IMPLICATIONS FOR PATIENTS WITH LYMPHOMA AS A RESULT OF CMS-1392-FC AS IT RELATES TO

BEXXAR® Therapeutic Regimen
(Tositumomab + Iodine 131 Tositumomab)
and
ZEVALIN® Therapeutic Regimen
(Ibritumomab Tiuxetan)

SUBMITTED TO:
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I. IMPLICATION OF FINAL RULE FOR PATIENTS

Reimbursement rates for Bexxar and Zevalin, as set forth in CY2008 CMS-1392-FC, Hospital Outpatient Prospective Payment System dated November 2007, are approximately one half their cost, which is likely to severely limit or deny patient access to these drugs. Though Congress mandated full reimbursement through June 30, 2008, we are concerned that, when the current legislation expires, CMS will defer to the Final Rule. If that were to happen, we fear that patients will no longer have access to these drugs which are critical, in some cases, to their very survival.

In this section, we describe why these treatments are essential to patients and why we implore CMS to fully reimburse for these drugs.

ABOUT LYMPHOMA AND ITS TREATMENT: Non-Hodgkin's lymphoma affects about 500,000 Americans and kills about 27,000 annually. Its incidence has nearly doubled since the 1970's.

Traditional treatments, i.e., chemotherapy and more recently chemotherapy with the addition of Rituxan (a monoclonal antibody) can be curative in some patients with certain forms of lymphoma. Unfortunately, for patients with what are termed "low-grade lymphomas," these treatments are not curative. Instead, they usually slow the disease for periods which vary among patients, but invariably the disease returns, requiring treatment with stronger drugs. Remission periods and response rates decrease with each successive treatment.[1] For patients with this disease, this often means a slow but certain death.

Radioimmunotherapy (RIT) is a new class of medicine approved for relapsed or refractory low-grade lymphoma or transformed low-grade lymphoma, which includes approximately 40% of the lymphoma population. RIT combines a monoclonal antibody with a radiolabeled antibody, which is a monoclonal antibody to which a radiation-emitting molecule or isotope is attached. The monoclonal antibody seeks a specific target on the surface of tumor cells, latches on, and calls the body's own immune system into action. For an extra lethal and dual-action effect, the radiolabeled antibody emits radiation directly to the tumor.

There are two FDA-approved treatments in this class of medicine: the BEXXAR® Therapeutic Regimen and the ZEVALIN® Therapeutic Regimen.

RADIOIMMUNOTHERAPY CAN REVERSE THE PATTERN OF RECURRING DISEASE: With the introduction of RIT into the list of available treatment options, patients finally have a treatment which has been shown to potentially reverse the pattern of decreasing response rates to chemotherapy and shorter response times, as several studies have shown (See Section II).

POTENTIAL CURE: Encouraging data is emerging that has some scientists whispering the word "cure" when speaking of RIT and its potential.

Says Dr. Richard Wahl, "Response rates of up to 95% have been reported and exciting new data are emerging from large trials again showing these drugs to be the most active single agents in lymphoma, working even when chemotherapy does not…Patients may be actually be cured with these agents."[2]

We know of many patients who have experienced long periods of remission far beyond what they previously experienced with chemotherapy and far beyond anyone's expectations, including some who were treated in clinical trials and have remained disease-free for more than ten years. From our own experience, neither Betsy de Parry nor Karl Schwartz's wife would be alive today without RIT.

ADDITIONAL PATIENT BENEFITS: In addition to its effectiveness in treating the disease, RIT offers additional benefits to the patient:

- Convenience – total treatment time is approximately 1 week
- Fewer side effects: "(RIT) comes without the hair loss, mouth sores, severe nausea or vomiting often accompanying conventional chemotherapy."[3]

RADIOIMMUNOTHERAPY MEETS A VITAL NEED: For patients who no longer respond to chemotherapy, RIT offers a valuable option that, for many, has proven to be life-saving. It offers:

- High response rates
- Long and durable remissions
- Potential effectiveness even when chemotherapies no longer work
- Curative potential

Optimal ways to utilize this valuable therapy are still being discovered.

II. COST EFFECTIVENESS AND APPROPRIATE REIMBURSEMENT

Although we recognize that CMS does not make comparisons between treatments when determining reimbursement rates, the following information on response rates is needed to show that radioimmunotherapy is a cost effective treatment.

Because low-grade lymphoma is typically marked by multiple recurrences, it is logical to support and encourage treatments which provide the longest periods of remission, i.e., periods when no money is spent on treatments.

COMPLETE RESPONSE RATES INFLUENCE REMISSION PERIODS: There is emerging evidence that achieving a complete response (CR) (complete detectable disappearance of disease) is an important factor for extending remission periods and for improving the survival of patients with low-grade lymphoma. Researchers from several institutions performed a meta-analysis of trials using literature published between 2001 and 2006 and reported that a higher CR rate was correlated with a lower hazard of disease progression.[4] By therapy, they reported the following CR rates:[5]

79% - Radioimmunotherapy
68% - Fludara-based regimens
53% - Chemotherapy regimens with the addition of Rituxan or Rituxan alone
37% - Chemotherapy regimen without Rituxan

Response rates and durations of response significantly improve when Bexxar is administered earlier in treatment, according to an analysis comparing ten clinical trials in which Bexxar was used. This analysis shows the CR rate by treatment sequence:[6]

78% - First line (141 patients)
46% - Second line (226 patients)
32% - Third line (228 patients)
23% - Fourth line (540 patients)

Although Bexxar and Zevalin are approved for use as second line treatment, it is significant to note that studies using them in previously untreated patients, alone or in combination with chemotherapy, have shown impressive results. A study using Bexxar as the sole treatment and as initial therapy showed the following:[7]

95% - Overall response
75% - Complete response (CR)
86% - Overall survival at 10 years
9.2 years - Median time to progression of disease among those who achieved CR

The efficacy and safety of radioimmunotherapy has been well documented, and it may be particularly appropriate for elderly patients who rely on Medicare and Medicaid and who

may have additional co-morbidities and poor functional status limiting the use of chemotherapy or combined modalities.[8]

RADIOIMMUNOTHERAPY PROLONGS PROGRESSION FREE SURVIVAL: A randomized study showed that Zevalin, when given directly after several different types of chemotherapy with and without the addition of Rituxan, resulted in prolonging progression free survival by two years compared to no additional treatment.[9]

COST OF CHEMOTHERAPY VERSUS RADIOIMMUNOTHERAPY: Several choices exist for the treatment of lymphoma and it is not within our expertise to compare the cost of each one. However, we do know that common chemotherapies include CHOP (cyclophosmomide, doxorubicin, vincristine, prednisone) and CVP (cyclophosmomide, vincristine, prednisone) with the addition of Rituxan (a monoclonal antibody). These treatments are given at three week intervals, six to eight times.

Additionally, a white blood cell stimulant (Neulasta) is normally indicated between each cycle to reduce risk of infection, particularly in the elderly population dependent on Medicare.

Using the shortest number of cycles – six – and <u>not</u> including the cost of chemotherapy drugs, these standard treatments cost:

Six cycles of Rituxan at $4,500 each:*	$27,000
Six doses of Neulasta at $2,700 each:	<u>$16,200</u>
TOTAL:	$43,200

**Based on Wholesale Acquisition Cost (WAC) using average dose of 900 mg. based on average body surface area (BSA) of 1.8 mg. per m^2.* [10]

Additionally, many physicians frequently administer Rituxan as "maintenance therapy" after chemotherapy. This practice requires patients to return to infusion centers for additional doses of the drug, typically one dose every three months for two years for a total of eight doses or four weekly doses every six months for two years for a total of sixteen doses. At $4,500 per dose, maintenance therapy adds between $36,000 to $72,000 to the cost of chemotherapy.

Furthermore, side effects and complications, though they vary, can often be expensive to the provider and life-threatening to the patient, as evidenced by the expenses of Betsy de Parry shown in Appendix II ($36,929.50 for radioimmunotherapy, $162,409.72 for chemotherapy and complications – in a period of one year).

It is also worth noting that bone marrow transplantation (BMT) or stem cell transplantation (SCT) are options for patients who no longer respond to chemotherapy, but these are high risk treatments and are not appropriate for all patients. Additionally, they are very expensive, with estimates ranging from $80,000 to $150,000,[11] and while these treatments can be effective, they have a significantly higher mortality risk.

Importantly, they are often contraindicated in older patients, the population most dependent on Medicare.

RADIOIMMUNOTHERAPY IS COST-EFFECTIVE: Indeed, recent studies show that radioimmunotherapy is cost-effective. A group studying Bexxar concluded that the treatment implies a possible survival gain and is favorably cost-effective compared to alternative strategies, including the Rituxan maintenance regimen.[12]

Swiss[13] and German[14] studies have likewise concluded that radioimmunotherapy is cost-effective when compared to alternative treatments, noting that the initial cost is higher but that superior response rates reduced the frequency of treatment by increasing the periods of remission, and thus the cost per disease-free year was lower.

ALTERNATIVES TO RIT MAY BE MORE EXPENSIVE: At a cost of about $30,000 for a single one week treatment, we recognize that radioimmunotherapy may seem expensive. However, when compared to common, alternative treatments in which Rituxan is included, the cost is actually less, as we have shown. And because radioimmunotherapy produces longer remission periods, its approximate cost of $30,000 diminishes with each year of remission and thus reduces Medicare's financial burden.

Clearly, the overall cost per patient increases with the frequency of treatment, so it may be both practical and advantageous to utilize treatments which induce remissions for the longest periods of time. Remission periods induced by radioimmunotherapy are often measured in years, during which treatment costs are reduced to zero. We also note that if relapsing patients have no access to RIT as a result of the Final Rule, they will still require treatment and that their alternatives may be less effective and more costly.

Therefore, adequate reimbursement for Bexxar and Zevalin is logical, appropriate and may actually be cost-saving.

III. THE BEXXAR® THERAPEUTIC REGIMEN AND THE ZEVALIN® THERAPEUTIC REGIMEN AS APPROVED BY THE FDA

The BEXXAR® Therapeutic Regimen and the ZEVALIN® Therapeutic Regimen belong to a class of medicine known as radioimmunotherapy (RIT) which combines a monoclonal antibody with a radiolabeled antibody. The purpose of its combined components is therapeutic.

Bexxar and Zevalin are unique treatments. They are the first – and only – drugs ever to be approved by the FDA in this class of medicine.

As approved by the FDA, treatment with Bexxar and Zevalin consists of two steps requiring administration over a period of up to fourteen days, and each step includes delivery of a monoclonal antibody (without a radioisotope label) plus a radiolabeled monoclonal antibody. The non-radioactive antibody is given just prior to the radioactive antibody to improve the targeting of the radioactive antibody to tumor sites and to more effectively activate immunological killing of tumor cells.

The monoclonal antibodies are:

For Bexxar: tositumomab
For Zevalin: rituximab.

The radiolabeled components are:

For Bexxar: Iodine-131 tositumomab
For Zevalin: Yttrium-90 ibritumomab tiuxetan.

The FDA approval considers all components of both treatments as a single course of therapeutic treatment, as shown below with CMS codes in parentheses:

BEXXAR® Therapeutic Regimen, as approved by the FDA, consists of the following components administered in two steps:

Step 1, Day 1: 2 components

1. Tositumomab (G3001, classified by CMS as Admin and Supply)
2. Iodine-131 tositumomab (A9544, classified by CMS as Iodine I-131 tositumomab, diagnostic)

Step 2, Day 7 (up to Day 14): 2 components

1. Tositumomab (G3001, classified by CMS as Admin and Supply)
2. Prescribed therapeutic dose of Iodine I-131 tositumomab (A9545, classified by CMS as Iodine I-131 tositumomab, therapeutic)

ZEVALIN® Therapeutic Regimen, as approved by the FDA, consists of the following components administered in two steps:

Step 1, Day 1: 2 components

1. Rituximab
2. In-111 ZEVALIN (A9542)

Step 2, Day 7 (up to Day 9): 2 components

1. Rituximab
2. Y90 ibritumomab (A9543, classified by CMS as Y90 ibritumomab, therapeutic)

Nuclear scans are performed between Steps 1 and 2 in both treatments. In the case of Zevalin, they are performed to ensure that the radioactive antibody is being properly distributed in the body and that Y-90 ibritutomab used in Step 2 will be given safely.

In the case of Bexxar, the scans not only show how the radioactive antibody is being distributed, but also how much radioactivity is in the patient at any given time. By quantifying this and determining the rate of clearance, a patient-specific dose of I-131 tositumomab for Step 2 is then calculated.

IV. CODING AND PAYMENT ISSUES FOR BEXXAR AND ZEVALIN

The fact that these drugs are unique may make them more difficult to categorize and thus to reimburse appropriately. However, as single therapeutic regimens, with components, it is our belief that they should not be split into parts for reimbursement purposes, but should be paid for as the single therapeutic regimens that they are, per the FDA approval and standard clinical practice.

However, under the CY2008 Final Rule, the components of Bexxar and Zevalin have been split up, using different methodologies for each component.

1. In the case of Bexxar, tositumomab (the monoclonal antibody used in Steps 1 and 2) is classified as a supply. We note that Rituxan is not classified as a supply when used as part of the ZEVALIN® Therapeutic Regimen.

2. The dosimetric (radiolabeled antibody) dose of Bexxar (A9544) and Zevalin (A9542) has been "packaged" with the nuclear scans for payment under "tumor imaging scans" (78804). Thus the dosimetric dose used in Step 1 is classified by CMS as a diagnostic radiopharmaceutical, which is generally used for medical diagnostic purposes and is different from radioimmunotherapy, which is therapeutic.

Additionally, CMS classifies the dosimetric dose of Bexxar (A9544) and the imaging dose of Zevalin (A9542) as "diagnostic," which is inaccurate. Patients have already been diagnosed. The purpose of the dosimetric dose is to assess the biodistribution of the imaging agent or to calculate the correct dosage of the therapeutic dose.

Several experts and professional organizations agree, including the American Society For Therapeutic Radiology and Oncology (ASTRO) which stated, "Zevalin and Bexxar therapies involve in part the intravenous administration of two distinct radiolabeled components on different days. The initial administration uses a lower level of radioactivity. It is used to assess the biodistribution of Zevalin or to calculate the therapeutic dose of Bexxar. For both products, a nuclear scan is performed after this administration; perhaps this is why CMS considers this component of therapy to be diagnostic. However, the scans are not truly diagnostic because the patient's diagnosis of non-Hodgkins lymphoma is already known. Rather, this component of radioimmunotherapy is an integral part of the FDA-approval therapeutic regimen. It represents the initiation of therapy, not the diagnosis of disease. The primary purpose of every component and step of radioimmunotherapy is therapeutic, not diagnostic."[15]

We note that the consequence of packaging the dosimetric dose with the nuclear scans is inadequate payment for this component of the treatment.

3. As we understand CY2008 Final Rule, the reimbursement rates for the radiolabeled component used in Step 2 of Bexxar and Zevalin are based on 2006 hospital claims data. Our concern is that CMS acknowledges that many claims were incorrectly submitted and some represented unusually low costs. In fact, the mean unit cost, as reported in the 2006

Outpatient Department Prospective Payment System (OPPS) claims data, starts at $16.57 (dx) and $4.34 (rx) for Bexxar and $37.27 (dx) and $4.77 (rx) for Zevalin, which are unrealistically low estimates of cost, and thus calls into question the validity of the calculated CMS payment rate to hospitals.

The agency also acknowledges that some claims were "incorrectly coded"[16] and thus "unlikely to represent claims for treatment with the products described as A9543 (Zevalin) and A9545 (Bexxar)."[17] Although CMS removed these "likely incorrectly coded claims in the ratesetting process,"[18] our concern is that CMS could not possibly be sure which claims were coded correctly and which were not, unless each reporting hospital were audited, which they were not. Using data that was known to be flawed, the new rate could not have been set accurately. Furthermore, the new rate penalizes those hospitals which did report correctly.

The resulting low payment based on faulty data led to Congressional intervention, but a permanent solution must be found.

PATIENT CONCERNS ABOUT MISCLASSIFICATION AND UNDER-PAYMENT: Regardless of how these products are coded or classified, patients are concerned only that inadequate payment will deny access to radioimmunotherapy, which is often the only option we have when chemotherapy no longer works. Surely, inadequate payment will force hospitals to choose between subsidizing or abandoning the treatment, and the latter seems more likely, a fear that has been echoed by numerous individual experts as well as clinical organizations.

In the Final Ruling, CMS disputes this fear, saying that "given that the Medicare population is such a dominant portion of the population to which these services are targeted, we do not believe that hospitals will cease to provide the service."[19] With all due respect, how does CMS expect hospitals to provide this service for which they will lose thousands of dollars per patient?

Additionally, CMS warns that "under 42 CFR 489.53(a)(2), CMS "may terminate the provider agreement of any hospital that furnishes this or any other service to its patients but fails to also furnish it to Medicare patients who need it."[20] Surely no hospital will jeopardize its provider agreement. Thus, if Bexxar and Zevalin are unavailable to Medicare patients, they will be unavailable to everyone else.

PROPOSED SOLUTIONS: We suggest the following as possible solutions:

- Effective immediately, CMS should separate the dosimetric doses from the nuclear scans and fully reimburse for this component.

- CMS must use a more accurate methodology than claims data to determine the true cost of these drugs. We note that respected organizations such as the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) have recommend the use of Average Sales Price (ASP).

- CMS should treat the entire Bexxar and Zevalin Therapeutic Regimens as a single therapeutic regimen, per FDA approval and standard clinical practice.

- Finally, any reimbursement solution should apply a single methodology to all components of these regimens, per FDA approval and standard clinical practice.

V. IMPLICATION OF FINAL RULE ON OTHER THERAPIES

Targeted, personalized therapy is the future for improving treatment for many kinds of cancers as well as other diseases. Patients with lymphoma are already benefiting from targeted, personalized therapies with the FDA-approved radioimmunotherapy drugs Bexxar and Zevalin, the very first in this class of medicine. These drugs are setting new standards for new and improved treatments for many types of illnesses.

If CMS chooses to default to the Final Rule after June 30, 2008, it will undoubtedly condemn these life-saving drugs to medical history, thereby creating a disturbing disincentive for the development of future innovative therapies, a fear that has been voiced by the American Society of Hematology, the American Society of Clinical Oncology, and by other clinical organizations and well-respected researchers.[21]

These two FDA-approved drugs represent major advances in the treatment of lymphoma, and among all cancer drugs, they are the only ones which are administered in a period of only one week. If CMS does not fully reimburse for these drugs, long term and devastating consequences are already being predicted by experts within the scientific community. Much worse, failing to support radioimmunotherapy will surely delay or halt promising therapies for many types of illnesses and condemn some patients to premature deaths.

We note that Bexxar and Zevalin were developed in large part with NIH/NCI funding and so they represent a true achievement, not only in translating science to practice, but also in using tax dollars to do so. For this reason, we urge CMS to complement the work of its sister agencies so that all Americans will have the opportunity to benefit from their work.

Therefore, we also urge CMS to recognize that the Final Rule has implications that far exceed its impact on lymphoma patients.

VI. SUMMARY

The role of radioimmunotherapy in the treatment of lymphoma is vital to the survival of patients, as we know from first hand experience.

From the standpoint of cost-effectiveness, radioimmunotherapy will relieve, not contribute to, the cost of health care. Both patients and providers benefit because RIT:

- Has very high response and complete response rates
- Can induce durable remissions even in patients with chemo-resistant disease, thereby extending periods of time during which no money is spent
- Has curative potential
- Can reverse the downward pattern of decreasing response to chemotherapy and shorter response times
- Is often easier on the patient to receive and tolerate than chemotherapies
- Is an option for patients who cannot tolerate other therapies
- Has the shortest period of administration of any cancer treatment – one week
- Does not cause hair loss
- Causes fewer infectious complications that require costly intervention
- Rarely causes nausea or vomiting

Ideally, therapies should be based on what our physicians deem most appropriate and likely to meet our clinical needs. In the case of radioimmunotherapy, a therapy which has life-saving potential for patients and is cost-effective for providers, it would be tragic to lose this option at all, let alone because CMS arrived at the Final Rule based on erroneous claims data and a misunderstanding and miscoding of the components of the treatment.

We respect that the Final Rule was well intentioned, but we fear that it will have long term and devastating consequences if allowed to take effect. We therefore urge CMS to immediately recognize and classify Bexxar and Zevalin as therapeutic regimens and to fully reimburse for these treatments, both until and after the current legislation expires on June 30, 2008. Lives are depending on it.

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APPENDIX I

ABOUT PATIENTS AGAINST LYMPHOMA (PAL)
www.lymphomation.org

Independent of health industry funding, PAL is a non-profit organization founded in 2002 by patients and caregivers, with a focus on providing the following:

- **Patient and caregiver support:** We moderate online support groups, focusing on providing support, sharing evidence-based information about lymphomas and its treatments with an emphasis on helping subscribers to critically assess medical information and sources.

  Forum subscribers: 1,900 subscribers as of Feb 1, 2008, in six support forums.

  Importantly, we ask for no identifying information of visitors who use our tools or content.

  Lymphomation.org usage for 2007: 12.8 million hits; 2.9 million page views, according to independent server statistics.

- **Education:** We provide comprehensive information on our website on all aspects of lymphomas based on visitor and support group questions.

  Guided by the medical literature and our medical advisors, we develop content on all aspects of lymphomas and its treatments as well as links to evidence-based resources.

  We also provide a Clinical Trial Locator service for helping patients or oncologists to efficiently locate lymphoma studies and identify trials of interest.

  Day or night, and without leaving home, patients can find answers in total privacy and without concern about asking a "dumb" question.

- **Advocacy:** We are liaisons between patients, researchers, the public, and sometimes our elected representatives; for example, providing patient perspectives on ethical clinical trial design, and the need for standardized biorepository centers serving efficient translational research.

For example, we are active participants in the FDA Patient Consulting Program and the NCI Biorepository Best Practices programs.

APPENDIX II

BETSY de PARRY
HISTORY OF DISEASE AND TOTAL TREATMENT COST*
*From actual bills paid by my insurance company

January 2002: Diagnosed with follicular lymphoma, stage IV. Bexxar and Zevalin were under FDA review. Chemotherapy was my only option.

April 2002: I entered a clinical trial using 8 rounds of CVP followed by a vaccine six months after treatment if I stayed in remission. CVP was suspended after two rounds because the disease was not responding.

Cost of 2 rounds of CVP:	$ 3,999.24
Note: Total cost for 8 rounds would have been $15,996.96	

May through July 2002: Next came R-CHOP, but it, too, was suspended after 4 of the planned 8 rounds because my disease was refractory to that as well.

Cost of 1 round of CHOP without Rituxan	$ 2,015.46
Cost of rounds 2 through 4 R-CHOP	$25,195.89
Note: Each round of R-CHOP was $8,398.63. Therefore, the additional 4 rounds would have cost another $33,594.52, making the total cost of this treatment $60,805.87.	

COST OF CHEMOTHERAPY:	$ 31,210.59

During these treatments, many side effects and complications had to be treated, some of which required hospitalization. There were also 5 CT scans at a cost of $18,488.88. Four of these could have been avoided had RIT been available and been used, for a total savings of $14,791.10.

COST OF DOCTOR VISITS, BLOOD TESTS, CT SCANS, HOSPITALIZATIONS, OTHER TESTS AND TREATMENT FOR SIDE EFFECTS AND COMPLICATIONS	$ 86,309.13

In August, when I became refractory to R-CHOP, Zevalin had been approved by the FDA but had not approved for payment by Medicare or insurance companies. Though my doctor felt that Zevalin was my best option, he also felt that my disease had been so resistant that a bone marrow transplant might become necessary. While writing a letter of medical necessity hoping to obtain Zevalin for me, a BMT donor was also sought.

COST FOR PRELIMINARY BONE MARROW TRANSPLANT SEARCH:	$ 44,809.00

In August 2002, my insurance company approved payment for Zevalin. The dosimetric dose was administered on 9/4/2002 followed by the therapeutic dose a week later, on 9/11/2002.

COST OF ZEVALIN THERAPEUTIC REGIMEN:*	$ 36,929.50
*Includes cost of drugs, all visits to doctor, scans and tests associated with treatment Cost of Zevalin alone was $25,762.	

TOTAL TREATMENT COST:	$199,339.22

NOTE: I have had no additional treatment since September 2002. My remission period is currently 5 years 5 months.

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