolonged progression-free survival of 31 months in first line therapy [46].

Furthermore, advanced prostate cancer is attractive for RIT since metastases from prostate cancer are almost exclusively located in bone marrow and lymph nodes (good access to antibodies) and the metastases are often small enough to ensure good antibody penetration [55, 56].

Goldenberg et al, were the first to demonstrate that a prostate-associated marker could be targeted and imaged by antibodies labelled with radionuclides [57]. Later Meredith et al. treated prostate cancer patients with ^{131}I -labelled CC49 monoclonal antibodies to TAG 72 [58]. Six of 10 symptomatic patients had bone pain relief, but no patients met the radiographic or prostate specific antigen (PSA) criteria for objective response [59].

The other radioimmunotherapeutic agent, ^{131}I -A5B7, is a carcinoembryonic antigen (CEA)-specific mouse monoclonal antibody that has been shown to localize to human colon carcinoma xenografts [60]. A previous phase I rial of single-agent ^{131}I -A5B7, done in patients with advanced colorectal cancer, defined bone marrow suppression as the dose-limiting toxicity at a maximum tolerated dose of 2,400 MBq/m². One out of ten subjects showed a partial response.

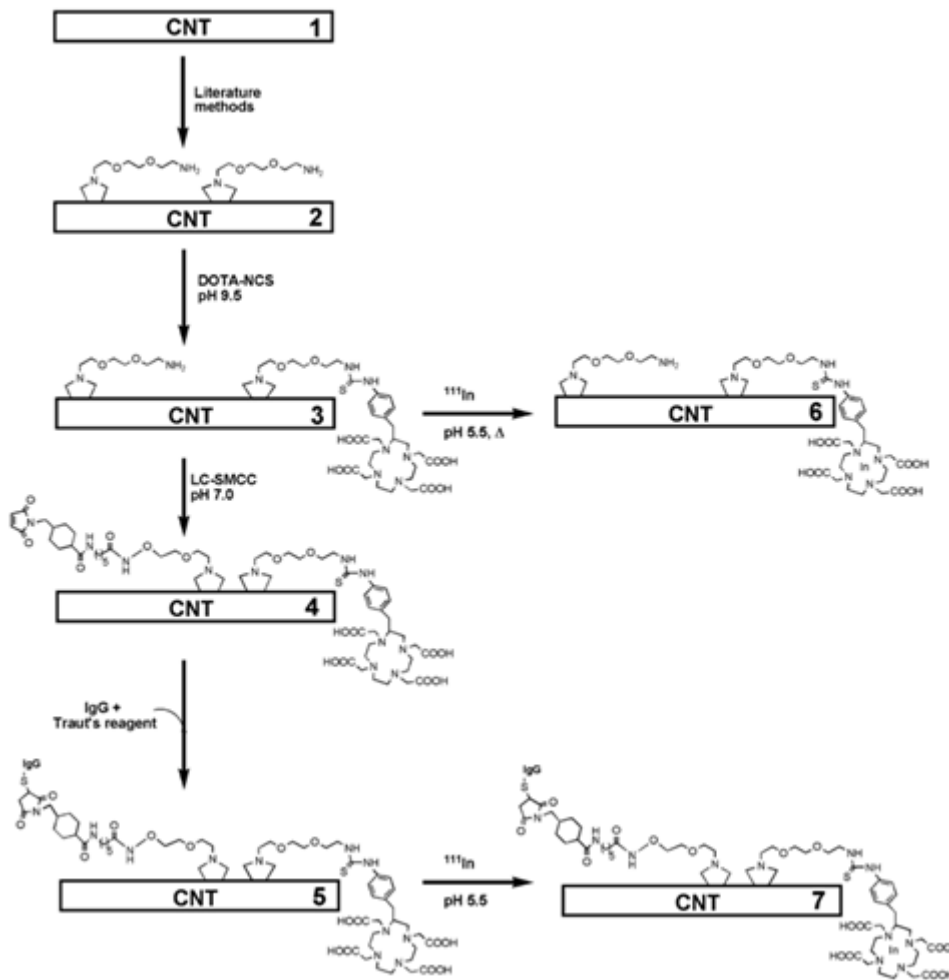


Fig 3. Reaction plot for all carbon nanotubes (CNT) assemblies. (Reprinted by permission of the Society of Nuclear Medicine from [62]).

However, the efficacy of radioimmunotherapy in solid tumors is limited by low tumor penetration into the poorly perfused central tumor areas and relative radioresistance of hypoxic tissue [61].

On other hand, novel nanotechnological discoveries can pave the way for nuclear medicine to achieve remarkable therapeutic value. In this query, single-walled carbon nanotubes (CNT) as a nanoparticle with specific characteristics such as high aspect ratio, having highly regular structures with defined periodicity were used in animal model [62]. Carbon nanotubes also showed exceptional mechanochemical features that can be utilized as specific drug delivery platforms [62].

McDevitt et al tested CNT in vitro by flow cytometry and cell-based immunoreactivity methods and in vivo in a murine xenograft model of lymphoma and achieved to encouraging results (Fig. 3) [62]. Table-1

shows some main studies of the radioimmunotherapy in the treatment of cancers.

CONCLUSION

In an ideal condition, the choice of cancer therapy for a specific patient should be based on the most effective therapy for that patient, and perhaps on its cost-effectiveness, without any influence from its profitability to the treating physician. It seems crucial for the future of RIT not only to demonstrate that these radiolabeled antibodies are effective and safe for treatment of patients with cancers in multiple clinical settings, but also to rationalize the process to provide easy referrals and better collaboration among specialists and to ensure that appropriate safeguards are developed. Also, seems that novel approaches promise to increase the durability of remissions achieved with radiolabeled antibody therapy.

Table 1. some main studies of the radioimmunotherapy in the treatment of cancers.

RIT Agent	Used Tumor	Efficacy	Reference
¹³¹ I-anti-B1 (anti-CD20) antibody	B-cell lymphoma	Four of the ten patients with complete remissions	[63]
¹³¹ I-tositumomab	Low-grade B-cell non-Hodgkin's lymphomas (Multicenter phase II study)	One third of patients had a complete remission	[64]
¹³¹ I-tositumomab	Follicular Lymphoma	Prolonged clinical and molecular remissions	[42]
⁹⁰ Y-ibritumomab tiuxetan	Follicular, or transformed B-cell non-Hodgkin's lymphoma	Well tolerated and produces statistically and clinically significant higher overall response rate and complete remission	[29]
⁹⁰ Y-ibritumomab tiuxetan	relapsed or refractory non-Hodgkin lymphoma	Safe and well tolerated	[43]
⁹⁰ Y-ibritumomab tiuxetan	advanced follicular lymphoma (Phase III trial)	Highly effective with no unexpected toxicities	[65]
⁹⁰ Y-ibritumomab tiuxetan and ¹³¹ I-tositumomab	non-hodgkin lymphoma (a phase II multicenter trial)	(40.9%) had treated patients	[66]
⁹⁰ Y-ibritumomab Tiuxetan	non-Hodgkin's lymphoma	Confirmed to be useful in assessing treatment response	[67]

REFERENCES

- Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. Clin Orthop Relat Res. 1991 Jan;(262):3-11.
- Cantani A. Specific immunotherapy in children: past and present. Eur Rev Med Pharmacol Sci. 1999 Mar-Apr;3(2):93-5.
- Cacciapaglia F, Spadaccio C, Chello M, Gigante A, Coccia R, Afeltra A, Amoroso A. Apoptotic molecular mechanisms implicated in autoimmune diseases. Eur Rev Med Pharmacol Sci. 2009 Jan-Feb;13(1):23-40.
- Cantani A, Micera M. Is specific immunotherapy safe and effective in children? Eur Rev Med Pharmacol Sci. 2000 Sep-Dec;4(5-6):139-43.
- Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975 Aug 7;256(5517):495-7.
- Köhler G, Milstein C. Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion. Eur J Immunol. 1976 Jul;6(7):511-9.
- Goldenberg DM. Targeted therapy of cancer with radiolabeled antibodies. J Nucl Med. 2002 May;43(5):693-713.
- Borghaei H, Smith MR, Campbell KS. Immunotherapy of cancer. Eur J Pharmacol. 2009 Dec 25;625(1-3):41-54.
- Mathas S, Rickers A, Bommert K, Dörken B, Mäpärä MY. Anti-CD20- and B-cell receptor-mediated apoptosis: evidence for shared intracellular signaling pathways. Cancer Res. 2000 Dec 15;60(24):7170-6.

10. Ruggiero A, Villa CH, Holland JP, Sprinkle SR, May C, Lewis JS, Scheinberg DA, McDevitt MR. Imaging and treating tumor vasculature with targeted radiolabeled carbon nanotubes. *Int J Nanomedicine*. 2010 Oct 5;5:783-802.
11. DeNardo SJ, Kukis DL, Miers LA, Winthrop MD, Kroger LA, Salako Q, Shen S, Lamborn KR, Gumerlock PH, Meares CF, DeNardo GL. Yttrium-90-DOTA-peptide-chimeric L6 radioimmunoconjugate: efficacy and toxicity in mice bearing p53 mutant human breast cancer xenografts. *J Nucl Med*. 1998 May;39(5):842-9.
12. Dreyling M, Hiddemann W; European MCL Network. Current treatment standards and emerging strategies in mantle cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2009:542-51.
13. Press OW, Unger JM, Brazier RM, Maloney DG, Miller TP, Leblanc M, Fisher RI; Southwest Oncology Group. Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: five-year follow-up of Southwest Oncology Group Protocol S9911. *J Clin Oncol*. 2006 Sep 1;24(25):4143-9.
14. Leonard JP, Coleman M, Kostakoglu L, Chadburn A, Cesarman E, Furman RR, Schuster MW, Niesvizky R, Muss D, Fiore J, Kroll S, Tidmarsh G, Vallabhajosula S, Goldsmith SJ. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I 131 tositumomab for untreated follicular lymphoma. *J Clin Oncol*. 2005 Aug 20;23(24):5696-704.
15. O'Donnell RT, DeNardo GL, Kukis DL, Lamborn KR, Shen S, Yuan A, Goldstein DS, Carr CE, Mirick GR, DeNardo SJ. A clinical trial of radioimmunotherapy with ⁶⁷Cu-2IT-BAT-Lym-1 for non-Hodgkin's lymphoma. *J Nucl Med*. 1999 Dec;40(12):2014-20.
16. van Zanten-Przybysz I, Molthoff CF, Roos JC, Plaizier MA, Visser GW, Pijpers R, Kenemans P, Verheijen RH. Radioimmunotherapy with intravenously administered ¹³¹I-labeled chimeric monoclonal antibody MOV18 in patients with ovarian cancer. *J Nucl Med*. 2000 Jul;41(7):1168-76.
17. Reilly RM. Radioimmunotherapy of solid tumors: the promise of pretargeting strategies using bispecific antibodies and radiolabeled haptens. *J Nucl Med*. 2006 Feb;47(2):196-9.
18. Wahl RL. Tositumomab and (¹³¹I) therapy in non-Hodgkin's lymphoma. *J Nucl Med*. 2005 Jan;46 Suppl 1:128S-40S.
19. Anderson KC, Bates MP, Slaughenhaupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood*. 1984 Jun;63(6):1424-33.
20. Tedder TF, Boyd AW, Freedman AS, Nadler LM, Schlossman SF. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. *J Immunol*. 1985 Aug;135(2):973-9.
21. Jacene HA, Filice R, Kasecamp W, Wahl RL. Comparison of ⁹⁰Y-ibritumomab tiuxetan and ¹³¹I-tositumomab in clinical practice. *J Nucl Med*. 2007 Nov;48(11):1767-76.
22. Witzig TE. Yttrium-90-ibritumomab tiuxetan radioimmunotherapy: a new treatment approach for B-cell non-Hodgkin's lymphoma. *Drugs Today (Barc)*. 2004 Feb;40(2):111-9.
23. Hagenbeek A. Radioimmunotherapy for NHL: experience of ⁹⁰Y-ibritumomab tiuxetan in clinical practice. *Leuk Lymphoma*. 2003;44 Suppl 4:S37-47.
24. Baechler S, Hobbs RF, Jacene HA, Bochud FO, Wahl RL, Sgouros G. Predicting hematologic toxicity in patients undergoing radioimmunotherapy with ⁹⁰Y-ibritumomab tiuxetan or ¹³¹I-tositumomab. *J Nucl Med*. 2010 Dec;51(12):1878-84.
25. Cardarelli PM, Quinn M, Buckman D, Fang Y, Colcher D, King DJ, Bebbington C, Yarranton G. Binding to CD20 by anti-B1 antibody or F(ab')(2) is sufficient for induction of apoptosis in B-cell lines. *Cancer Immunol Immunother*. 2002 Mar;51(1):15-24.
26. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. *J Immunol*. 1980 Oct;125(4):1678-85.
27. Davis TA, Kaminski MS, Leonard JP, Hsu FJ, Wilkinson M, Zelenetz A, Wahl RL, Kroll S, Coleman M, Goris M, Levy R, Knox SJ. The radioisotope contributes significantly to the activity of radioimmunotherapy. *Clin Cancer Res*. 2004 Dec 1;10(23):7792-8.
28. Wiseman GA, Kornmehl E, Leigh B, Erwin WD, Podoloff DA, Spies S, Sparks RB, Stabin MG, Witzig T, White CA. Radiation dosimetry results and safety correlations from ⁹⁰Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from 4 clinical trials. *J Nucl Med*. 2003 Mar;44(3):465-74.
29. 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 low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 May 15;20(10):2453-63.
30. Witzig TE, White CA, Gordon LI, Wiseman GA, Emmanouilides C, Murray JL, Lister J, Multani PS. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-hodgkin's lymphoma. *J Clin Oncol*. 2003 Apr 1;21(7):1263-70.
31. Marcus R. Use of ⁹⁰Y-ibritumomab tiuxetan in non-Hodgkin's lymphoma. *Semin Oncol*. 2005 Feb;32(1 Suppl 1):S36-43.
32. Schilder R, Molina A, Bartlett N, Witzig T, Gordon L, Murray J, Spies S, Wang H, Wiseman G, White C. Follow-up results of a phase II study of ibritumomab tiuxetan radioimmunotherapy in patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma and mild thrombocytopenia. *Cancer Biother Radiopharm*. 2004 Aug;19(4):478-81.
33. Goldenberg DM, Rossi EA, Sharkey RM, McBride WJ, Chang CH. Multifunctional antibodies by the Dock-and-Lock method for improved cancer imaging and therapy by pretargeting. *J Nucl Med*. 2008 Jan;49(1):158-63.
34. Wiseman GA, Conti PS, Vo K, Schilder RJ, Gordon LI, Emmanouilides C, Silverman DH, Witzig TE, Darif M, Molina A. Weight-based dosing of Yttrium 90 ibritumomab tiuxetan in patients with relapsed or refractory B-cell non-Hodgkin lymphoma. *Clin Lymphoma Myeloma*. 2007 Sep;7(8):514-7.

35. 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 Sep;5(2):98-101.
36. Jacene HA, Filice R, Kasecamp W, Wahl RL. 18F-FDG PET/CT for monitoring the response of lymphoma to radioimmunotherapy. *J Nucl Med*. 2009 Jan;50(1):8-17.
37. Ansell SM, Ristow KM, Habermann TM, Wiseman GA, Witzig TE. Subsequent chemotherapy regimens are well tolerated after radioimmunotherapy with yttrium-90 ibritumomab tiuxetan for non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 Sep 15;20(18):3885-90.
38. 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 Apr;47(4):629-36.
39. Schaefer NG, Ma J, Huang P, Buchanan J, Wahl RL. Radioimmunotherapy in non-Hodgkin lymphoma: opinions of U.S. medical oncologists and hematologists. *J Nucl Med*. 2010 Jun;51(6):987-94.
40. Juweid ME. Radioimmunotherapy of B-cell non-Hodgkin's lymphoma: from clinical trials to clinical practice. *J Nucl Med*. 2002 Nov;43(11):1507-29.
41. Delaloye AB, Antonescu C, Louton T, Kuhlmann J, Hagenbeek A. Dosimetry of 90Y-ibritumomab tiuxetan as consolidation of first remission in advanced-stage follicular lymphoma: results from the international phase 3 first-line indolent trial. *J Nucl Med*. 2009 Nov;50(11):1837-43.
42. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, Regan D, Kison P, Fisher S, Kroll S, Wahl RL. 131I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med*. 2005 Feb 3;352(5):441-9.
43. Wiseman GA, Gordon LI, Multani PS, Witzig TE, Spies S, Bartlett NL, Schilder RJ, Murray JL, Saleh M, Allen RS, Grillo-López AJ, White CA. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood*. 2002 Jun 15;99(12):4336-42.
44. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, Cripe L, Wiseman G, Olejnik T, Multani PS, White CA. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol*. 2002 Aug 1;20(15):3262-9.
45. Gupta D, Crosby ME, Almasan A, Macklis RM. Regulation of CD20 expression by radiation-induced changes in intracellular redox status. *Free Radic Biol Med*. 2008 Feb 15;44(4):614-23.
46. Gopal AK, Rajendran JG, Gooley TA, Pagel JM, Fisher DR, Petersdorf SH, Maloney DG, Eary JF, Appelbaum FR, Press OW. High-dose [131I]tositumomab (anti-CD20) radioimmunotherapy and autologous hematopoietic stem-cell transplantation for adults > or = 60 years old with relapsed or refractory B-cell lymphoma. *J Clin Oncol*. 2007 Apr 10;25(11):1396-402.
47. 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 Jan 1;26(1):90-5.
48. Montoto S, Canals C, Rohatiner AZ, Taghipour G, Sureda A, Schmitz N, Gisselbrecht C, Fouillard L, Milpied N, Haioun C, Slavin S, Conde E, Fruchart C, Ferrant A, Leblond V, Tilly H, Lister TA, Goldstone AH; EBMT Lymphoma Working Party. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study. *Leukemia*. 2007 Nov;21(11):2324-31.
49. Sacchi S, Marcheselli L, Bari A, Marcheselli R, Pozzi S, Luminari S, Lombardo M, Buda G, Lazzaro A, Gobbi PG, Stelitano C, Morabito F, Quarta G, Brugiattelli M. Secondary malignancies after treatment for indolent non-Hodgkin's lymphoma: a 16-year follow-up study. *Haematologica*. 2008 Mar;93(3):398-404.
50. Gregory SA, Hohloch K, Gisselbrecht C, Tobinai K, Dreyling M. Harnessing the energy: development of radioimmunotherapy for patients with non-Hodgkin's lymphoma. *Oncologist*. 2009;14 Suppl 2:4-16.
51. 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 Jul 1;110(1):54-8.
52. Gisselbrecht C, Vose J, Nademanee A, Gianni AM, Nagler A. Radioimmunotherapy for stem cell transplantation in non-Hodgkin's lymphoma: in pursuit of a complete response. *Oncologist*. 2009;14 Suppl 2:41-51.
53. 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 Nov 1;27(31):5213-8.
54. Gopal AK, Rajendran JG, Petersdorf SH, Maloney DG, Eary JF, Wood BL, Gooley TA, Bush SA, Durack LD, Martin PJ, Matthews DC, Appelbaum FR, Bernstein ID, Press OW. High-dose chemo-radioimmunotherapy with autologous stem cell support for relapsed mantle cell lymphoma. *Blood*. 2002 May 1;99(9):3158-62.
55. Smith-Jones PM, Pandit-Taskar N, Cao W, O'Donoghue J, Philips MD, Carrasquillo J, Konner JA, Old LJ, Larson SM. Preclinical radioimmunotargeting of folate receptor alpha using the monoclonal antibody conjugate DOTA-MORAb-003. *Nucl Med Biol*. 2008 Apr;35(3):343-51.
56. Jakobovits A. Monoclonal antibody therapy for prostate cancer. *Handb Exp Pharmacol*. 2008;(181):237-56.
57. Goldenberg DM, DeLand FH, Bennett SJ, Primus FJ, Nelson MO, Flanigan RC, McRoberts JW, Bruce AW, Mahan DE. In vivo use of radioactive antibodies against prostatic acid phosphatase for diagnosis and detection of prostatic cancer by nuclear imaging. *JAMA*. 1983 Aug 5;250(5):630-5.
58. Meredith RF, Bueschen AJ, Khazaeli MB, Plott WE, Grizzle WE, Wheeler RH, Schlom J, Russell CD, Liu T, LoBuglio AF. Treatment of metastatic prostate

- carcinoma with radiolabeled antibody CC49. *J Nucl Med.* 1994 Jun;35(6):1017-22.
59. Gerke O, Poulsen MH, Bouchelouche K, Høilund-Carlson PF, Vach W. PET/CT in cancer: moderate sample sizes may suffice to justify replacement of a regional gold standard. *Mol Imaging Biol.* 2009 Nov-Dec;11(6):381-5.
 60. Pedley RB, Boden J, Keep PA, Harwood PJ, Green AJ, Rogers GT. Relationship between tumour size and uptake of radiolabelled anti-CEA in a colon tumour xenograft. *Eur J Nucl Med.* 1987;13(4):197-202.
 61. Flynn AA, Green AJ, Boxer GM, Casey JL, Pedley RB, Begent RH. A novel technique, using radioluminography, for the measurement of uniformity of radiolabelled antibody distribution in a colorectal cancer xenograft model. *Int J Radiat Oncol Biol Phys.* 1999 Jan 1;43(1):183-9.
 62. McDevitt MR, Chattopadhyay D, Kappel BJ, Jaggi JS, Schiffman SR, Antczak C, Njardarson JT, Brentjens R, Scheinberg DA. Tumor targeting with antibody-functionalized, radiolabeled carbon nanotubes. *J Nucl Med.* 2007 Jul;48(7):1180-9.
 63. Kaminski MS, Zasadny KR, Francis IR, Milik AW, Ross CW, Moon SD, Crawford SM, Burgess JM, Petry NA, Butchko GM, et al. Radioimmunotherapy of B-cell lymphoma with [¹³¹I]anti-B1 (anti-CD20) antibody. *N Engl J Med.* 1993 Aug 12;329(7):459-65.
 64. Vose JM, Wahl RL, Saleh M, Rohatiner AZ, Knox SJ, Radford JA, Zelenetz AD, Tidmarsh GF, Stagg RJ, Kaminski MS. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol.* 2000 Mar;18(6):1316-23.
 65. 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, van Oers MH, van Putten W, Bischof-Delaloye A, Rohatiner A, Salles G, Kuhlmann J, Hagenbeek A. 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 Nov 10;26(32):5156-64.
 66. Schaefer NG, Huang P, Buchanan JW, Wahl RL. Radioimmunotherapy in non-Hodgkin lymphoma: opinions of nuclear medicine physicians and radiation oncologists. *J Nucl Med.* 2011 May;52(5):830-8.
 67. Lopci E, Santi I, Tani M, Maffione AM, Montini G, Castellucci P, Stefoni V, Rubello D, Fonti C, Zinzani P, Fanti S. FDG PET and ⁹⁰Y ibritumomab tiuxetan in patients with follicular lymphoma. *Q J Nucl Med Mol Imaging.* 2010 Aug;54(4):436-41.