⁹⁰Y-Daclizumab (Anti-CD25), High-Dose Carmustine, Etoposide, Cytarabine, and Melphalan Chemotherapy and Autologous Hematopoietic Stem Cell Transplant Yielded Sustained Complete Remissions in 4 Patients with Recurrent Hodgkin's Lymphoma

Kevin C. Conlon,¹ Claude Sportes,² Martin W. Brechbiel,³ Daniel H. Fowler,² Ronald Gress,² Milos D. Miljkovic,¹ Clara C. Chen,⁴ Millie A. Whatley,⁴ Bonita R. Bryant,¹ Erin M. Corcoran,¹ Karen A. Kurdziel,⁵ Stefania Pittaluga,⁶ Chang H. Paik,⁵ Jae Ho Lee,⁵ Thomas A. Fleisher,⁷ Jorge A. Carrasquillo,^{4,*} and Thomas A. Waldmann¹

Abstract

Background: Despite advances in therapy of Hodgkin's lymphoma (HL), a proportion of patients will not respond or relapse. The authors had previously identified CD25, IL-2R α , as a target for systemic radioimmunotherapy of HL since most normal cells do not express CD25, but it is expressed by a minority of Hodgkin/Reed-Sternberg (HRS) cells and most Tregs rosetting around HRS cells.

Study Design and Treatment: This was a single institution, nonrandomized, open-label phase I/II trial of radiolabeled ⁹⁰Y-daclizumab, an anti-CD25 monoclonal antibody, BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning treatment followed by autologous hematopoietic stem cell transplant (ASCT). Four patients with refractory and relapsed HL were treated in this trial with 3 patients receiving a single dose of 564.6–574.6 MBq ⁹⁰Y-daclizumab and the fourth patient receiving two doses of 580.9–566.1 MBq ⁹⁰Y-daclizumab followed by high-dose chemotherapy and ASCT.

Results: All 4 evaluable patients treated with ⁹⁰Y-daclizumab obtained complete responses (CRs) that are ongoing 4.5–7 years following their stem cell transplant.

The spectrum and severity of adverse events were mild and more importantly none of the patients, including several with multiple therapies before this treatment, developed the myelodysplastic syndrome.

Discussion: Targeting by daclizumab was not directed primarily at tumor cells, but rather the nonmalignant CD25-expressing T cells adjacent to the HRS cells and ⁹⁰Y-daclizumab provided strong enough β emissions to kill CD25-negative tumor cells at a distance by a crossfire effect. Furthermore, the strong β irradiation killed normal cells in the tumor microenvironment.

Conclusions: ⁹⁰Y-daclizumab (anti-CD25), high-dose BEAM chemotherapy and ASCT was well tolerated and yielded sustained complete remissions in all 4 patients with recurrent HL patients who completed their treatment.

Significance: Despite advances, a proportion of patients with HL will not have a CR to their initial treatment, and some with CRs will relapse. They demonstrated that the addition of ⁹⁰Y-daclizumab into the preconditioning

¹Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

²Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA.

³Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA.

⁴Nuclear Medicine Department, Radiation and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, Maryland, USA.

⁵Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

⁶Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.

⁷Department of Laboratory Medicine, NIH Clinical Center, National Institutes of Health, Bethesda, Maryland, USA.

*Current affiliation: Molecular Imaging and Therapy Service, Radiology Department, Memorial Sloan Kettering Cancer Center, New York, New York, USA.

Address correspondence to: Thomas A. Waldmann; Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health; 10 Center Drive, Building 10, Room 4N117, Bethesda, MD 20892-1374, USA
E-mail: tawald@helix.nih.gov

regimen for refractory and relapsed HL patients with high-dose BEAM chemotherapy and ASCT provided sustained CRs in the 4 patients studied. Two of these patients were highly refractory to multiple prior treatments with bulky disease at entry into this study, including 1 patient who never entered a remission and had failed 6 different therapeutic regimens. Despite the small number of patients treated in this study, the sustained clinical benefit in these patients indicates a highly effective treatment. The daclizumab was directed primarily not at HRS cells themselves but toward nonmalignant T cells rosetting around malignant cells. ^{90}Y provided strong β emissions that killed antigen nonexpressing tumor cells at a distance by a crossfire effect. Furthermore, the strong β radiation killed normal cells in the tumor microenvironment that nurtured the malignant cells in the lymphomatous mass. The present study supports expanded analysis of ^{90}Y -daclizumab as part of the regimen of ASCT in patients with refractory and relapsed HL.

Keywords: ^{90}Y -daclizumab, autologous hematopoietic stem cell transplant, BEAM chemotherapy Hodgkin's lymphoma, radioimmunotherapy

Introduction

There were ~8500 new cases of Hodgkin's lymphoma (HL) in 2018 and 1050 patients died of their disease according to SEER database, based on November 2017 SEER data submission (posted to the SEER website, April 2018).¹ Although treatment with modern combination chemotherapy regimens is associated with about an 80% complete remission rate, 10%–15% of patients will not respond to treatment or will relapse.^{2–7} High-dose chemotherapy with autologous hematopoietic stem cell support (ASCT) has become the treatment of choice. Brentuximab vedotin has been approved for the treatment of relapsed HL.^{8–10} Furthermore, anti-programmed death (PD)-1 agents have shown outstanding results in classical HL.¹¹ However, despite this aggressive treatment, a meaningful fraction of patients will not respond, and a proportion of patients will develop recurrent disease.

To date, more than 30 different monoclonal antibody preparations directed toward antigens expressed by malignant Hodgkin/Reed-Sternberg (HRS) cells have been studied.⁸ These include monoclonal antibodies linked to drugs and targeting CD30 or CD25 expressed on HRS cells. Brentuximab vedotin, an anti-CD30 antibody drug conjugate, has induced a significant number of responses in refractory HL.^{9,10} Although other antibody immunotoxins have demonstrated some clinical efficacy they have yielded few complete responses (CRs).^{12,13} An alternative strategy has been to arm monoclonal antibodies with radionuclides. Radioimmunotherapy (RIT) using ^{131}I -anti-CD30 and ^{90}Y -anti-ferritin antibodies have provided partial responses (PRs) and CRs in HL.^{14–17} Deficiencies in these approaches reflect the small number of CD30-expressing HRS cells in the tumor and the lack of tumor specificity of ferritin-targeted antibodies.

We have identified CD25, the IL-2R α subunit (IL-2R α), as an alternative more favorable target for systemic RIT of HL.^{3,18–24} The scientific rationale is that with the exception of Tregs, CD25 is not expressed by many normal cells but is expressed on both a minority of HRS cells and pivotally on Treg cells rosetting around the HRS cells.^{25–28} ^{90}Y , an energetic β particle emitter that travels a mean of ~3 mm in soft tissue, acts through crossfire throughout the tumor masses, providing a strategy for killing tumor cells at a distance of several cell diameters, including CD25^{negative} HRS cells, provided that CD25⁺T cells in their vicinity express the target antigen.^{25–29} Previously the authors reported a trial in which

they treated 46 patients with recurrent or refractory HL with ^{90}Y -daclizumab every 6–10 weeks for up to 7 doses depending on hematological recovery.³ Among the 46 evaluable patients, there were 14 CRs and 9 PRs, 14 patients with stable disease (SD), and only 9 patients whose best response was progressive disease. Responses were observed both in patients whose HRS cells expressed CD25 and in those whose neoplastic cells were CD25 negative provided that associated rosetting cells expressed CD25.³ Toxicities in this advanced disease population were transient bone marrow suppression and the myelodysplastic syndrome (MDS) in 6 patients who had not been evaluated with bone marrow karyotype analysis before therapy.

Given that recurrent disease remains the single most common cause of treatment failure after ASCT in patients with relapsed HL and given the 50% response rate achieved with ^{90}Y -daclizumab, they sought to improve the long-term disease-free survival achieved by ASCT by incorporating ^{90}Y -daclizumab into the transplant preconditioning regimen. In the present study, patients with refractory or relapsed HL who had not undergone previous autologous stem cell transplant (ASCT) were treated in the Phase I dose-escalation trial with the initial cohort receiving a single administration of ^{90}Y -labeled daclizumab 566–570 MBq followed by a 4-day myeloablative regimen with carmustine, etoposide, cytarabine, and melphalan (BEAM) and ASCT. Subsequent cohorts were to receive additional treatments with ^{90}Y -daclizumab before BEAM-ASCT; however, the study was ended prematurely as the radiopharmacy production facility for the radiolabeled antibody was no longer available. In this study, they report the results of the four patients treated on the study, all of whom remain in CR without evidence of treatment-related MDS after at least 4.5 years of follow-up.

Materials and Methods

Eligibility and qualifying testing

This was a single institution, nonrandomized, open-label phase I/II trial. From September 2012 to September 2014 patients with refractory and relapsed (classical nodular Hodgkin's lymphoma nodular sclerosis subtype were excluded) HL who had not undergone a previous ASCT were treated in phase I dose escalation of ^{90}Y -daclizumab followed by the standard preparative (carmustine, etoposide, cytarabine [Ara-C], and melphalan [BEAM]) chemotherapy regimen and then ASCT (Table 1). To be eligible for this

TABLE 1. PATIENT CHARACTERISTICS PRIOR TO THERAPY

Patient Stage and Diagnosis		Prior chemotherapy treatments	XRT	⁹⁰ Y-daclizumab (MBq)
1	NS IIIB → IVB	3. (AVBD, ICE, BV)	Y	571.3
2	NS IVB	6. (AVBD, ICE, BV, GV, EPOCH-RC, EPOCH)	N	564.6
3	NS IVB	3. (ABVD, IGEV, BV)	Y	574.6
4 ^a	NS IVB	4. (AVBD, ICE, BV, GemOx)	N	No treatment
5 ^b	NS IIIB → IVB	4. (ABVD, ICE, HD/CCNU/VP-16/CDDP, BV)	N	570.2*
6	NS IVA	3. (AVBD, ICE, BV)	Y	580.9 and 566.1

^aWithdrew from protocol

^bRemoved from protocol due to noncompliance with treatment plan after initial Yttrium daclizumab treatment

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ICE, Ifosfamide, carboplatin, etoposide; BV, brentuximab vedotin; GV, gemcitabine, vinorelbine; IGEV, Ifosfamide, gemcitabine, vinorelbine; EPOCH-RC, etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide, Revlimid, alemtuzumab; EPOCH, etoposide, prednisone, vincristine, Adriamycin, cyclophosphamide; GemOx, Gemcitabine, Oxaliplatin; HD Dex, high-dose dexamethasone; CCNU, Lomustine; CDDP, Cisplatin; VP-16: Etoposide

protocol, adult patients were required to have radiographically measurable disease, adequate biochemical (renal, hepatic), hematologic function (pulmonary, cardiac), absence of infections (HepB, HepA, HIV), and ECOG performance status ≤1.

Furthermore, the patients must have had at least one of the following: (1) initial relapse <12 months after achieving a CR with primary chemotherapy for HL; (2) stage III/IV disease at diagnosis; (3) chemotherapy-resistant disease, or (4) did not achieve a CR with cytoreductive chemotherapy before a planned transplant. Pretreatment evaluation included standard biochemical panels, complete blood count, confirmation of HL pathologic diagnosis by NIH Pathology Department, and that more than 10% of cells in the tumor sample were immunohistochemically positive for CD25, the target of daclizumab. The HRS cells could be negative for CD25 provided the Tregs rosetting around these cells were positive. In addition to qualify for the study, patients needed adequate respiratory function in formal pulmonary function testing and an absence of cardiac pathology on echocardiograph and EKG.

Pretreatment staging procedures included bone marrow (biopsy and aspirate) to assess for bone marrow involvement, computed tomography (CT) scan of neck, chest, abdomen, and pelvis, and FDG positron emission tomography (PET)/CT scan to assess extent of disease, and when appropriate, magnetic resonance imaging of the brain to confirm absence of central nervous system involvement that would disqualify the patient for the trial. Six patients qualified and were consented for the protocol with 4 receiving their full treatment. Patient 4 was removed from the study for protocol-defined criteria for failure to mobilize an adequate number of CD34⁺ stem cells and never received any therapeutic treatment. Patient 5 received initial ⁹⁰Y-daclizumab treatment without significant difficulties but withdrew his consent for treatment and was removed from the protocol before BEAM-ASCT (see Supplementary Data).

Treatment, dose escalation, and dose-limiting toxicity

Approximately 1 month before the start of therapy, all patients had CD34⁺ stem cell mobilization using high-dose G-CSF (granulocyte colony-stimulating factor; 10–16 μg/kg/d × 5 or 6 d) with plerixafor (Mozobil) mobilization (240 μg/kg within 6 h) before the stem cell pheresis to obtain 4 × 10⁶ CD34⁺ cells/kg that were stored for later hematopoietic reconstitution. The radioimmunotherapy dose escalation plan used the standard 3 + 3 phase I design with the initial patient cohort receiving a single administration of ⁹⁰Y-daclizumab

555 MBq. Subsequent cohorts were planned to receive the same amount of ⁹⁰Y-daclizumab followed 42 d later with the second ⁹⁰Y-daclizumab treatment and in the absence of dose-limiting toxicity (DLT) at progressively higher doses of the second treatment of ⁹⁰Y-daclizumab 555, 1110, 1665, 2220, 2775, and 3330 MBq.

The therapeutic ⁹⁰Y-daclizumab was administered with unconjugated daclizumab to bring the total combined mass of antibody to 5 mg. In addition, for 3 d after their ⁹⁰Y-daclizumab infusion all patients received repeat infusions of trisodium calcium diethylenetriaminepentaacetate (Ca-DTPA) to chelate and promote excretion of any free ⁹⁰Y. Ten days (2.7 half-lives) after their last ⁹⁰Y-daclizumab treatment, all patients began their 4-d myeloablative regime with BEAM regimen. Treatment with Keratinocyte Growth Factor (KGF/Palifermin) was initiated 3 d before the start of BEAM chemotherapy for mucositis prophylaxis.

One day after completion of their myeloablative treatment, all patients received their ASCT infusion (2–4 × 10⁶ CD34⁺ cells/kg of actual weight) and 3 d later began G-CSF that was given until neutrophil recovery ≥1000/μL for 3 consecutive days. All patients received standard post stem cell transplant supportive care, including prophylactic antibacterial and antiviral antibiotics until recovery of their other hematopoietic functions.

Dose-Limiting Toxicities were defined as ≥grade 3 (CTCAE v4.0) nonhematologic toxicity related to ⁹⁰Y-daclizumab with the exception of fatigue lasting for more than 5 d and occurring before the start of the BEAM chemotherapy.

This study was approved by the Institutional Review Board of the National Cancer Institute. This trial is registered as NCT01468311. All patients gave written informed consent for participating in the protocol. This study was performed under the conditions of the Helsinki accords (see Supplementary Data).

⁹⁰Y-and ¹¹¹In-labeled daclizumab

Daclizumab (Hoffmann-La Roche, Nutley, NJ) was conjugated with 2-p-isothiocyanatobenzyl-transcyclohexyldiethylenetriamine pentaacetic acid (CHX-A) and was radio-labeled with ⁹⁰Y for therapy and with ¹¹¹In for imaging as similar to previously described.^{3,29}

¹¹¹In-labeled daclizumab imaging

Simultaneous with administration of therapeutic ⁹⁰Y, ¹¹¹In-labeled daclizumab was administered to identify biodistribution

and tumor targeting. The patients received 185–188.7 MBq of ^{111}In daclizumab with 0.4 mg of CHX-A-conjugated daclizumab mixed together with 566.1–580.9 MBq of ^{90}Y -daclizumab on 0.4–0.6 mg of CHX-A daclizumab; these antibodies were mixed and 4–4.2 mg of cold daclizumab was added to bring the mass to 5 mg. Purity of all radiolabeled antibodies determined by instant thin-layer chromatography ranged from 99% to 100% and median immunoreactivity for ^{111}In daclizumab was 88% and for ^{90}Y daclizumab was 86% using an HPLC assay. The antibodies were administered intravenously as a 1.8–2 h infusion.

Patients also received a 250 mg/m² infusion of diethylenetriaminepentaacetic acid (DTPA) to bind any free ^{90}Y . No acute toxicity was noted related to antibody infusion. All patients, including those whose Reed-Sternberg cells did not express CD25, had positive localization of ^{111}In -daclizumab at disease sites. On the basis of this and a previous study, the estimated tissue radiation dose per 555 MBq of ^{90}Y -daclizumab was 173 cGy to bone marrow, 263 cGy to liver, 1062 cGy to spleen, and 33 cGy to the whole body. The estimated tumor dose with 555 MBq ranged from 210 to 365 cGy.³

Immune responses to daclizumab

The method used to define immune responses to treatment was described previously.³

Assessment of extent of disease

All patients underwent baseline contrast-enhanced CT and PET scan within $\times 28$ d of the start of treatment and at regular intervals following their ASCT. Index lesions were selected for response evaluation criteria in solid tumors assessment of their pretreatment FDG PET/CT and were reassessed in the subsequent restaging scans. In brief, PET/CT images were acquired after a 60-min uptake period and no patient was hyperglycemic. Images were read clinically and then re-read together with prior FDG images as well as with antibody immunoscintigraphy.

All patients underwent single-proton emission computed tomography CT imaging from neck to proximal thigh at 2 h postadministration of ^{111}In -daclizumab and at 96–144 h. Images were interpreted by an experienced nuclear medicine physician and compared with baseline and subsequent PET/CT scans.

Results

This was a single-institution, nonrandomized, open-label phase I/II trial. Six patients were evaluated and 4 patients with refractory and relapsed HL were treated with radiolabeled ^{90}Y -daclizumab anti-CD25 monoclonal antibody incorporated into the preconditioning regimen before BEAM conditioning therapy with an ASCT (Table 1).

Treated patients

As seen (Table 2), the patients were heavily pretreated with a median 3 prior chemotherapy regimens and all had progressive multisite disease at the time they began the protocol treatment regimen as summarized below in Table 2. Patients 1 through 3 were treated with a single 564.6–574.6 MBq infusion and patient 6 received two 580.9 and 566.1 MBq infusions of ^{90}Y -daclizumab 15 mCi before BEAM. Using immunohistochemical analysis in only one biopsy (in 4 patients) did $>10\%$ of the HL neoplastic cells express

CD25 (Fig. 1B), whereas the associated rosetting cells expressed CD25 in all 4 cases examined (Fig. 1A–D).

Three patients received a single dose of 564.6–574.6 MBq ^{90}Y -daclizumab (day 15), followed by high-dose beam chemotherapy (beginning day 6) with ASCT performed on day 0. One patient received 2 doses of ^{90}Y -daclizumab 6 d apart (days 56 and 15), followed by high-dose chemotherapy (beginning day 6) ASCT day 0.

Patients 1, 2, 3, and 6 completed their protocol prescribed treatment without experiencing DLT or severe or unexpected adverse events (AEs). As seen in Table 3, the spectrum and severity of AEs were generally mild, the vast majority grade 1 or 2 and consistent with the safety profile of most patients with HL undergoing ASCT. All but one patient had bone or back pain related to their high-dose G-CSF stem cell mobilization. Patients 2 and 4 had grade 2 pain related to research biopsies of tumor-involved lymph nodes post- ^{90}Y -daclizumab infusion. All patients had grade 1 pain related to sites of disease and interestingly 3 of the patients had slight flare of pain after their ^{90}Y -daclizumab infusions. All the patients had the common BEAM-related nausea, vomiting, and other gastrointestinal AEs. Three of the patients had cutaneous reactions to the plerixafor or KGF.

Patient 6 had two less common, more serious but not unexpected, grade 3 AEs. The first event was catheter-related (strep mitis) bacteremia that occurred during her period of neutropenia after her BEAM treatment. The patient's central venous catheter was removed, she began empiric antibiotic treatment and her bacteremia cleared quickly. She completed a 2-week course of appropriate antibiotics without sequelae or complications. This patient was also noted to have irregular periods after completing her protocol requiring 1 year of Depo-Provera birth control, and developed amenorrhea and increasingly frequent "hot flashes" at the 18-month posttransplant evaluation. Hormonal analysis at this time showed elevated luteinizing hormone (LH), follicle-stimulating hormone (FSH), and low serum estradiol levels. The patient remained amenorrheic and continued to have intermittent hot flashes through her year 2 follow-up visit and repeat hormonal analysis showed the same pattern that was consistent with premature ovarian failure (POF). The patient was started on replacement calcium, vitamin D, and daily Levonorgestrel/Ethinyl Estradiol and had serial analysis of LH, FSH, and serum estradiol levels. At her 4-year follow-up visit the patient reported return of intermittent menses in the previous 2 months. Repeat hormonal analyses showed a dramatic decrease in her LH, FSH levels, and very elevated serum estradiol level (>100 pg/mL) indicating return of ovarian function. At her 4.5-year follow-up visit, the patient reported continued improvement toward more regular menses and laboratories again indicated return of ovarian function. There were no instances of serious infection or febrile neutropenia that occurred during the ^{90}Y daclizumab treatments or associated with the myeloablative BEAM chemotherapy.

Immune response to daclizumab

None of the patients had baseline human anti-human antibodies (HAHA) to daclizumab nor did they develop them after treatments.

Hematopoietic recovery and hospital discharge

Given their significant prior treatment history and the nature of the protocol treatment, significant, at least transient,

TABLE 2. PATIENT CLINICAL FEATURES AND ⁹⁰Y-DACLIZUMAB TREATMENT

<i>Patient initial diagnosis</i>	<i>Symptoms and sites of disease</i>	<i>Line of treatment</i>	<i>Therapy</i>	<i>Response</i>	<i>Sites of disease at start of protocol treatment</i>	<i>⁹⁰Y daclizumab (MBq)</i>
1—Nodular sclerosing IIB	Fevers, weight loss, pruritis, cervical LNs; CT scans showed diffuse bulky axillary, hilar, retroperitoneal, pelvic and inguinal LNs Multiple left inguinal, femoral and internal iliac LNs	Initial Salvage 1 Salvage 2	ABVD×8; consolidative mantle and inverted-Y XRT ICE×4 Brentuximab vedotin×4	CR PD PR	Multiple iliac and inguinal LNs	571.3
2—Nodular sclerosing IVB	Pruritis, night sweats, dyspnea and shortness of breath; CT and PET scans showed massive mediastinal involvement, bilateral pleural effusions, bilateral axillary, supraclavicular, retroperitoneal, pelvic and inguinal LNs and positive bone marrow enhancement on PET scan	Initial	ABVD×8	PR	Mediastinal mass, parenchymal lung lesions, lytic bone lesions, bilateral axillary, supraclavicular, retroperitoneal, pelvic and inguinal LNs	564.6
3—Nodular sclerosing IVB	Mediastinal mass, bilateral axillary, supraclavicular, retroperitoneal, pelvic and inguinal LNs Night sweats, weight loss, cervical and axillary LNs; CT scans showed cervical, axillary, hilar, retroperitoneal LNs and adrenal gland Cervical, axillary, hilar, retroperitoneal LNs and adrenal gland Right supraclavicular and axillary LNs Right supraclavicular, axillary, portocaval, splenic LNs and spleen	Salvage 1 Salvage 2 Salvage 3 Salvage 4 Salvage 5 Initial Salvage 1 Salvage 2 Salvage 3	ICE×3 Brentuximab vedotin×3 GV×2 EPOCH-RC×6 EPOCH×1 ABVD×6 IGEV×4 Brentuximab vedotin×5 XRT to spleen, thoracic and cervical LNs	PD PD PD SD PD PD PR PD PR	Right axillary, multiple mediastinal, multiple paraaortic and inguinal LNs	574.6 ^a

(continued)

TABLE 2. (CONTINUED)

<i>Patient initial diagnosis</i>	<i>Symptoms and sites of disease</i>	<i>Line of treatment</i>	<i>Therapy</i>	<i>Response</i>	<i>Sites of disease at start of protocol treatment</i>	<i>⁹⁰Y daclizumab (MBq)</i>
4—Nodular sclerosing IVA	Chest pain, CT scans showed bulky supraclavicular, mediastinal, axillary, abdominal LNs and pulmonary parenchymal lesions Supraclavicular, mediastinal, axillary, abdominal LNs Supraclavicular, mediastinal, axillary, abdominal LNs	Initial Salvage 1 Salvage 2 Salvage 3 Initial	ABVD × 5 ICE × 2 Brentuximab vedotin × 6 GemOx ABVD × 6	PD PR SD SD CR	Right cervical, bilateral axillary, prevertebral, subcarinal and precaval LNs	No treatment; withdrew consent
5—Nodular sclerosing IIIB	Night sweats, fevers, weight loss, cervical LNs; CT scans showed cervical, bilateral axillary LNs Cervical, submandibular, axillary LNs Inguinal, abdominal LNs	Salvage 1 Salvage 2 Salvage 3 Salvage 4 Initial	ICE × 3 HD Dex → CCNU, CDDP, VP-16 × 2 IF XRT BV ABVD × 6	CR SD PD SD PR	Cervical, supraclavicular, multiple mediastinal, large porta hepatis mass, aortocaval, bilateral iliac LNs and right ribs	570.2 ^a
6—Nodular sclerosing IVA	Porta hepatitis, aortocaval, iliac LNs Right sided cervical LNs → bilateral axillary LNs; CT and PET scan showed extensive bulky cervical, mediastinal, celiac LNs and splenic uptake Right cervical, supraclavicular and axillary LNs	Salvage 1 Salvage 2	ICE × 3 Brentuximab vedotin × 3	SD PD	Multiple bulky right cervical, bilateral axillary and left paratracheal mass	580.9 and 566.1

^aRemoved from protocol for noncompliance with treatment plan.

CT, computed tomography; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; XRT, radiation therapy; CR, complete response; ICE, ifosfamide, carboplatin, etoposide; PR, partial response; GV, gemcitabine, vinorelbine; EPOCH-RC, etoposide, prednisone, vincristine, cyclophosphamide, Revlimid, alemtuzumab; SD, stable disease; EPOCH, etoposide, prednisone, vincristine, adriamycin, cyclophosphamide; IGEV, ifosfamide, gemcitabine, vinorelbine; GemOx, gemcitabine, oxaliplatin; HD Dex, high dose dexamethasone; CCNU, lomustine; CDDP, cisplatin; VP-16, etoposide, GemOx (Gemcitabine, Oxaliplatin); HD Dex: high-dose dexamethasone; PD, progressive disease; LN, lymph node.

FIG. 1. All cases were rich in HRS cells often forming large clusters associated with CD25 positive T cells and macrophages. Only in **(B)** the HRS cells were positive for CD25 (patient number 3), **(A)** is from patient number 6, **(C)** from patient number 1 and **(D)** from patient number 2. HRS, Hodgkin/Reed-Sternberg.

TABLE 3. ADVERSE EVENTS

AE term	Grade			
	1	2	3	4
Agitation/insomnia	1			
Anorexia	1			
Gastritis	2			
Abdominal pain	1			
Bone or back pain	2			
Leg pain	1			
Diarrhea	2			
Fatigue	2	1		
Fever	1	1		
Catheter related infection			1	
LN pain	1	2		
Nasal congestion	1			
Noncardiac CP	1			
Oral or throat pain	1			
Rectal pain		1		
Rash	1			
Sinus tachycardia	1			
Nausea	2			
Vomiting	1			
Irregular menses			1	
Pruritis	2			
Flushing	1			
Mucositis/gingival bleeding	3			
Headache	2	1		
Paresthesias	2			
Weight loss		1		
Sinus congestion	1			

AE, adverse event; CP, chest pain.

trilineage cytopenias were expected. All patients had brief periods of absolute neutropenia following their BEAM chemotherapy. Hemoglobin (Hgb) was also affected with grade 3 anemia (Hgb <8 g) occurring in 3 of these 4 patients (nadirs 7.4, 7.2, 9.4, and 6.9 g) with the two lowest nadirs occurring in patient 2 and 5 who were already anemic at the start of treatment. Platelet counts nadired at 10,000/ μ L or lower in the week after the subcutaneous infusion. However, as shown in Table 4 below, there was no evidence that ⁹⁰Y daclizumab had any significant negative impact on hematopoietic recovery with 11 (range 10–12) d being the median time to recovery of absolute neutrophil count to >500/ μ L and 10 (range 8–11) d being the median time to recovery to untransfused platelet count >20,000/ μ L for the 4 patients who completed their planned protocol treatment and had their SCT. The patient's rapid recovery from their treatment is reflected in the timing of their discharge from hospital being essentially 2 weeks after receiving their SC infusion.

TABLE 4. HEMATOPOIETIC RECOVERY AND HOSPITAL DISCHARGE

Patient	Days to ANC >500/ μ L	Days to untransfused platelet count >20,000/ μ L	Date of hospital discharge
1	11	11	Day 14
2	12	8	Day 14
3	11	10	Day 15
6	10	8	Day 13

ANC, absolute neutrophil count.

Response to treatment

The pattern of response assessment by CT scans and PET scans showed a similar pattern for the 4 patients who are evaluable for response (Figs. 2–4). All had sizable or bulky lesions that began to shrink promptly in their regular posttreatment restaging CT scans. As seen in Table 5, all 4 patients had very significant shrinkage in the index lesions (61%–87% decreases) in the 12–24 months after treatment that plateaued, leaving small residual masses at the site of their larger metastatic lesions. The first post-ASCT treatment FDG PET scan showed dramatic resolution of many sites of disease, although a few sites still had increased FDG that eventually resolved. “No active lesions” PET scans occurred between 30 and 48 months after treatment.

All the patients had a somewhat evanescent or random pattern of transiently increased standardized uptake value at known sites of disease after apparent normalization of these previously involved areas that made it impossible to assess the patient as a CR. However, given the highly refractory nature of their HL at the start of protocol treatment and the absence of regrowth of previous sites of disease or new lesions and consistently diminishing sites in restaging PET scan has led us to assess all 4 patients as CRs now ranging 4.5 to nearly 8 years post autoSCT.

Discussion

The standard treatment for relapsed and primary refractory HL is salvage chemotherapy, followed by high-dose

chemotherapy and autologous stem cell transplantation, which has shown a 5-year progression—survival of ~50%–60%.^{30–34} A series of diverse clinical prognostic factors such as those used in the present study have been useful in predicting prognosis in refractory and relapsed HL patients. Freedom from ASCT failure in the presence of 0, 1, 2, or 3 factors have ranged between 45%–93%, 27%–59%, and 10%–18%, respectively.^{35–37} All of these patients had at least one factor.

A large number of monoclonal antibodies have been approved for the therapy of cancer.²³ The CD30 antibody/drug conjugate brentuximab vedotin and the PD-1 directed antibodies nivolumab and pembrolizumab are highly efficacious in treating relapsed and/or refractory HL.^{9–11,38} In a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory HL, objective responses were induced in 75% of patients with complete remissions in 34% of patients.³⁸ The median progression-free survival of all patients was 5.6 months and the median duration of response for those in CR was 20.5 months. The most common treatment-related AEs were peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhea. On March 20, 2018, brentuximab vedotin in combination with chemotherapy was granted FDA approval to be used in adult patients with previously untreated stage III or IV classical HL.

Preclinical studies suggested that HRS cells exploit the PD-1 pathway to evade immune detection. In classic HL alteration in chromosome 9p24.1 increased the abundance of

FIG. 2. FDG study (not shown) with evidence of hypermetabolic lesions consistent with lymphoma in nodal sites above the diaphragm including right, left cervical (SUV_{max} 12.9), right and left axillary (SUV_{max} 17), mediastinal (SUV_{max} 22.5), right inguinal, lung (SUV_{max} 19.8) and sternum (SUV_{max} 15.2). Post-treatment ^{111}In -daclizumab maximum intensity projection image from SPECT study obtained on 6/25/2013, 4 days after injection of ~185 MBq of ^{111}In -daclizumab that was co-infused with 564.6 MBq of ^{90}Y -daclizumab uptake in bilateral cervical, bilateral axillary, mediastinum, lung, and right inguinal, corresponding to sites seen on baseline FDG, although somewhat less obvious given the lower resolutions of SPECT. Post ^{90}Y -daclizumab and post autologous stem cell transplant treatment a follow-up FDG scan obtained October 15, 2013 shows that resolution of uptake in all the lesions with exception of some residual uptake in left cervical region (SUV_{max} 7.99) that was either residual disease or inflammatory. FDG PET CT of July 15, 2014 shows residual left cervical uptake that was slightly less than the October 15, 2013 scan that given the lack of increase in size or uptake was probably nonmalignant, also nonspecific low level bilateral hilar uptake was also noted. The last scan of December 12, 2018 did not show any abnormal hypermetabolic sites suspicious for lymphoma. Note that nonspecific FDG uptake is noted in the thyroid in all post treatment FDG scans, probably reflecting inflammatory/autoimmune disease. SUV, standardized uptake value.

FIG. 3. Patient (number 6) Baseline FDG PET CT on July 28, 2014 shows hypermetabolic lesions consistent with lymphoma in right cervical (SUV_{max} 24.1), right axillary (SUV_{max} 21.3), and left axillary (SUV_{max} 20.6). ^{111}In -daclizumab co-administered with 580.9 MBq of ^{90}Y -daclizumab on August 25, 2014, shows uptake in right cervical and bilateral axillary nodules. The 9/30/2014 post initial treatment FDG shows decreased but persistent abnormal uptake in right cervical (SUV_{max} 7.3) and right axillary (SUV_{max} 18.0) and left axillary nodes (SUV_{max} 6.6). A repeat administration of ^{111}In -daclizumab co-administered with 566.1 MBq of ^{90}Y -daclizumab on October 6, 2014 shows persistent uptake in right cervical and bilateral axillary nodes that while decreased from previous was still present. A FDG on January 22, 2015 post second treatment with ^{90}Y -daclizumab and BEAM plus transplant shows resolution of right cervical node, nonspecific uptake in left cervical node, bilateral axillary nodes and left hilar node. Follow-up FDG on October 29, 2015 shows uptake in right cervical that was suspicious for lymphoma and nonspecific minimal bilateral axillary uptake. The February 25, 2016 FDG scan shows persistent right cervical uptake and nonspecific axillary nodal uptake. FDG on October 18, 2018 shows nonspecific right cervical and right axillary node uptake with no evidence of FDG avid lymphoma. BEAM, carmustine, etoposide, cytarabine and melphalan.

FIG. 4. Patient (number 3) Baseline FDG PET CT study on June 17, 2013 shows abnormal hypermetabolic lesion in right axilla (SUV_{max} 14.3), mediastinum (SUV_{max} 12.5), right supradiaphragmatic (SUV_{max} 11.2), retroperitoneal (SUV_{max} 12.2), splenic (SUV_{max} 7.4) and left proximal femur (SUV_{max} 8.0). Uptake in the left submandibular area is nonspecific (SUV_{max} 4.83). ^{111}In -daclizumab co-administered with 574.6 MBq of ^{90}Y -daclizumab shows uptake in the right axilla, mediastinum, retroperitoneum, splenic focus, and left proximal femur. Lesion in the liver was not identified, cervical region is out of the field of view. Follow-up FDG scan on November 12, 2013. ~3.5 months later, shows increased abnormal uptake in left cervical region and resolution of axillary, mediastinal, supradiaphragmatic, retroperitoneal lesions and probable resolution of left proximal femoral lesion. FDG scan of August 14, 2014 shows unchanged persistent left cervical node, very mild nonspecific uptake in axillary and inguinal nodes, bilateral hilar nodes. A large called RUL nodule on this and prior. Follow-up FDG scan of August 13, 2015 shows persistent uptake in the left cervical node and minimal nonspecific unchanged uptake in bilateral hilar. FDG of July 28, 2016 shows persistent left cervical node uptake and some mild non-specific uptake in bilateral axillary nodes. FDG of July 19, 2018 shows nonspecific bilateral axillary and hilar uptake with no sites of abnormal uptake suggestive of lymphoma.

TABLE 5. SUMMARY OF RADIOGRAPHIC FINDINGS

Patient	CT scan assessment		PET scan assessment
	Maximum decrease in marker lesions (%)	Time to plateau in regression (months)	Timing of first negative scan (months)
1	61	24	30
2	78	24	48
3	69	20	30
6	87	12	30

PD-1, ligands, PD-L1, and PD-L2 and promote their induction through Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling.³⁹ PD-1 blockade with nivolumab in relapsed or refractory HL of 23 studied patients after relapse following autologous stem cell transplantation and/or following receipt of brentuximab vedotin was associated with an objective response in 27 patients (87%), including 17% with a CR and 70% with a PR.¹¹ The remaining 3 patients (13%) had SD. The rate of progression-free survival at 24 weeks was 86%.

Although these studies change the landscape for classical HL management, in 2018 ~ 1000 patients with HL died of their disease.¹ In particular, a significant proportion of patients with HL will not respond or will relapse. The arming of monoclonal antibodies by linking them to cellular toxins or radionuclides is to target these agents specifically to tumors.^{3,9,10,12–18,23,40–50} One advantage of the use of a radiolabeled monoclonal antibody conjugate for therapy over unmodified monoclonal antibodies or monoclonal antibodies linked to toxins is that with the appropriate choice of radionuclide radiolabeled antibodies can kill cells at a distance of several cell diameters and thereby make targets of the antigen-negative tumor cells adjacent to antigen-expressing normal cells.

Various monoclonal antibodies with different antigenic targets have been employed to deliver targeted RIT.^{3,14–18,23,40–50} In an effort to evaluate RIT as part of the salvage regimen pre-ASCT, there have been a number of trials of ⁹⁰Y ibritumomab tiuxetan (Zevalin anti-CD20), followed by BEAM-conditioning regimen and autologous hematopoietic stem cell transplantation (ASCT) in relapsed and refractory high-risk B cell non-HL. In each of the studies, the combined use of RIT with BEAM plus autologous stem hematopoietic cell transplant was feasible with acceptable toxicity even in elderly and heavily pretreated patients. However, with the exception of one case that showed borderline efficacy, the addition of ⁹⁰Y did not confer a further survival benefit when compared with rituximab added to BEAM and autologous hematopoietic stem cell transplant.

The current study used daclizumab (humanized anti-Tac, anti-CD25) armed with the energetic β' -particle emitter ⁹⁰Y. Daclizumab targets the 55kDa/IL-2R (CD25) subunit that is constitutively expressed on Treg cells, but not on other resting normal cells.^{19,51} In contrast, CD25 is overexpressed on certain lymphoid malignancies, including select patients with anaplastic large cell lymphoma, adult T cell leukemia/lymphoma, chronic lymphocytic leukemia, cutaneous T cell lymphoma, Hairy cell leukemia, and in HL.^{21,51} Unmodified murine anti-CD25 was evaluated in a trial involving patients

with adult T-cell leukemia. Seven of 19 treated patients responded to the antibody.^{19,51} In a subsequent trial 9 of 16 evaluable patients with ATL responded to ⁹⁰Y-labeled murine anti-CD25.⁸

Subsequently, 46 patients with relapsed or refractory HL received 370–555 MBq of ⁹⁰Y-daclizumab every 6–10 weeks for up to 7 doses.³ Among the 46 patients treated with multiple doses of ⁹⁰Y-daclizumab 14 achieved a complete remission and 9 manifested a PR. In a separate study of unconjugated antibody using saturating amounts of daclizumab in 22 patients with Hodgkin's disease, there were no PRs or CRs.³ Freedom from disease progression in the ⁹⁰Y-daclizumab-treated patients ranged from 28 to 788 d with a median response duration of 151 d (range 28–720 d). Median CR duration was 328 d not counting the period in the PR. Thus, although 14 patients manifested a CR, the lack of cures indicated that monotherapy with this agent was not optimal.

Given the 50% response rate achieved with ⁹⁰Y-daclizumab RIT in a heavily pretreated population, the authors sought to improve the long-term disease-free survival achievable with ASCT by incorporating escalating doses of ⁹⁰Y-daclizumab into the preconditioning regimen that included high-dose chemotherapy with carmustine, etoposide, cytarabine, doxorubicin, and melphalan (BEAM). They hypothesized that this use of an autologous hematological stem cell transplant using cells harvested from the patient before the administration of ⁹⁰Y-daclizumab should permit an escalation of ⁹⁰Y-daclizumab doses because the hematological stem cell transplant should ameliorate the otherwise dose-limiting hematological toxicity of the radiolabeled anti-CD25 monoclonal antibody. Furthermore, they hoped that use of the nonirradiated stem cell transplant would reduce the incidence of the development of MDS.

The spectrum in severity of AEs were mild with ⁹⁰Y-daclizumab plus ASCT in HL (Table 3). The only serious AE observed during the trial was transient POF, an expected complication of stem cell transplant that is more common in patients who have had multiple treatment regimens for their cancers, so it is not possible to determine the possible contribution of ⁹⁰Y-daclizumab treatment to this AE. There were 6 MDS in the previous study of 46 patients.³ These 6 occurred in the 30 patients who had not had a cytogenetic study of bone marrow specimens before initiation of systemic RIT, whereas none of the 16 patients after such analysis developed this disorder. Although the present study is too small to draw meaningful conclusions, the fact that only one or two doses of ⁹⁰Y-daclizumab rather than up to seven, as in the previous study, as well as the fact that autologous stem hematopoietic cell transplant of unirradiated bone marrow was provided after the ⁹⁰Y, may be factors in reducing this complication. Nevertheless, a subsequent clinical trial should require pretreatment cytogenetic studies of bone marrow specimens before initiation of systemic RIT.

In contrast to the fact that none of the 46 patients in the previous study, including the 14 patients that manifested a CR were cured of their HL by the administration of ⁹⁰Y-daclizumab alone, all 4 of the patients in the present study who received ⁹⁰Y-daclizumab in high-dose BEAM therapy autologous hematopoietic stem cell transplant remain in CR 4.5 to almost 8 years following therapy. In previous studies 50%–60% of patients with refractory and relapsed HL receiving an autologous hematopoietic stem cell transplant

alone achieved a sustained CR.^{30–34} In the present study, responses were observed both in the patient whose HRS cells expressed CD25 and the remainder whose neoplastic cells were CD25 negative; thus the daclizumab was directed primarily not at the tumor cells themselves but toward nonmalignant Treg cells rosetting around the HRS cells.

Yttrium-90 provided strong β' -emissions that killed antigen-nonexpressing tumor cells at a distance by a cross-fire effect. Furthermore, the strong β' -irradiation killed normal cells in the tumor microenvironment that nurtured the malignant cells in the lymphomatous mass. In addition, the ionizing radiation increases the generation of tumor-associated antigen and neoantigens as well as increasing expression of MHC molecules and antigen presentation suggesting that it might be of value to combine RIT with murine checkpoint blockers. Therefore, the ⁹⁰Y-daclizumab infusions may provide meaningful therapy for select HL patients. The encouraging results of the present study support future similar studies of ⁹⁰Y anti-CD25 monoclonal antibody into the BEAM, ASCT preconditioning regimen.

Acknowledgments

The study was performed under the conditions of the Helsinki accords. All patients signed a written informed consent for participation in clinical studies. Clinical studies were approved by the Intramural Review Board of the National Cancer Institute.

Author Contributions

Concept and design: T.A.W., K.C.C., C.S., R.G., M.W.B., and J.A.C. Development of methodology: J.A.C., M.W.B., and T.A.W. Acquisition of data (managed patients' administration of ⁹⁰Y-daclizumab): K.C.C., C.S., D.H.F., C.C.C., M.A.W., and T.A.F. Analyses and interpretation of data: T.A.W., K.C.C., M.D.M., J.A.C., and K.A.K. Writing review and or revision of article: T.A.W., K.C.C., M.D.M., M.W.B., and J.A.C. Administrative, technical, or material support (i.e., reporting or organizing data): E.M.C. and B.R.B. Study supervision: T.A.W. and K.C.C. Other (acquired photomicrograph images of histology slides, manufacturing and testing of IL-15): J.H.L., C.H.P., and S.P. All coauthors have reviewed and approved for publication of the article before submission.

Disclosure Statement

The authors declare no potential conflicts of interest.

Funding Information

This work was supported by the Intramural Research Program of the Center for Cancer Research, National Cancer Institute, NIH.

Supplementary Material

Supplementary Data

References

- Noone AM, Howlader N, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975–2015. Bethesda, MD: National Cancer Institute. Online document at <https://seer.cancer.gov/csr/19752015> based on November 2019 SEER data submission.
- DeVita VT, Jr., Hubbard SM. Hodgkin's disease. *N Engl J Med* 1993;328:560.
- Janik JE, Morris JC, O'Mahony D, et al. ⁹⁰Y-daclizumab, an anti-CD25 monoclonal antibody, provided responses in 50% of patients with relapsed Hodgkin's lymphoma. *Proc Natl Acad Sci U S A* 2015;112:13045.
- Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478.
- Longo DL, Duffey PL, DeVita VT, Jr., et al. Treatment of advanced-stage Hodgkin's disease: Alternating non-crossresistant MOPP/CABS is not superior to MOPP. *J Clin Oncol* 1991;9:1409.
- Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med*. 2003; 348:2386; dosage error in text corrected in *N Engl J Med* 2005;353:744.
- Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. *Lancet* 2002;359:2065.
- Schnell R, Borchmann P, Schulz H, et al. Current strategies of antibody-based treatment in Hodgkin's disease. *Ann Oncol* 2002;13(suppl1):57.
- de Claro RA, McGinn K, Kwitkowski V, et al. U.S. Food and Drug Administration approval summary: Brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma or relapsed systemic anaplastic large-cell lymphoma. *Clin Cancer Res* 2012;18:5845.
- Younes A, Forero-Torres A, Bartlett NL, et al. Objective responses in a phase I dose-escalation study of SGN-35, a novel antibody-drug conjugate (ADC) targeting CD30, in patients with relapsed or refractory Hodgkin lymphoma. *J Clin Oncol* 2008;26:Abstract 8526.
- Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015;372:311.
- Engert A, Diehl V, Schnell R, et al. A phase-I study of an anti-CD25 ricin A-chain immunotoxin (RFT5-SMPT-dgA) in patients with refractory Hodgkin's lymphoma. *Blood* 1997;89:403.
- Kreitman RJ, Wilson WH, White JD, et al. Phase I trial of recombinant immunotoxin anti-Tac(Fv)-PE38 (LMB-2) in patients with hematologic malignancies. *J Clin Oncol* 2000; 18:1622.
- Vriesendorp HM, Herpst JM, Germack MA, et al. Phase I-II studies of yttrium-labeled antiferritin treatment for end-stage Hodgkin's disease, including Radiation Therapy Oncology Group 87-01. *J Clin Oncol* 1991;9:917.
- Vriesendorp HM, Quadri SM, Wyllie CT, et al. Fractionated radiolabeled antiferritin therapy for patients with recurrent Hodgkin's disease. *Clin Cancer Res* 1999;5(10suppl): 3324s.
- Decaudin D, Levy R, Lokiec F, et al. Radioimmunotherapy (RIT) of refractory or relapsed Hodgkin's lymphoma (HL) with ⁹⁰Y-labelled antiferritin antibody. *Anticancer Drugs* 2007;18:725.
- Schnell R, Dietlein M, Staak JO, et al. Treatment of refractory Hodgkin's lymphoma patients with an iodine-131-

- labeled murine anti-CD30 monoclonal antibody. *J Clin Oncol* 2005;23:4669.
18. Waldmann TA, White JD, Carrasquillo JA, et al. Radioimmunotherapy of interleukin-2R alpha-expressing adult T-cell leukemia with Yttrium-90-labeled anti-Tac. *Blood* 1995;86:4063.
 19. Waldmann TA, White JD, Goldman CK, et al. The interleukin-2 receptor: A target for monoclonal antibody treatment of human T-cell lymphotropic virus I-induced adult T-cell leukemia. *Blood* 1993;82:1701.
 20. Queen C, Schneider WP, Selick HE, et al. A humanized antibody that binds to the interleukin 2 receptor. *Proc Natl Acad Sci U S A* 1989;86:10029.
 21. Waldmann TA, Greene WC, Sarin PS, et al. Functional and phenotypic comparison of human T cell leukemia/lymphoma virus positive adult T cell leukemia with human T cell leukemia/lymphoma virus negative Sézary leukemia, and their distinction using anti-Tac. Monoclonal antibody identifying the human receptor for T cell growth factor. *J Clin Invest* 1984;73:1711.
 22. Uchiyama T, Broder S, Waldmann TA. A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T cells. I. Production of anti-Tac monoclonal antibody and distribution of Tac (+) cells. *J Immunol* 1981;126:1393.
 23. Waldmann TA, Morris JC. Development of antibodies and chimeric molecules for cancer immunotherapy. *Adv Immunol* 2006;90:83.
 24. Vincenti F, Kirkman R, Light S, et al. Daclizumab Triple Therapy Study Group. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998;338:161.
 25. Antony PA, Restifo NP. CD4⁺ CD25⁺ T regulatory cells, immunotherapy of cancer, and interleukin-2. *J Immunother* 2005;28:120.
 26. Koenecke C, Ukena SN, Ganser A, et al. Regulatory T cells as therapeutic target in Hodgkin's lymphoma. *Expert Opin Ther Targets* 2008;12:769.
 27. Aldinucci D, Gloghini A, Pinto A, et al. The classical Hodgkin's lymphoma microenvironment and its role in promoting tumour growth and immune escape. *J Pathol* 2010;221:248.
 28. Baecher-Allan C, Viglietta V, Hafler DA. Human CD4⁺CD25⁺ regulatory T cells. *Semin Immunol* 2004;16:89.
 29. Carrasquillo JA, White JD, Paik CH, et al. Similarities and differences in ¹¹¹In- and ⁹⁰Y-labeled 1B4M-DTPA antiTac monoclonal antibody distribution. *J Nucl Med* 1999;40:268.
 30. Puig N, Pintilie M, Seshadri T, et al. Different response to salvage chemotherapy but similar post-transplant outcomes in patients with relapsed and refractory Hodgkin's lymphoma. *Haematologica* 2010;95:1496.
 31. Nademanee A, O'Donnell MR, Snyder D, et al. High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease: Results in 85 patients with analysis of prognostic factors. *Blood* 1995;85:1381.
 32. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: Analysis by intent to treat and development of a prognostic model. *Blood* 2001;97:626.
 33. Reece DE, Connors JM, Spinelli JJ, et al. Intensive therapy with cyclophosphamide, carmustine, etoposide +/- cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination therapy. *Blood* 1994;83:1193.
 34. Lavoie JC, Connors JM, Phillips GL, et al. High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: Long-term outcome in the first 100 patients treated in Vancouver. *Blood* 2005;106:1473.
 35. Brice P, Bouabdallah R, Moreau P, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: Analysis of 280 patients from the French registry. Société Française de Greffe de Moëlle. *Bone Marrow Transplant* 1997;20:21.
 36. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 2002;20:221.
 37. Sureda A, Constans M, Iriando A, et al. Prognostic factors affecting long-term outcome after stem cell transplantation in Hodgkin's lymphoma autografted after a first relapse. *Ann Oncol* 2005;16:625.
 38. Younes A, Bartlett NL, Leonard JP, et al. Brentuzimab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med* 2010;363:1812.
 39. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood* 2010;116:3268.
 40. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. *N Engl J Med* 1993;329:1219.
 41. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [¹³¹I] anti-B1 (anti-CD20) antibody. *N Engl J Med* 1993;329:459.
 42. Milenic DE, Brady ED, Brechbiel MW. Antibody-targeted radiation cancer therapy. *Nat Rev Drug Discov* 2004;3:488.
 43. Bethge WA, Lange T, Meisner C, et al. Radioimmunotherapy with yttrium-90-ibritumomab tiuxetan as part of a reduced-intensity conditioning regimen for allogeneic hematopoietic cell transplantation in patients with advanced non-Hodgkin lymphoma: Results of a phase 2 study. *Blood* 2010;116:1795.
 44. Winter JN, Inwards DJ, Spies 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.
 45. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine, etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: Results from the BMT CTN 0401 Trial. *J Clin Oncol* 2013;31:1662.
 46. Bento L, Boumendil A, Finel H, et al. Radioimmunotherapy-augmented BEAM chemotherapy vs BEAM alone as the high-dose regimen for autologous stem cell transplantation (ASCT) in relapsed follicular lymphoma (FL): A retrospective study of the EBMT Lymphoma Working Party. *Bone Marrow Transplant* 2017;52:1120.

47. Buchmann I, Bunjes D, Kotzerke L, et al. Myeloablative radioimmunotherapy with Re-188-anti-CD66-antibody for conditioning of high-risk leukemia patients before stem cell transplantation: Biodistribution, biokinetics and immediate toxicities. *Cancer Biother Radiopharm* 2002;17:151.
48. Wagner JY, Schwarz K, Schreiber S, et al. Myeloablative anti-CD20 radioimmunotherapy plus/-high-dose chemotherapy followed by autologous stem cell support for relapsed/refractory B-cell lymphoma results in excellent long-term survival. *Oncotarget* 2013;4:899.
49. Hohloch K, Sahlmann CO, Lakhani VJ, et al. Tandem high-dose therapy in relapsed and refractory B-cell lymphoma: Results of a prospective phase II trial of myeloablative chemotherapy, followed by escalated radioimmunotherapy with I-131-anti-CD20 antibody and stem cell rescue. *Ann Hematol* 2011;90:1307.
50. Pagel JM, Appelbaum FR, Eary JF, et al. I-131-anti-CD45 antibody plus busulfan and cyclophosphamide before allogeneic hematopoietic cell transplantation for treatment of acute myeloid leukemia in first remission. *Blood* 2006;107:2184.
51. Waldmann TA. Anti-Tac (daclizumab, Zenapax) in the treatment of leukemia, autoimmune diseases, and in the prevention of allograft rejection: A 25-year personal odyssey. *J Clin Immunol* 2007;27:1.