Patients Against Lymphoma

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9/11/2007

The Honorable Herb B. Kuhn
Deputy Administrator
Centers for Medicare and Medicaid Services (CMS)
Department of Health and Human Services
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, DC 20201

Re: CMS-1392-P - Proposed reimbursement rates for Radioimmunotherapy: Bexxar (I131 tositumomab) and Zevalin (Y90 ibritumomab)

Dear Administrator Kuhn:

Patients Against Lymphoma is a non-profit organization, independent of health industry funding. In this letter we are representing the concerns of many lymphoma survivors and their loved ones[i] regarding proposed CMS payment policies for radioimmunotherapy (RIT) agents (Bexxar and Zevalin), administration, and supply.[ii]

As shown in the enclosed chart [iii], the proposed reimbursement for Bexxar (I131Tositumomab) is regrettably less than half its cost, which causes hospitals to lose money, which if approved would force hospitals to subsidize its use, which is highly unlikely.

These are our main concerns about proposed reimbursement rates for RIT for patients with life-threatening lymphomas:

- **It will limit patient access to highly effective radioimmunotherapy** [iv] by creating a strong disincentive to prescribe it.
- **It will exacerbated the "disuse"**[1] **of RIT**, contributing to **lost opportunities**[v] for patients to live longer and better with lymphomas.
- **It will contribute to the termination of radioimmunotherapy** in the near future.[1, vi]
- **It will be a strong disincentive for companies to develop novel therapies for lymphomas and other cancers in future**.

[1] Market Forces Cited in Lymphoma Drugs' Disuse - New York Times | Journal of the National Cancer Institute, Volume 99, Issue 7, April 4, 2007
http://www.nytimes.com/2007/07/14/health/14lymphoma.html?ei=5070&en=842431405e3dca74&ex=1188100800&pagewanted=all

We agree with Dr. Mark Kaminski, [2] a principal inventor of radioimmunotherapy, that the low payment policies for RIT will have a *"devastating"* effect on lymphoma patients living with the disease today, on future patients, and on cancer research in general – creating a **domino effect**[vi] described in the appendix.

The need: Each person's lifetime risk of developing a lymphoma is approximately 1 in 50. Presently, in the United States about 500,000 individuals live with the disease. [3] Most, but not all lymphomas are of the b-cell type, which carries the target receptor for currently approved RIT.

The proven importance of RIT: Radioimmunotherapy is a targeted antibody-based treatment that more selectively binds to cancer cells and delivers radioactive isotopes, which kill the tumor cells.

It combines radiotherapy with immunotherapy, which may explain both the potency and the long duration of benefit that is often achieved and measured in years. [iv] Indeed, RIT therapeutics are the *most potent and effective therapeutic agents ever invented for lymphoma*, and arguably for any cancer:

> Dr. Bruce Cheson – an internationally recognized expert on lymphomas and long-standing former member of the FDA Oncological Drug Advisory committee – recently stated:
>
> *"RIT is the most effective, least used treatment in oncology. "Companies are both losing money. Done once, it's over. 70-80% CR (complete response rates); up to half the patients depending on the context. It's easily tolerated, but you can't sell it. .... Reasons you can't do it?" Complicated, but mainly: Requires the oncologist to send the patient somewhere else to get treatment."* [4]

Also, in order to highlight the impact of RIT:

> *"In clinical trials of Bexxar, objective response rates ranged from 54%-71% in heavily pretreated patients. In the pivotal trial, the number of patients with a longer duration of response after treatment with Bexxar was significantly greater than the number of patients with a longer duration of response after their last qualifying chemotherapy regimen. In 76 newly diagnosed patients, the objective response rate was 97%, and 63% of patients achieved complete responses."*
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> *Bexxar: novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-*

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[2] Letter to CMS from Dr. Mark Kaminski dated 10/10/2006

[3] SEER FastStats
http://seer.cancer.gov/faststats/sites.php?stat=Incidence&site=Non-Hodgkin+Lymphoma&x=10&y=12

[4] Follicular Lymphomas, Dr. Bruce Cheson, LRF Education Forum - 2006
http://www.presentme.com/FLASH/20061027LRFCheson/

Hodgkin's lymphoma. Oncologist. 2004;9(2):160-72. Review. PMID: 15047920 See for details and other study findings below. [iv]

It's worth noting that RIT is many times an alternative to more expensive and higher-risk stem cell transplantation[5] (SCT), which can be effective but has a significantly higher mortality risk and a greater negative impact on quality of life. Importantly, SCT is often contraindicated in older patients – which is the population most dependent on Medicare.

So we urge the leadership within CMS to *reconsider* the "mean unit methodology" for determining payments to hospitals for RIT in order to safeguard and utilize a proven effective treatment for patients in need, as outlined in the appendix [viii]

In summary:

Low payment rates to hospitals for RIT sets a dangerous and disturbing precedent that:

- **Would increase pain, suffering, and loss of life.**

  Real people, such as my spouse as well as the undersigned,[i] and many thousands more may lose the opportunity to benefit from RIT in order to live longer and better, to provide for themselves and their families and to contribute to society.

  The alternative to RIT will many times be death, or rescue via less effective or higher-risk therapy and more expensive in-patient treatments, such as Stem Cell Transplantation.

- **Would limit a physician's ability to prescribe a highly effective therapy today**

  A well-established body of literature clearly shows that RIT is highly effective yet underutilized; and that RIT can induce *durable complete responses* in a sizable percentage of patients refractory to chemotherapies.

- **Could lead to the termination of radioimmunotherapy in the near future.**

  These drugs are already at a financial disadvantage because oncologists must refer patients to nuclear medicine physicians or radiation oncologists and thus oncologists are more likely to prescribe drugs which they can administer.

  CMS statistics on usage already shows that these agents are rarely prescribed in relation to other protocols that are not as effective. [ix]

  The marketplace difficulties faced by both Bexxar and Zevalin have both been well documented in national press, including a recent feature in the NY Times and JCNI.

  Coupled with the referral problem, many experts and advocates believe that the proposed reimbursement will spell the end of these drugs.

- **Would be a disincentive for the pharmaceutical industry to develop new cancer drugs.**

[5] Blood and marrow transplantation compensation: perspective in payer and provider relations. Biol Blood Marrow Transplant. 2004 Jul;10(7):427-32. Review. PMID: 15205664

As you know, developing and testing new cancer drugs is high risk, time-consuming, and expensive process. Recent estimates show the cost may be as high as $900 million to develop and assess a new cancer drug.

We need to adopt policies that will make companies more willing to take the considerable financial risks, not less willing, if we to make good on our society's commitment to wage war on cancers.

It's important to note and to fully consider that most new drugs don't win marketing approval. Thus, it's *essential* that sponsors who succeed in developing urgently needed drugs for cancer benefit financially.
Profit incentive drives innovation and sustains the *"war against cancers",* diseases that takes such a mighty toll on Americans each year. [x]

<u>The reporting system does not lend itself to stakeholder participation and comments:</u>

- **The <u>people affected by cancer</u> and their loved ones, <u>are the primary stakeholders</u>, as are patients who will be diagnosed in future (the public).**

  As patients and caregivers of cancer patients, we respectfully request that CMS consider evaluating and modifying the manner in which regulatory information is conveyed. As a group, we include individuals well versed in medical terminology and reading regulatory publications. Nonetheless, we hope it will be helpful to CMS to know that although we worked as a group, we found it extremely difficult to decipher the meaning and impact of the proposed regulations affecting reimbursement for Zevalin and Bexxar. It's our hope that CMS will modify the manner in which such information is conveyed in order for laypeople to comprehend the content and it's potential impact on our lives.

In closing, we cannot afford to ignore these issues or to be silent. Underpaying hospitals for costs of providing radioimmunotherapy is already having a negative impact on the level of care for patients with lymphoma, who now have an improving hope of conquering or better managing the disease and living normal, productive lives. We, as well as the undersigned [i] who share their concerns in the attachments to this letter, urge CMS to fully reimburse for the use of Bexxar and Zevalin.

We also urge CMS, the medical community, advocates, and our elected representatives, to work cooperatively in order to fully fund CMS and identify responsible ways to reduce health care costs in order to meet the urgent needs of cancer patients, present and future. Thank you for your attention to our concerns.

Respectfully,

Karl Schwartz (caregiver) President, Patients Against Lymphoma
Betsy de Parry (survivor)
Kate Corsmeier (caregiver) Esq.
Linda Gerstley (caregiver) Ph.D.

cc: our representatives

Appendix i – ix (details and references)

[i] *The public outcry against the proposed cuts is further evidenced by the fact that this letter was endorsed by more than **1,500 citizens** representing every region of the United States in the very short time period of approximately **14 days** since we learned about this issue. Among the names are **physicians who specialize in treating lymphoma patients**, which validates and reinforces our concerns.*

The confidential list has been mailed separately because of the privacy concerns of some patients.

[ii] **Federal Register / Vol. 72, No. 148 / Thursday, August 2, 2007 / Proposed Rules**
http://www.cms.hhs.gov/QuarterlyProviderUpdates/downloads/cms1392p.pdf

Proposed mean cost for Bexxar: 8,283.41 and Zevalin: 12,030.02 (page 42740)

pg 42740 / 42845
A9545 . I131 tositumomab, rx 1645 ..... K ..... 8,283.41 (Proposed CY 2008 mean cost/payment rate)
A9545 I131 tositumomab, rx 1645 ..... K ..... 8,283.41 (Proposed CY 2008 mean cost/payment rate)

Pg 43035
G3001 ..... Admin + supply, tositumomab $1,925.11 (Proposed CY 2008 payment rate)

[iii] **Table: Estimated Cost versus Reimbursement - produced by Patients Against Lymphoma**

COMPARISON OF COST TO PROPOSED REIMBURSEMENT FOR I131TOSITUMOMAB

	COST	PROPOSED REIMBURSEMENT	LOSS
DOSIMETRIC DOSE*			
DOSE 1	$2,188.75	$1,925.11	$263.64
DOSE 2	$2,188.75	$1,925.11	$263.64
DIAGNOSTIC (DX) DOSE**	$2,317.50	$1,022.88	$1,294.62
THERAPEUTIC (RX) DOSE	$20,085	$8,283.41	$11,801.59
COMPOUNDING	$3,000	$0.00	$3,000.00
TOTAL	**$29,780.00**	**$13,156.51**	**$16,623.49**

*Categorized as Admin and Supply
**Categorized as Tumor Imaging, Whole Body

[iv] **Select RIT Abstracts – highlighting the ability of RIT to induce durable remissions**

* **Bexxar radioimmunotherapy for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience.**
Blood. 2000 Aug 15;96(4):1259-66. PMID: 10942366

"*For all 42 responders, the median progression-free survival was 12 months, 20.3 for those with CR. Seven patients remain in CR 3 to 5.7 years. Sixteen patients were re-treated after progression; 9 responded and 5 had a CR. Reversible hematologic toxicity was dose limiting."*

**** Targeted Radio-Immunotherapy with Bexxar Produces Durable Remissions in Patients with Late Stage Low Grade Non-Hodgkin's Lymphomas.***
Trans Am Clin Climatol Assoc. 2004;115:255-72. PMID: 17060972

"Response rates were 56% (overall) and 30% (complete). With a median follow-up of 44.6 months, 30% of the patients achieved a long-term, durable response; median time to progressive disease or death was 5 years. Bexxar radioimmunotherapy for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood. 2000 Aug 15;96(4):1259-66. PMID: 10942366 | Related abstracts

For all 42 responders, the median progression-free survival was 12 months, 20.3 for those with CR. Seven patients remain in CR 3 to 5.7 years. Sixteen patients were re-treated after progression; 9 responded and 5 had a CR. Reversible hematologic toxicity was dose limiting.

* ***Efficacy and safety of Bexxar in B-cell lymphoma, progressive after rituximab.***
J Clin Oncol. 2005 Feb 1;23(4):712-9. Epub 2004 Dec 21. PMID: 15613695

the OR and CR rates were 86% and 57%. Estimated 3-year Progression Free Survival (PFS) in this subgroup was 48%, compared with 11% for all others (P = .002).
Transient grade 3 to 4 marrow toxicity was seen in 50% of patients. Two patients, one of whom received two subsequent chemotherapy regimens, developed secondary myelodysplasia.

CONCLUSION: (131)I tositumomab is effective in CD20-positive lymphoma progressive after rituximab, with a 65% OR rate and median Progression Free Survival (PFS) of 24.5 months for responders. Patients with follicular grade 1 or 2 histology and tumors < or = 7 cm achieved very high OR and CR rates, with 48% PFS at 3 years."

* **Bexxar: novel radioimmunotherapy for the treatment of low-grade and transformed low-grade non-Hodgkin's lymphoma. Oncologist.** 2004;9(2):160-72. Review. PMID: 15047920

In clinical trials of Bexxar, objective response rates ranged from 54%-71% in heavily pretreated patients. In the pivotal trial, the number of patients with a longer duration of response after treatment with Bexxar was significantly greater than the number of patients with a longer duration of response after their last qualifying chemotherapy regimen. In 76 newly diagnosed patients, the objective response rate was 97%, and 63% of patients achieved complete responses.

** A clinical and scientific overview of tositumomab (Zevalin) and iodine I 131 tositumomab (Bexxar). Semin Oncol. 2003 Apr;30(2 Suppl 4):22-30. Review. PMID: 12728404*

"these studies show that tositumomab and iodine I 131 tositumomab treatment is safe and induces high response rates and durable remissions in heavily pretreated patients with low-grade or transformed low-grade NHL"

* **Tositumomab (Zevalin) and iodine-131 tositumomab (Bexxar) produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas.** J Clin Oncol. 2005 Oct 20;23(30):7565-73. Epub 2005 Sep 26. PMID: 16186600

Response rates in the five trials ranged from 47% to 68%; CR rates ranged from 20% to 38%.

"With a median follow-up of 5.3 years, the 5-year progression-free survival was 17%. Eighty-one (32%) of 250 patients had a time to progression of > or = 1 year (termed durable response population). For the durable response population, 44% had not progressed at > or = 2.5 to > or = 9.5 years and had a median duration of response of 45.8 months.

The median duration of complete response was not reached. The durable response population had many poor prognostic characteristics, including bone marrow involvement (41%), bulky disease > or = 5 cm (49%), and transformed histology (23%). Forty-three percent of the patients had been treated with more than four prior therapies and 36% had not responded to their most recent therapy."

* **Zevalin radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma.** Clin Lymphoma. 2004 Sep;5(2):98-101. PMID: 15453924

"In patients achieving a CR/CRu, the median TTP was 24.7 months for patients treated with 90Y ibritumomab tiuxetan compared with 13.2 months for rituximab-treated patients (P = 0.41), and ongoing responses of > 5 years have been observed.

** Durable responses after ibritumomab tiuxetan radioimmunotherapy (Zevalin) for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. Blood. 2004 Jun 15;103(12):4429-31. Epub 2004 Mar 11. PMID: 15016644*

"Nine patients (24% of responding patients) had a TTP of more than 3 years. Long-term responders (> 5 years) have been identified."

* **Leonard JP, Zelenetz AD, Vose JM, et al. Iodine I 131 tositumomab (Bexxar) for patients with low grade or transformed low grade NHL: complete response data.** Blood. 2000;96(suppl 1):728a. Abstract 3148.

"*Summary data on 251 patients treated on various phase 1 to 3 tositumomab trials from 1990 to 1999. Those characteristics statistically associated with a lower probability of achieving CR include bulky disease, prior chemotherapy, lack of response to last chemotherapy, and prior radiotherapy.*

Nonetheless, CR rates of 30% (confirmed) to 35% (not confirmed) may be expected in the group as a whole, with 3-year median duration of CR in those without confirmed CR and almost 5 years in those with confirmed CR status."

[v] Lost opportunities:

For patients – the primary stakeholders – the low payment rates to hospitals for RIT have almost certainly led to lost opportunities to live longer and better with lymphomas.

This assertion is strongly suggested by the durable remissions resulting from RIT, among patients with advanced disease, refractory to standard chemotherapy in clinical trials. [iii]

Notably, the remissions from RIT can last many years - a sizable number of very durable remissions suggesting that some of these patients may even be cured.

[vi] The domino effect:

We submit that the concerns expressed by leading investigators, patient advocates, and industry organizations about the future of RIT are already taking place in part because of market factors influenced by CMS payment policies.

The domino effect:
(A) **hospitals lose money when RIT is prescribed**,
(B) leading physicians to prescribe it less often,
(C) reducing sales; and causing the companies to lose money.", [3,vi]
(D) leading the companies to consider discontinuing, or trying to sell, the drugs, [vi]
(E) resulting in fewer patients having the opportunity to benefit from highly effective RIT therapy,
(F) leading to a disincentive for other companies to develop novel targeted drugs for any cancer.

[vii] CMS Table on <u>Minimum Unit Costs</u>

CMS1392P_Drug_Biologicals_and_radiopharmaceuticals_Median_File_REVISED_.xls

CY 2006 CPT/ HCPCS	CY 2006 Description	CY 2006 Days	CY 2006 Units	CY 2006 Min Unit Cost	CY 2006 Max Unit Cost	CY 2006 Mean Unit Cost
A9544	I131 tositumomab, dx	225	227	**16.57**	18,997.21	1,547.92
A9545	I131 tositumomab, rx	243	320	**4.34**	65,830.73	8,283.41
A9543	Y90 ibritumomab, rx	413	420	**4.77**	51,156.48	12,030.02

[viii] **Regarding CMS calculations:**

Since Zevalin's approval in 2002 and Bexxar's approval in 2003, CMS has classified the components of the treatment separately. For Calendar Year (CY) 2008, CMS proposes payment rates to hospitals for RIT agents, administration and supply based on *mean unit cost* as reported in the 2006 Outpatient Department Prospective Payment System (OPPS) claims data.

Standing out in our analysis is that the range from which the mean is calculated starts at 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** for radio pharmaceuticals, which also calls into question the validity of the calculated CMS payment rate to hospitals.

Whatever the basis for the mean costs by CMS – in both the therapeutic (rx) and diagnostic (dx) setting – the calculations, according to multiple reliable sources, results in substantial reimbursement reductions, resulting in payments to hospitals that "*are too low and inadequate*". *

* ASTRO letter to CMS: MS-1206-FC: Medicare Program; Changes to the Hospital Outpatient Prospective Payment System and Calendar Year 2003 Payment Rates https://www.astro.org/PublicPolicy/CommentLettersTestimonyAndReports/documents/cy03oppsfr1202.pdf

[ix] **CMS-1506-P Page 281:**

Units recorded by CMS ranged from 191 to 362 for CY2005 for tositumomab and Zevalin, respectively HCPCS codes: **C1080 = 249** units, **C0181 = 191** units , **C1083 = 362 units** in 2005

[x] **SEER** data Informs us that directly or indirectly almost every American family will experience cancer

1 in 3 men, 1 in 2 women will get a serious cancer.

In 2003 new cases topped 1.3 million, resulting in approximately 556,500 deaths in that year alone.