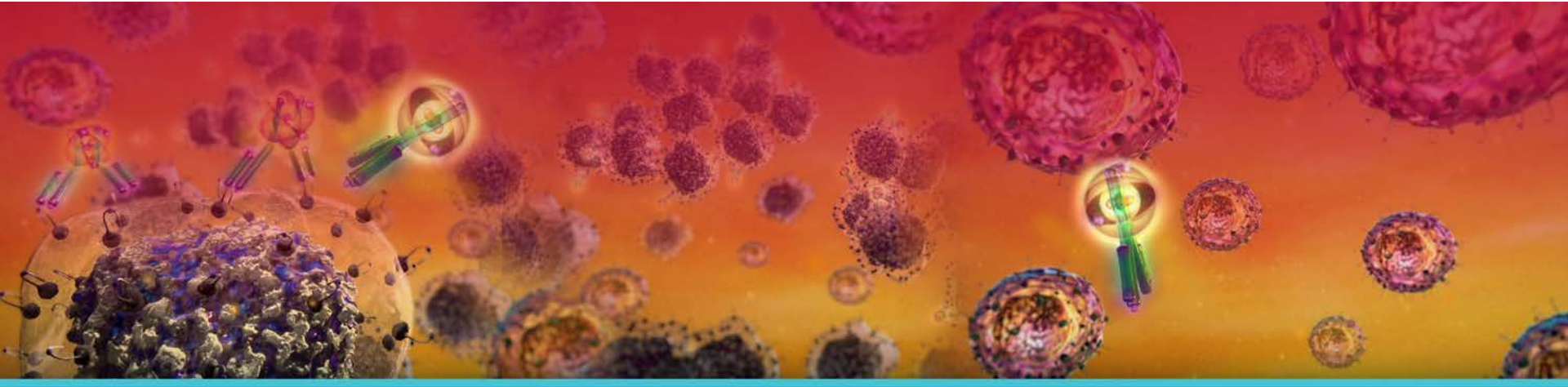

0133-049104

# ZEVALIN® (ibritumomab tiuxetan) Information for Authorized Users and Administration Facilities

**Please see slides 3-7 for BOXED WARNINGS and Important Safety Information.**

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**Please see full Prescribing Information available with this program, or Click Here.**

# Indications and Usage

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- ZEVALIN is a CD20-directed radiotherapeutic antibody administered as part of the ZEVALIN therapeutic regimen indicated for the treatment of patients with:

1. Relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL)

*OR*

2. Previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy

**Please see slides 3-7 for Important Safety Information, including BOXED WARNINGS.**
**Please see full Prescribing Information available with this program, or Click Here.**

ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Boxed Warnings

ZEVALIN®
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INJECTION FOR INTRAVENOUS USE

**WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS**

- **Serious Infusion Reactions:** Deaths have occurred within 24 hours of rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most (80%) fatalities occurred with the first rituximab infusion. Discontinue rituximab and Y-90 ZEVALIN infusions in patients who develop severe infusion reactions.
- **Prolonged and Severe Cytopenias:** Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. Do not administer Y-90 ZEVALIN to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve.
- **Severe Cutaneous and Mucocutaneous Reactions:** Severe cutaneous and mucocutaneous reactions, some fatal, can occur with the ZEVALIN therapeutic regimen. Discontinue rituximab and Y-90 ZEVALIN infusions in patients experiencing severe cutaneous or mucocutaneous reactions.
- **Dosing:** The dose of Y-90 ZEVALIN should not exceed 32.0 mCi (1184 MBq).

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Warnings and Precautions

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

## Risk of Developing Myelodysplastic Syndrome, Leukemia and Other Malignancies:

- The radiation dose resulting from therapeutic exposure to Y-90 radiolabeled ZEVALIN may result in secondary malignancies.
- Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to diagnosis of MDS or AML was 1.9 years following treatment with the ZEVALIN therapeutic regimen; however, the cumulative incidence continues to increase.
- Among 204 patients receiving Y-90-ZEVALIN following first-line chemotherapy, 26 (12.7%) patients in the ZEVALIN arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving ZEVALIN, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the ZEVALIN arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the ZEVALIN arm compared to no patients in the control arm.

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Warnings and Precautions, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Extravasation:** Monitor for extravasation and terminate infusion if it occurs. Resume infusion in another limb.

**Immunization:** Do not administer live viral vaccines to patients who have recently received ZEVALIN.

**Radionuclide Precautions:** During and after radiolabeling ZEVALIN with Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

**Embryo-fetal Toxicity:** May cause fetal harm if given during pregnancy.

**Impairment of Fertility:** There is a potential risk that the ZEVALIN® therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

**Nursing Mothers:** Patients should be advised to discontinue nursing during and after ZEVALIN treatment.

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Additional Important Safety Information

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**Adverse Reactions:**

**The most common adverse reactions of ZEVALIN are:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**Common adverse reactions (≥10%) in clinical trials:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**The most serious adverse reactions of ZEVALIN are:** prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

**Adverse Reactions for First-Line Patients:**

When administered following first-line chemotherapy, grade 3/4 adverse reactions of ZEVALIN include prolonged and severe cytopenias (thrombocytopenia [51%], neutropenia [41%], leukopenia [36%], lymphopenia [18%], and anemia [5%]) and secondary malignancies (12.7%).

Cytopenias were more severe and more prolonged among eleven (5%) patients who received ZEVALIN after first-line fludarabine or a fludarabine-containing chemotherapy regimen as compared to patients receiving non-fludarabine-containing regimens.

**Please see full Prescribing Information available with this program, or Click Here.**

ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Additional Important Safety Information, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Adverse Reactions for First-Line Patients (Continued):**

Grade 3/4 infections occurred in 8% of ZEVALIN-treated patients and in 2% of controls and included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, lower respiratory tract infection, sinusitis, and upper respiratory tract infection.

**Adverse Reactions for Relapsed or Refractory NHL Patients:**

Grade 3/4 adverse reactions of ZEVALIN in relapsed or refractory NHL patients include prolonged and severe cytopenias (thrombocytopenia [63%], neutropenia [60%], anemia [17%], and ecchymosis [<1%]) and secondary malignancies (5.2%).

Serious infections occurred in 3% of patients (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection).

Life-threatening infections were reported in 2% of patients (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis).

**Please see full Prescribing Information available with this program, or Click Here.**

ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Program Outline

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

- NHL overview
- Zevalin Structure and Mechanism of Action
- First line Efficacy and Safety Data in Follicular NHL
- Relapsed/Refractory NHL Safety and Efficacy Data in Follicular or Low Grade NHL
- Administration Information
- Radiation Safety
- Important Safety Information
- Support and Ordering

**Please see slides 3-7 for Important Safety Information, including BOXED WARNINGS.**
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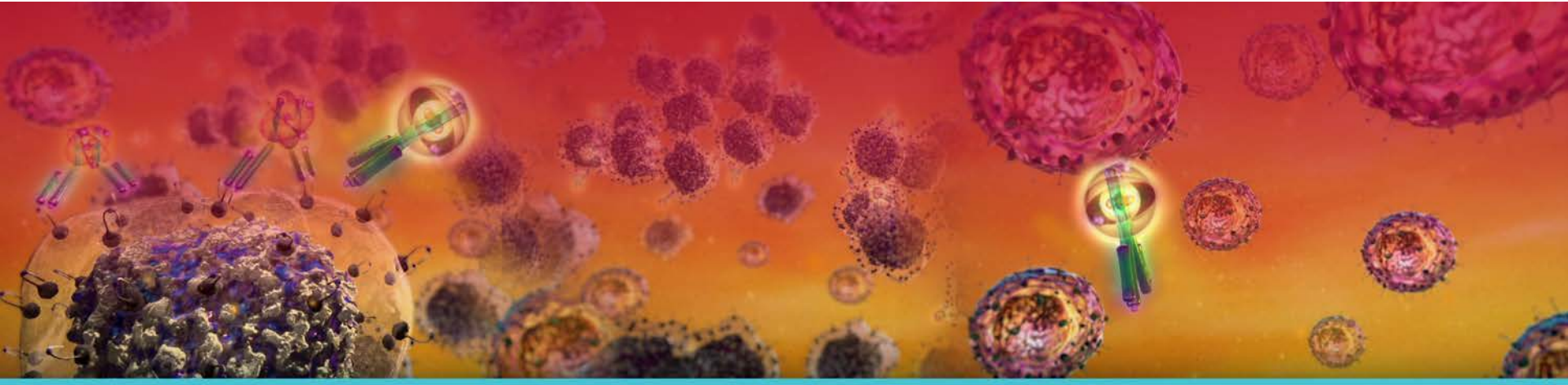


# Non-Hodgkin’s Lymphoma (NHL) Overview

# Non-Hodgkin's Lymphoma

- Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of B-cell, T-cell, and NK-cell neoplasms with differing patterns of growth and response to treatment.

- Treatment of NHL depends on histologic type, stage of disease, and patient characteristics.

**The Non-Hodgkin's Lymphoma Classification Project. Blood. 1997: 89:3909-3918.**

# Non-Hodgkin Lymphoma (NHL) Incidence

## Leading New Cancer Cases and Deaths – 2014 Estimates

| Estimated New Cases* | | Estimated Deaths | |
|---|---|---|---|
| **Male** | **Female** | **Male** | **Female** |
| Prostate<br>233,000 (27%) | Breast<br>232,670 (29%) | Lung & bronchus<br>86,930 (28%) | Lung & bronchus<br>72,330 (26%) |
| Lung & bronchus<br>116,000 (14%) | Lung & bronchus<br>108,210 (13%) | Prostate<br>29,480 (10%) | Breast<br>40,000 (15%) |
| Colon & rectum<br>71,830 (8%) | Colon & rectum<br>65,000 (8%) | Colon & rectum<br>26,270 (8%) | Colon & rectum<br>24,040 (9%) |
| Urinary bladder<br>56,390 (7%) | Uterine corpus<br>52,630 (6%) | Pancreas<br>20,170 (7%) | Pancreas<br>19,420 (7%) |
| Melanoma of the skin<br>43,890 (5%) | Thyroid<br>47,790 (6%) | Liver & intrahepatic bile duct<br>15,870 (5%) | Ovary<br>14,270 (5%) |
| Kidney & renal pelvis<br>39,140 (5%) | Non-Hodgkin lymphoma<br>32,530 (4%) | Leukemia<br>14,040 (5%) | Leukemia<br>10,050 (4%) |
| Non-Hodgkin lymphoma<br>38,270 (4%) | Melanoma of the skin<br>32,210 (4%) | Esophagus<br>12,450 (4%) | Uterine corpus<br>8,590 (3%) |
| Oral cavity & pharynx<br>30,220 (4%) | Kidney & renal pelvis<br>24,780 (3%) | Urinary bladder<br>11,170 (4%) | Non-Hodgkin lymphoma<br>8,520 (3%) |
| Leukemia<br>30,100 (4%) | Pancreas<br>22,890 (3%) | Non-Hodgkin lymphoma<br>10,470 (3%) | Liver & intrahepatic bile duct<br>7,130 (3%) |
| Liver & intrahepatic bile duct<br>24,600 (3%) | Leukemia<br>22,280 (3%) | Kidney & renal pelvis<br>8,900 (3%) | Brain & other nervous system<br>6,230 (2%) |
| All sites<br>855,220 (100%) | All sites<br>810,320 (100%) | All sites<br>310,010 (100%) | All sites<br>275,710 (100%) |

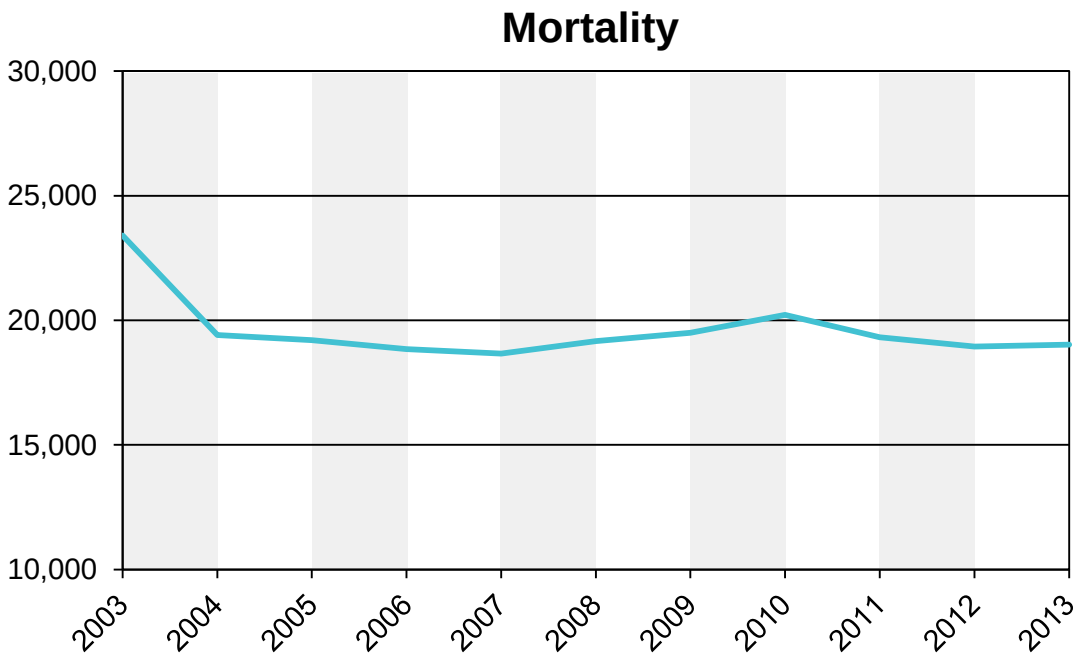
*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.



**1. American Cancer Society (ACS). Cancer Facts & Figures 2014. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index Accessed April 7, 2014.**

# NHL: Facts & Figures

- Though incidence has been stable over the past decade, NHL mortality has declined steadily.
- The ACS projects 18,990 NHL deaths in 2014[2] This number has been declining since 2002.



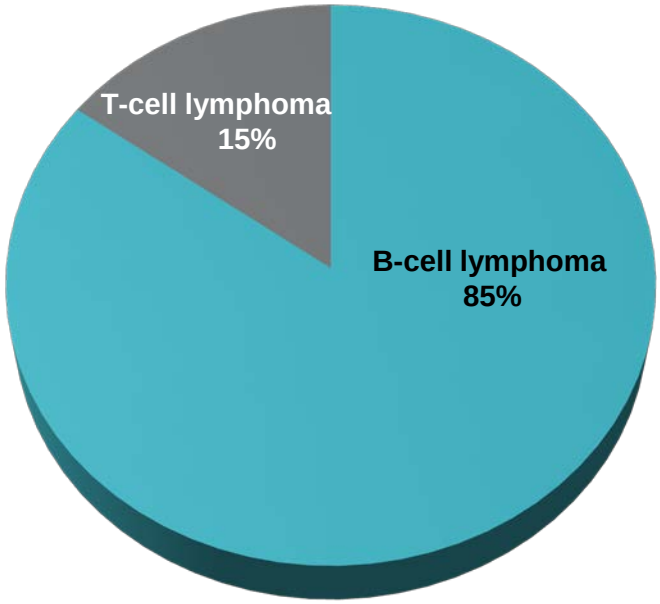


**1. National Cancer Institute (NCI). B-cell Lymphoma. http://www.cancer.gov/aboutnci/budget_planning_leg/plan-2013/profiles/lymphoma. Accessed April 7, 2014.**

**2. American Cancer Society (ACS). Estimated Cancer Cases & Deaths by State for 20 Cancer Sites. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041774.pdf. Accessed April 7, 2014.**

# NHL: Facts & Figures

**All NHL[1]**




- Lymphomas represent ~5% of all cancers diagnosed in the United States[1]
  - NHL represents the majority of these
- B-cell lymphomas account for 85% of all NHLs[2]
- 95% of NHL patients are adults, and approximately half are over 65 years of age[2]

1. American Cancer Society (ACS). Cancer Facts & Figures 2014. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/index Accessed April 7, 2014.

2. American Cancer Society (ACS). Types of NHL. http://www.cancer.org/cancer/non-hodgkinlymphoma/detailedguide/non-hodgkin-lymphoma-types-of-non-hodgkin-lymphoma Accessed April 7, 2014.

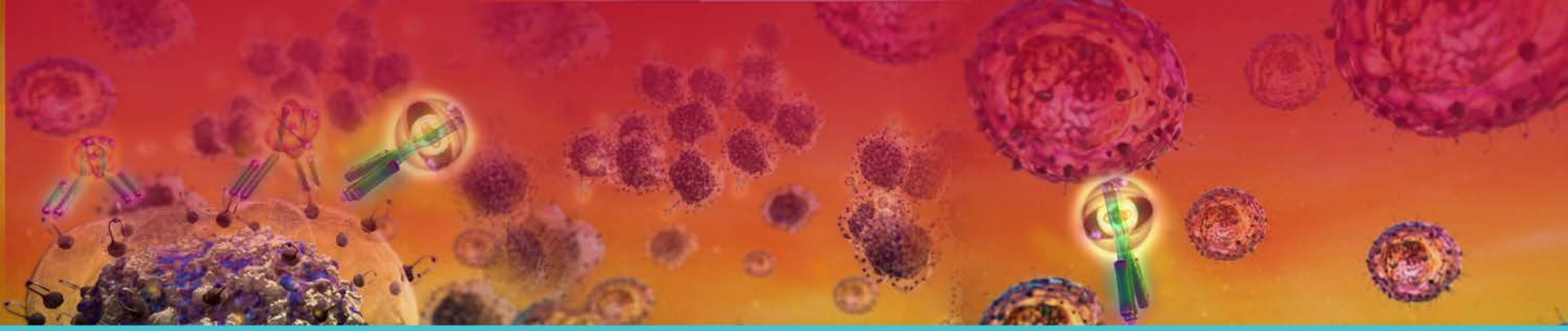
# Improving Outcomes in Follicular Lymphoma

- Ultimate Goal: To strive to improve progression free survival
  - As with other diseases, this may be accomplished through
    - Increasing response rates
    - Improving duration of response / progression free survival
- Approaches that may improve outcomes are:
  - “Consolidation” following initial tumor reduction
    - Radioimmunotherapy
    - High-dose chemotherapy/Transplantation
  - Development of new agents
  - Maintenance or extended dosing

# Treatment Options

- Watchful Waiting
- Chemotherapy
- Immunotherapy/Chemo-immunotherapy
- Radiation Therapy
- Radio-labeled Monoclonal Antibodies
- Stem Cell Transplantation
- Clinical Trials

**Understanding Non-Hodgkin's Lymphoma 3rd edition, 2010**



# What is ZEVALIN®?

## Structure and Mechanism of Action

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

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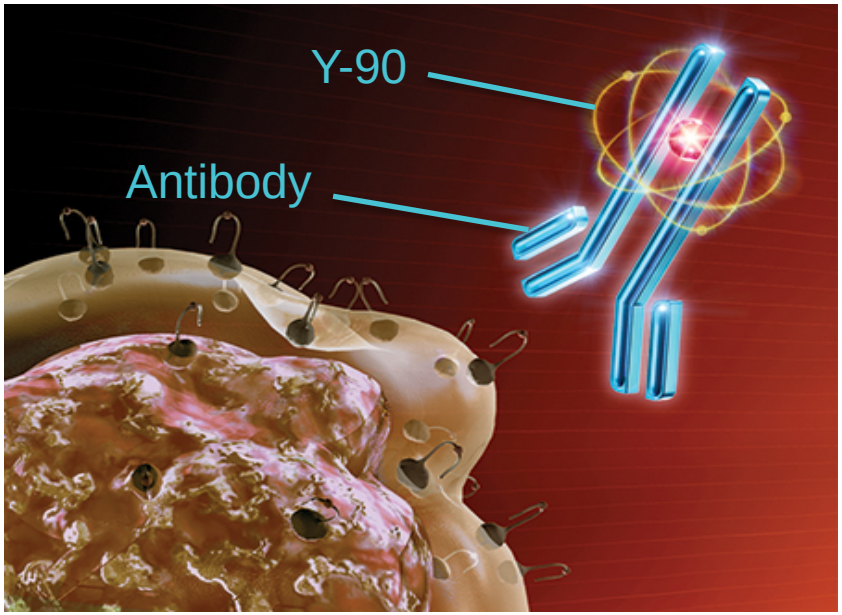
# What is ZEVALIN®?

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- Antibody[1,2]
  - Ibritumomab is a monoclonal antibody that targets the CD20 antigen found on >90% of B-cells
- Chelator
  - The chelate tiuxetan, which tightly binds Yttrium-90, is covalently linked to ibritumomab
- Radioisotope[1,2]
  - Yttrium-90 is the high-energy beta emitter in ZEVALIN




**Radionuclide Precautions:** During and after radiolabeling ZEVALIN with Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

**Please see slides 3-7 for Important Safety Information, including BOXED WARNINGS.**
**Please see accompanying full Prescribing Information associated with this program or Click here.**

1. Witzig TE, et al. *J Clin Oncol*. 1999:17(12):3793-3803.
2. Krasner C, et al. *Curr Pharm Biotechnol*. 2001;2(4):341-349.

# ZEVALIN® Mechanism of Action

ZEVALIN
(ibritumomab tiuxetan)
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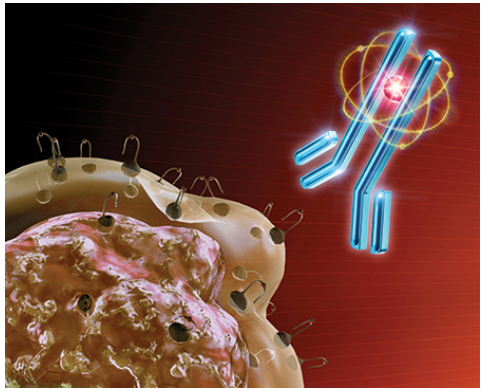
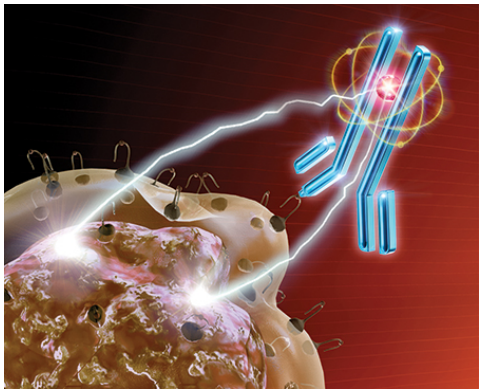
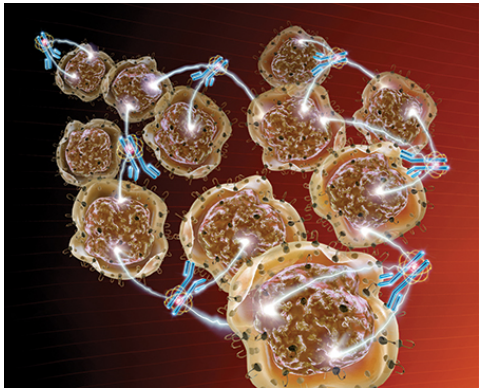


**Monoclonal antibody targets the CD20 antigen found on >90% of B-cells[1]**



**Y-90 isotope attacks surrounding B-cells with high energy beta radiation[1]**



**Y-90 beta emissions induce cellular damage in target and neighboring cells via free radicals[1]**

- **ZEVALIN is a pure beta emitter. It can affect healthy cells within a 5mm radius around CD20 expressing B-cells**
- **ZEVALIN treatment has been shown to cause severe and prolonged cytopenias**
- **Other potential side effects related to ZEVALIN are secondary malignancies or radiation injury to tissues near areas of lymphomatous involvement**

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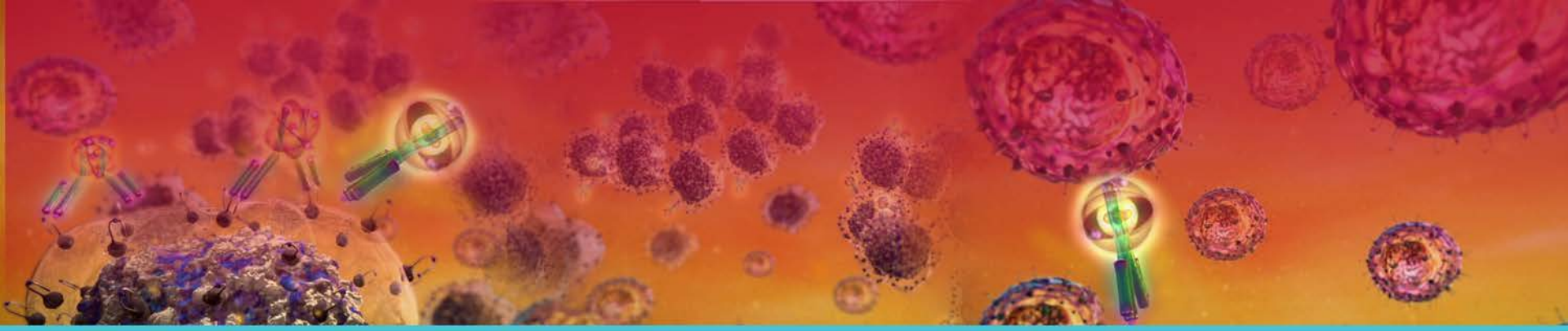
ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.



# Efficacy and Safety in First line Follicular Non Hodgkins Lymphoma

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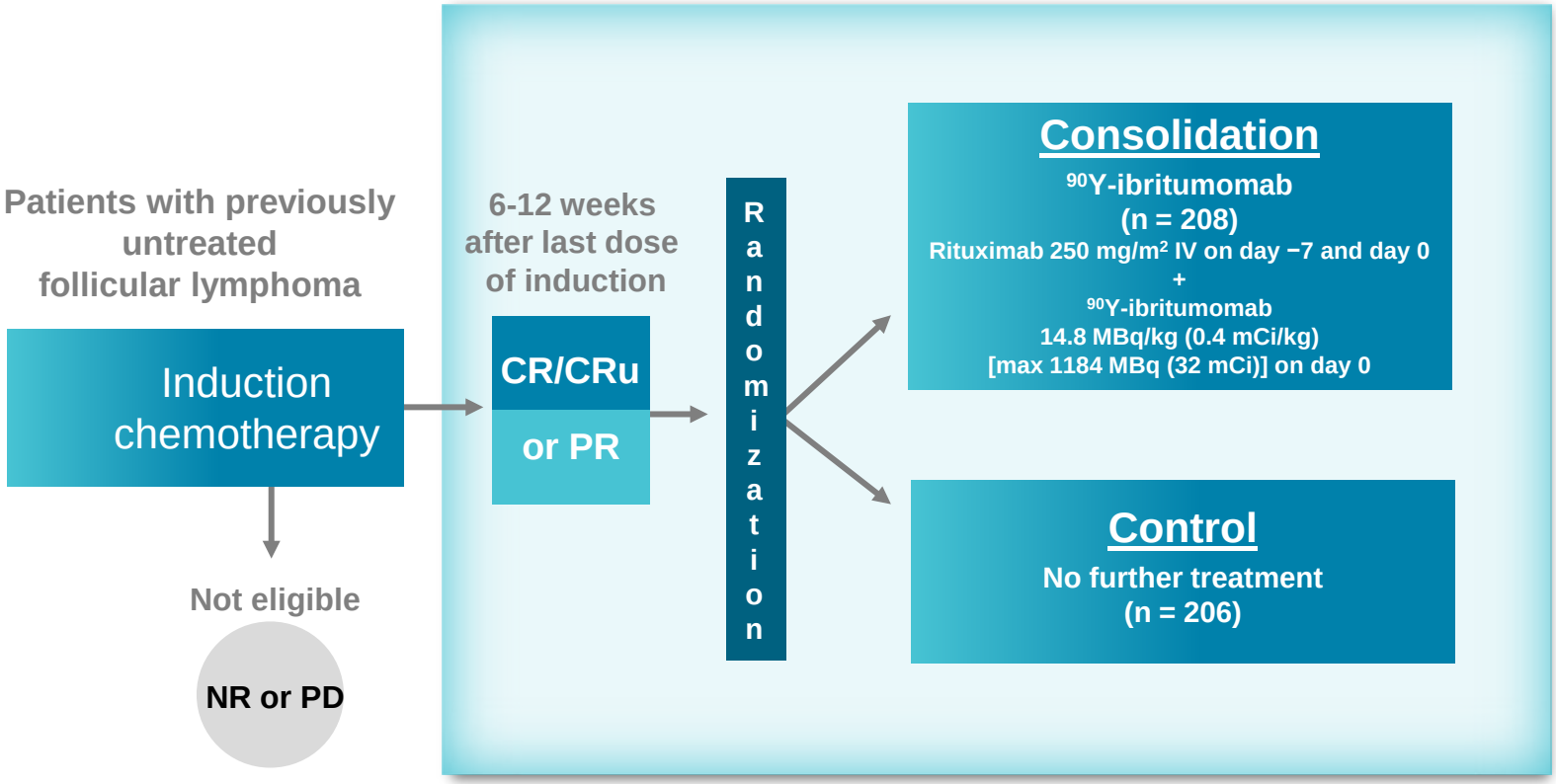
# Registrational Phase III Study in Previously Untreated Follicular NHL (n=414) FIT Trial

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Clinical Study Primary endpoint was PFS*

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*PFS was assessed by study investigators using the 1999 International Workshop to Standardize Response Criteria for NHL.


**ZEVALIN® [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.**
**Morschhauser F, et al. *J Clin Oncol*. 2008; 26:5156-5164.**

# Key Eligibility Criteria

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

- Histologically confirmed CD20+, Stage III or IV, grade 1 or 2, follicular lymphoma
- A PR or CR/CRu to first-line chemotherapy
- <25% bone marrow involvement
- No prior external beam radiation or myeloablative therapy
- No other anticancer treatment for NHL except for the preceding first-line chemotherapy
- Recovery of platelets to ≥150,000/$mm^3$

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**ZEVALIN® [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.**
**Morschhauser F, et al. *J Clin Oncol.* 2008;26(32):5156-5164.**

# First-Line Chemotherapy Regimens

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

| Total population = 414 | n (%) |
|---|---|
| Cyclophosphamide-containing combination chemotherapy | 294 (71) |
| - CHOP | 127 (31) |
| - CHOP-like | 61 (15) |
| - CVP/COP | 106 (26) |
| Rituximab-containing combination chemotherapy | 59 (14) |
| Chlorambucil | 39 (9.4) |
| Fludarabine or fludarabine-containing chemotherapy regimens | 22 (5) |

**CVP = cyclophosphamide, vincristine, prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone.**

**Please see full Prescribing Information available with this program, or Click Here.**

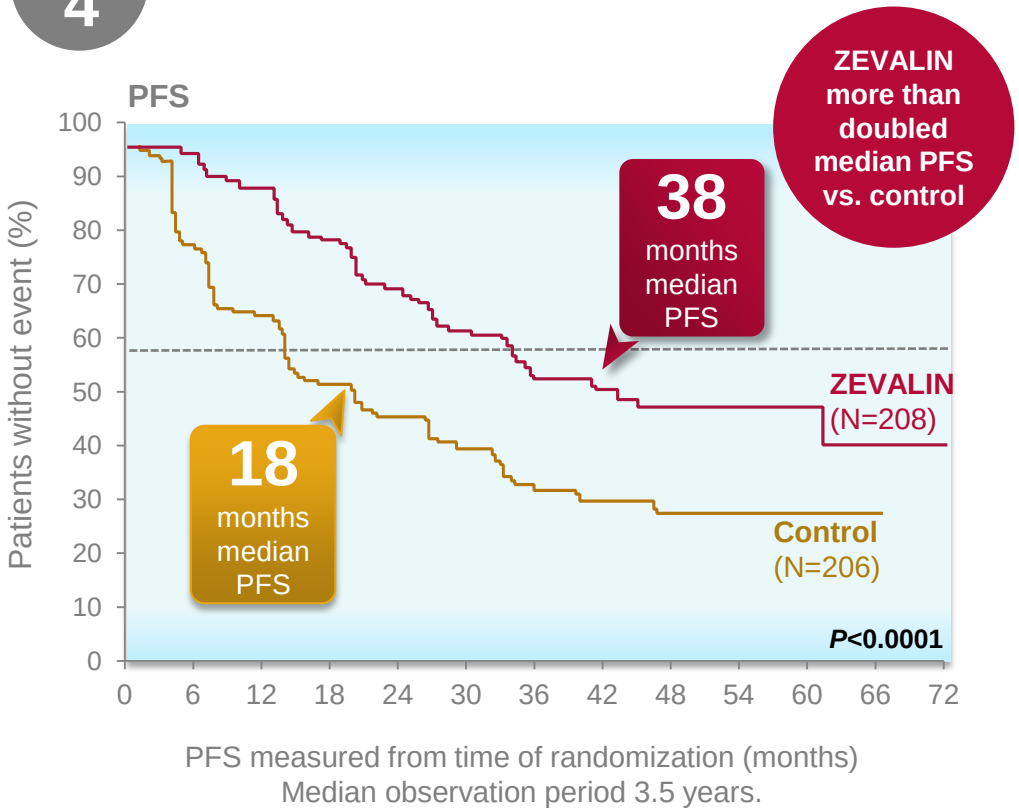
**ZEVALIN® [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.**
**Morschhauser F, et al. *J Clin Oncol.* 2008;26(32):5156-5164.**

# ZEVALIN® Increased Median PFS by 20 Months Versus No Further Treatment

ZEVALIN (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 4

## At 3.5-year follow-up, ZEVALIN increased median PFS by 20 months versus no further treatment




PFS measured from time of randomization (months)
Median observation period 3.5 years.

**Common adverse reactions (≥10%) in clinical trials:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**The most serious adverse reactions of ZEVALIN are:** prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

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ZEVALIN® [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.

# Most Serious Adverse Reactions to ZEVALIN®

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Prolonged and severe cytopenias

- Grade 3/4 cytopenia incidence rates in 206 patients who received ZEVALIN
  - Thrombocytopenia (51%)
  - Neutropenia (41%)
  - Anemia (5%)
  - Leukopenia (36%)
  - Lymphopenia (18%)

## Secondary Malignancies

- Among 204 patients receiving Y-90-ZEVALIN following first-line chemotherapy, 26 (12.7%) patients in the Zevalin arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%,7/204) were diagnosed with MDS/AML after receiving Zevalin, compared to one patient (0.5%,1/205) in the control arm, with a median follow-up of 7.3 years

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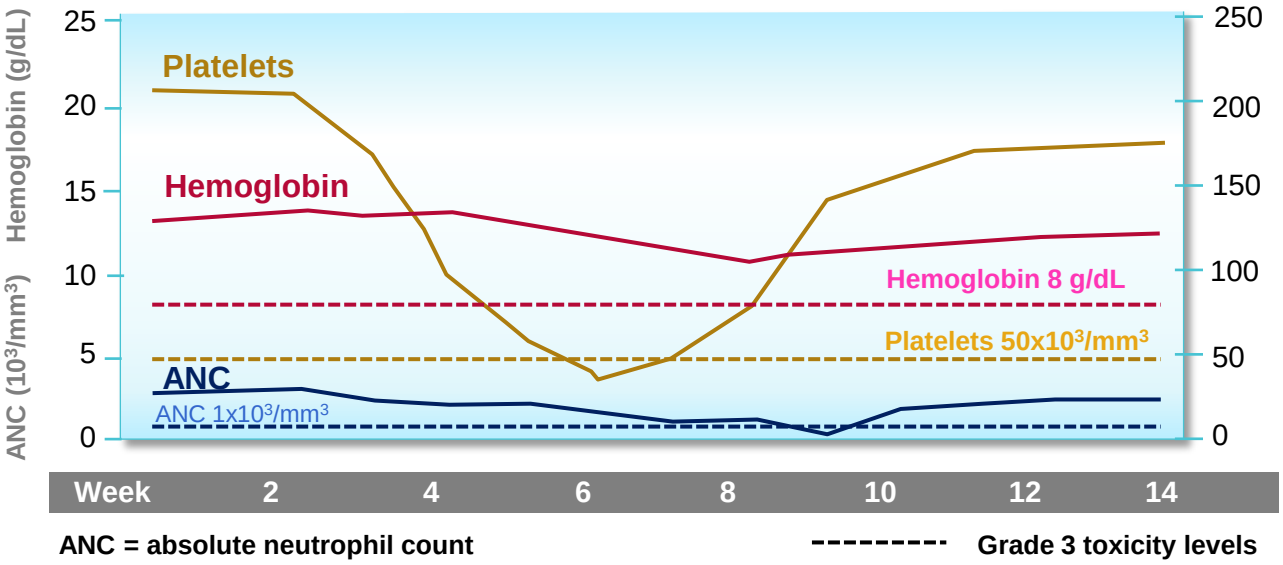
**ZEVALIN® [package insert]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2013.**

# Anticipated Timelines for Prolonged and Severe Cytopenias

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Grade 3/4 hematologic side effects in first-line patients




**ANC = absolute neutrophil count** **Grade 3 toxicity levels**

Line graph adapted from Clinical Study Report (SAG 304820). Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2011.

- Median recovery time from nadir to grade 1 toxicity or baseline is approximately 2 weeks for neutrophils and platelets.
- Cytopenias were more severe and prolonged in patients receiving ZEVALIN after first-line fludarabine or fludarabine-containing chemotherapy.

- The median time to cytopenia was similar across patients with relapsed/refractory NHL and those completing first-line chemotherapy, with median ANC nadir at 61-62 days, platelet nadir at 49-53 days, and hemoglobin nadir at 68-69 days after Y-90 Zevalin administration.

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**Data on file. Irvine, CA: Spectrum Pharmaceuticals, Inc.**
**SAG 304820 Clinical Study Report.**

# Most Common Non-Hematologic Adverse Reactions to ZEVALIN®

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Non-Hematologic Adverse Reactions

- Fatigue (33%)
- Nasopharyngitis (19%)
- Nausea (18%)
- Abdominal Pain (17%)
- Asthenia (15%)
- Diarrhea (11%)
- Cough (11%)
- Pyrexia (10%)

## Infections

- Grade 3 or 4 infections occurred in 8% of ZEVALIN-treated patients and in 2% of controls
- Included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, upper and lower respiratory tract infection, and sinusitis

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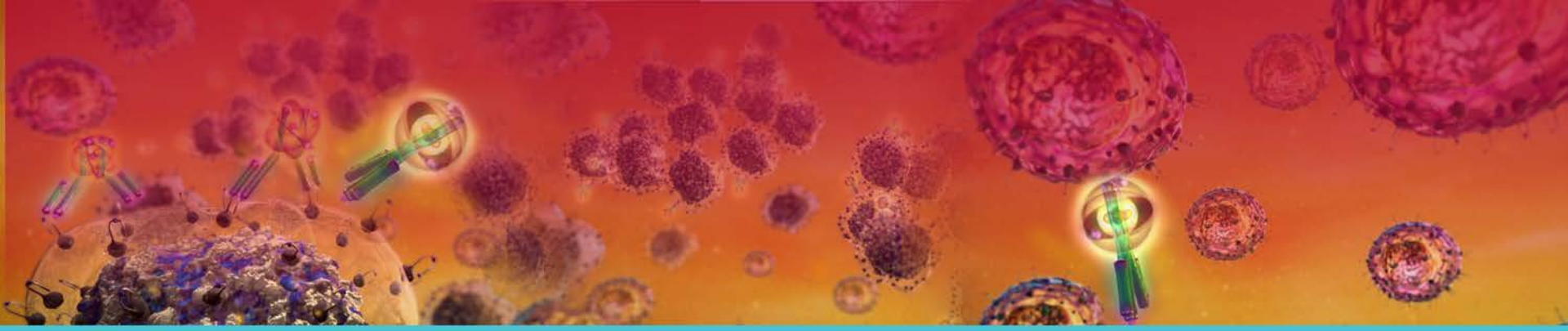

# Efficacy and Safety in Relapsed or Refractory Follicular or Low Grade NHL

ZEVALIN®
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INJECTION FOR INTRAVENOUS USE

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# Registrational Study 1 in Relapsed Follicular Lymphoma (Refractory to Rituximab)[1,2]

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 1

| Type | N | Primary Endpoint | Population |
|---|---|---|---|
| Single arm study | 54 | ORR* | Relapsed follicular NHL (refractory** to rituximab) |

*ORR was assessed by study investigators using the 1999 International Workshop Response Criteria (IWRC) for NHL.

** Refractory to rituximab was defined as failure to achieve a complete or partial response or time-to-disease-progression (TTP) of < 6 months.

**Please see slides 3-7 for Important Safety Information, including BOXED WARNINGS.**
**Please see accompanying full Prescribing Information associated with this program or Click here.**

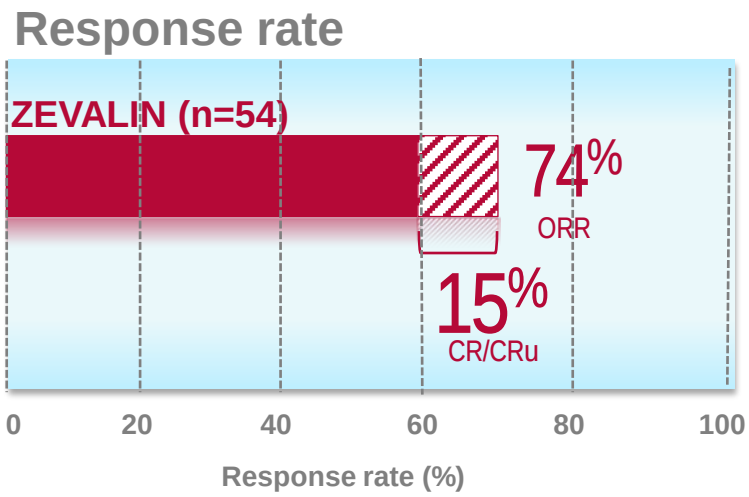

1. ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.
2. Witzig TE, et al. *J Clin Oncol.* August 2002; 20(15):3262-9.

# ZEVALIN® Delivers High Response Rates in Relapsed Patients Refractory to Rituximab

ZEVALIN (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 1

## Relapsed Follicular Lymphoma (Refractory to Rituximab Treatment)




**MDS in Relapsed or Refractory NHL:**

Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to diagnosis of MDS or AML was 1.9 years following treatment with the ZEVALIN therapeutic regimen; however, the cumulative incidence continues to increase.

- ZEVALIN patients experienced a median duration of response of 6.4 months

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Registrational Study 2 in Relapsed or Refractory, Low-Grade or Follicular Lymphoma[1,2]

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 2

| Type | N | Primary Endpoint | Population |
|---|---|---|---|
| Randomized, Open label, Multicenter study<br>• ZEVALIN, n=64<br>• Rituximab, n=66 | 130 | **ORR*** | Relapsed or refractory **low-grade or follicular NHL** |

*ORR was assessed by study investigators using the 1999 International Workshop Response Criteria (IWRC) for NHL.

**Please see slides 3-7 for Important Safety Information, including BOXED WARNINGS.**
**Please see accompanying full Prescribing Information associated with this program or Click here.**


1. ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.
2. Witzig TE, et al. *J Clin Oncol*. May 2002; 20:2453-2463.

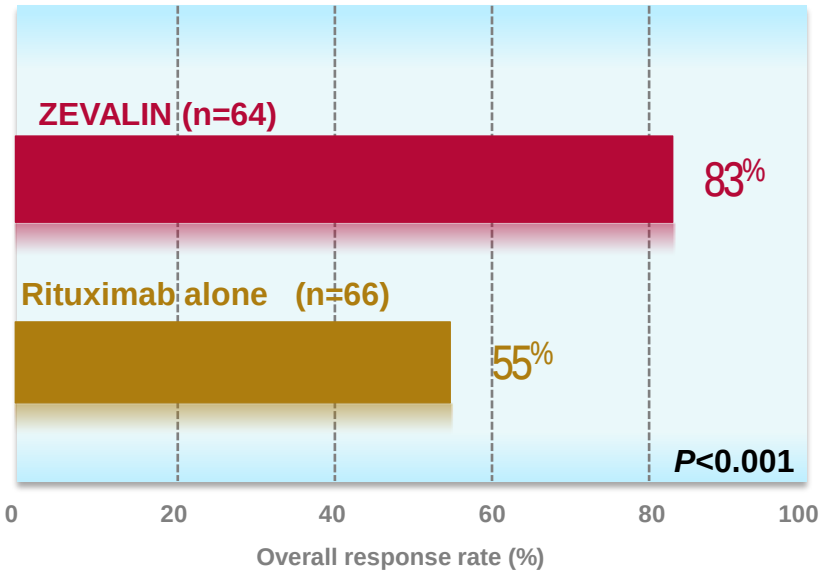
# Versus Rituximab Alone, ZEVALIN® Delivered Higher Response Rates

ZEVALIN (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 2

## Relapsed or Refractory, Low-grade or Follicular NHL

### Overall response rate (ORR)




**Grade 3/4 Adverse Reactions for Relapsed or Refractory NHL Patients:**

Prolonged and severe cytopenias (thrombocytopenia [63%], neutropenia [60%], anemia [17%], and ecchymosis [<1%]) and secondary malignancies (5.2%).

- Median duration of response was 14.3 mos in ZEVALIN arm vs.11.5 mos in rituximab arm

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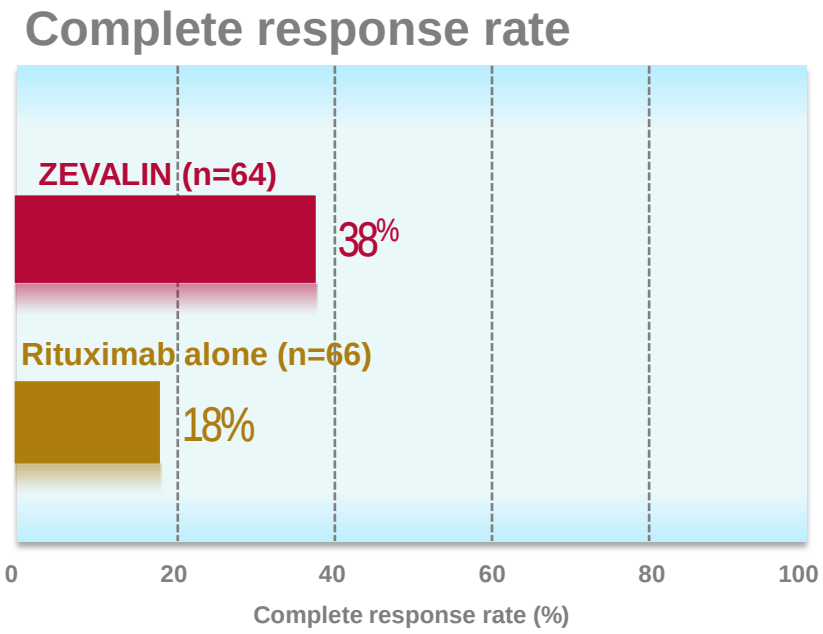
ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Versus Rituximab Alone, ZEVALIN® Delivered Higher Response Rates

ZEVALIN (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 2

## Relapsed or Refractory, Low-grade or Follicular NHL




**Additional Adverse Reactions for Relapsed or Refractory NHL Patients: Infections**

Serious infections occurred in 3% of patients (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection).

Life-threatening infections were reported in 2% of patients (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis).

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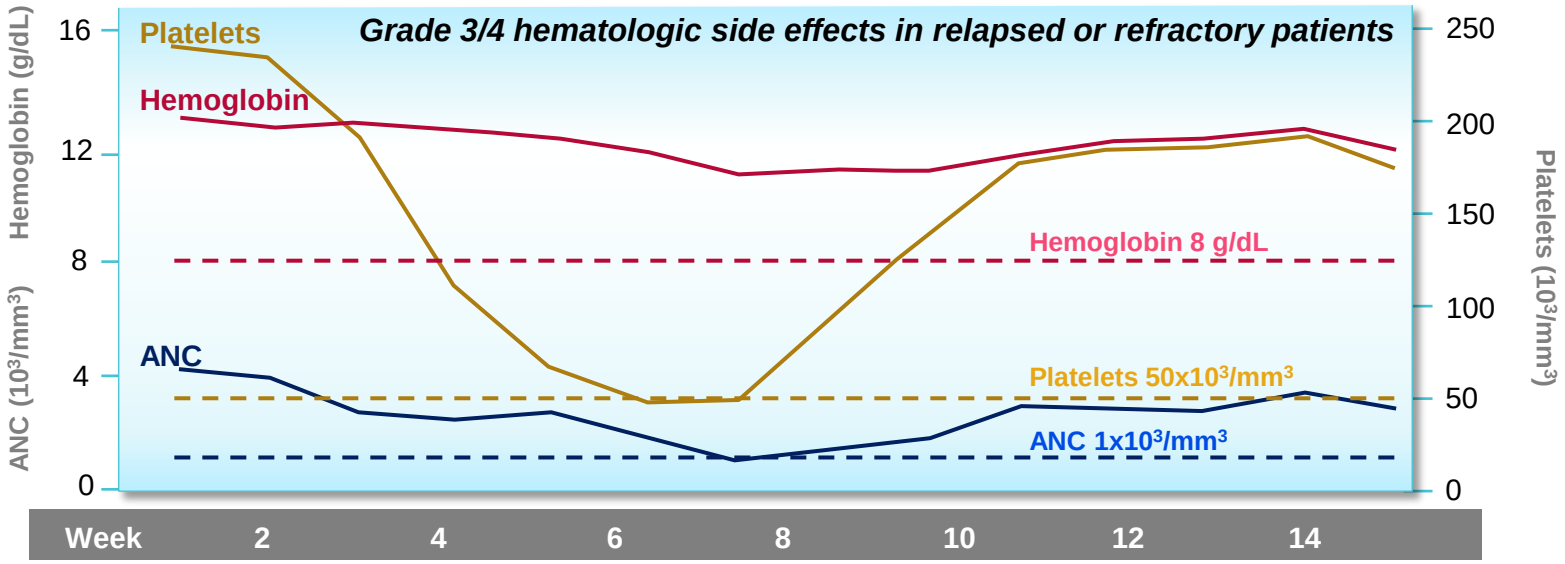
ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Anticipated Timelines for Prolonged and Severe Cytopenias

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

Registrational Study 2




**ANC = absolute neutrophil count**

- The median time to cytopenia was similar across patients with relapsed/refractory NHL and those completing first-line chemotherapy, with median ANC nadir at 61-62 days, platelet nadir at 49-53 days, and hemoglobin nadir at 68-69 days after Y-90 ZEVALIN administration.
- Median recovery time from nadir to Grade 1 toxicity or baseline is approximately 2 weeks for neutrophils and platelets.
- Cytopenias were more severe and prolonged in patients receiving ZEVALIN after first-line fludarabine or fludarabine-containing chemotherapy.

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**ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.**
**Adapted with permission from Witzig TE, et al. *J Clin Oncol*. May 2002; 20:2453-2463.**

# Most Common Non-Hematologic Adverse Reactions to ZEVALIN®

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Non-Hematologic Adverse Reactions

- Fatigue (33%)
- Nasopharyngitis (19%)
- Nausea (18%)
- Abdominal Pain (17%)
- Asthenia (15%)
- Diarrhea (11%)
- Cough (11%)
- Pyrexia (10%)

## Infections

- Grade 3 or 4 infections occurred in 8% of ZEVALIN-treated patients and in 2% of controls
- Included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, upper and lower respiratory tract infection, and sinusitis

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**ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.**

# Boxed Warnings

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS**

- **Serious Infusion Reactions:** Deaths have occurred within 24 hours of rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most (80%) fatalities occurred with the first rituximab infusion. Discontinue rituximab and Y-90 ZEVALIN infusions in patients who develop severe infusion reactions.
- **Prolonged and Severe Cytopenias:** Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. Do not administer Y-90 ZEVALIN to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve.
- **Severe Cutaneous and Mucocutaneous Reactions:** Severe cutaneous and mucocutaneous reactions, some fatal, can occur with the ZEVALIN therapeutic regimen. Discontinue rituximab and Y-90 ZEVALIN infusions in patients experiencing severe cutaneous or mucocutaneous reactions.
- **Dosing:** The dose of Y-90 ZEVALIN should not exceed 32.0 mCi (1184 MBq).

**Please see full Prescribing Information available with this program, or Click Here.**

ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Warnings and Precautions

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

## Risk of Developing Myelodysplastic Syndrome, Leukemia and Other Malignancies:

- The radiation dose resulting from therapeutic exposure to Y-90 radiolabeled ZEVALIN may result in secondary malignancies.
- Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to diagnosis of MDS or AML was 1.9 years following treatment with the ZEVALIN therapeutic regimen; however, the cumulative incidence continues to increase.
- Among 204 patients receiving Y-90-ZEVALIN following first-line chemotherapy, 26 (12.7%) patients in the ZEVALIN arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving ZEVALIN, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the ZEVALIN arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the ZEVALIN arm compared to no patients in the control arm.

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Warnings and Precautions, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Extravasation:** Monitor for extravasation and terminate infusion if it occurs. Resume infusion in another limb.

**Immunization:** Do not administer live viral vaccines to patients who have recently received ZEVALIN.

**Radionuclide Precautions:** During and after radiolabeling ZEVALIN with Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

**Embryo-fetal Toxicity:** May cause fetal harm if given during pregnancy.

**Impairment of Fertility:** There is a potential risk that the ZEVALIN® therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

**Nursing Mothers:** Patients should be advised to discontinue nursing during and after ZEVALIN treatment.

**Please see full Prescribing Information available with this program, or Click Here.**

ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Additional Important Safety Information

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Adverse Reactions:**

**The most common adverse reactions of ZEVALIN are:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**Common adverse reactions (≥10%) in clinical trials:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**The most serious adverse reactions of ZEVALIN are:** prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

**Adverse Reactions for First-Line Patients:**

When administered following first-line chemotherapy, grade 3/4 adverse reactions of ZEVALIN include prolonged and severe cytopenias (thrombocytopenia [51%], neutropenia [41%], leukopenia [36%], lymphopenia [18%], and anemia [5%]) and secondary malignancies (12.7%).

Cytopenias were more severe and more prolonged among eleven (5%) patients who received ZEVALIN after first-line fludarabine or a fludarabine-containing chemotherapy regimen as compared to patients receiving non-fludarabine-containing regimens.

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Additional Important Safety Information, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Adverse Reactions for First-Line Patients (Continued):**

Grade 3/4 infections occurred in 8% of ZEVALIN-treated patients and in 2% of controls and included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, lower respiratory tract infection, sinusitis, and upper respiratory tract infection.

**Adverse Reactions for Relapsed or Refractory NHL Patients:**

Grade 3/4 adverse reactions of ZEVALIN in relapsed or refractory NHL patients include prolonged and severe cytopenias (thrombocytopenia [63%], neutropenia [60%], anemia [17%], and ecchymosis [<1%]) and secondary malignancies (5.2%).

Serious infections occurred in 3% of patients (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection).

Life-threatening infections were reported in 2% of patients (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis).

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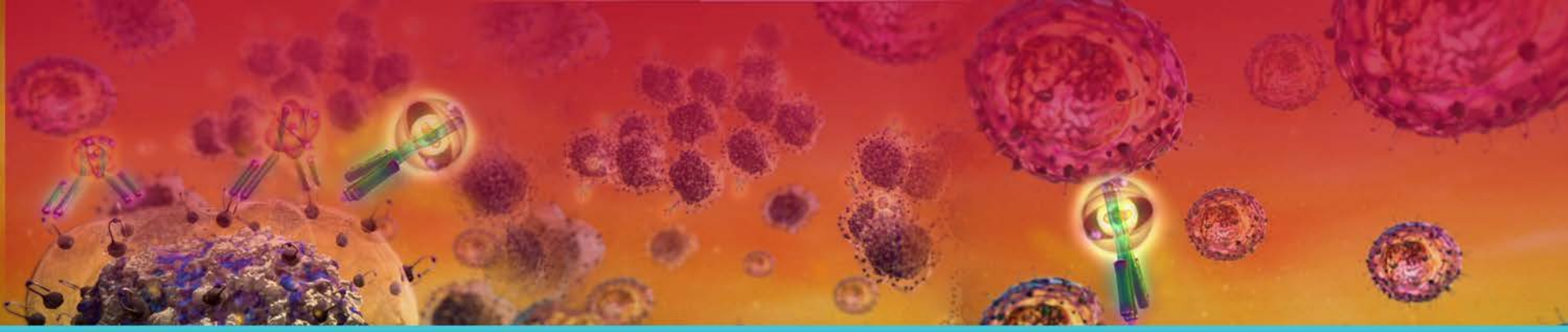
ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.



# ZEVALIN®
# Dosing & Administration

**Please see slides 35-39 for BOXED WARNINGS and Important Safety Information.**

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**Please see full Prescribing Information available with this program, or Click Here.**

# Basic Facility Requirements

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

- Small, secure area to receive and store patient ready dose until use
  - A complete “hot lab” is **not** required
- Preferably, a private administration room
  - Open suite is acceptable in many cases
  - Patient does not need to be isolated following Zevalin administration
- *Check your facility Radioactive Materials License for additional guidance*
- **Only administer RITUXAN®/ZEVALIN in facilities where immediate access to resuscitative measures is available**

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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# Patient Criteria

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- Patients with previously untreated follicular NHL who achieve a PR or CR/CRu to first-line chemotherapy
  - Platelet counts ≥150,000/mm$^3$
  - <25% bone marrow involvement
- Patients with relapsed or refractory NHL
  - Platelet counts ≥150,000/mm$^3$
  - Platelet counts ≥100,000 but ≤149,000/mm$^3$ receive a lower dose
  - <25% bone marrow involvement
- Embryo-fetal Toxicity Category D
- Should not be used in pregnant women, nursing mothers, and effectiveness has not been established in pediatric patients
- Impairment of Fertility
  - There is a potential risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraception methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

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# RRZ Dosing and Administration

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## ZEVALIN® is delivered in a single treatment course

### RRZ: the ZEVALIN treatment regimen simplified

**FDA removed Indium-111 bioscan 11/2011**


- Premedicate with acetaminophen 650 mg and diphenhydramine 50 mg orally prior to rituximab infusion
- Intravenous injection of ZEVALIN over 10 minutes as follows:
  - 0.4 mCi/kg (14.8 MBq per kg) for patients with normal platelet count
  - 0.3 mCi/kg (11.1 MBq per kg) in relapsed or refractory patients with platelet count of ≥100,000 – ≤149,000 cells/mm$^3$
  - The maximum dose of Y-90 ZEVALIN is 32.0 mCi (1184 MBq)
- **Only administer RITUXAN®/ZEVALIN in facilities where immediate access to resuscitative measures is available**

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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**ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.**

**Rituxan® is a registered trademark of Biogen Idec, Inc..**

# RRZ Dosing and Administration

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## ZEVALIN® is delivered in a single treatment course

### RRZ: the ZEVALIN treatment regimen simplified

**FDA removed Indium-111 bioscan 11/2011**


- Discontinue rituximab and ZEVALIN infusions in patients who develop severe infusion reactions or severe cutaneous or mucocutaneous reactions
- Monitor for extravasation and terminate infusion if it occurs. Resume infusion in another limb
- Obtain complete blood counts (CBC) and platelet counts at least weekly

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**ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.**

**Rituxan® is a registered trademark of Biogen Idec, Inc..**

# Infusion Reactions And Extravasation

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- Immediately stop the rituximab infusion for severe infusion reactions and discontinue the ZEVALIN® regimen.
- Temporarily slow or interrupt rituximab infusion for less severe infusion reactions.
- Monitor patients closely for evidence of extravasation occurrence during injection of ZEVALIN. If signs or symptoms occur, terminate and restart in another limb.

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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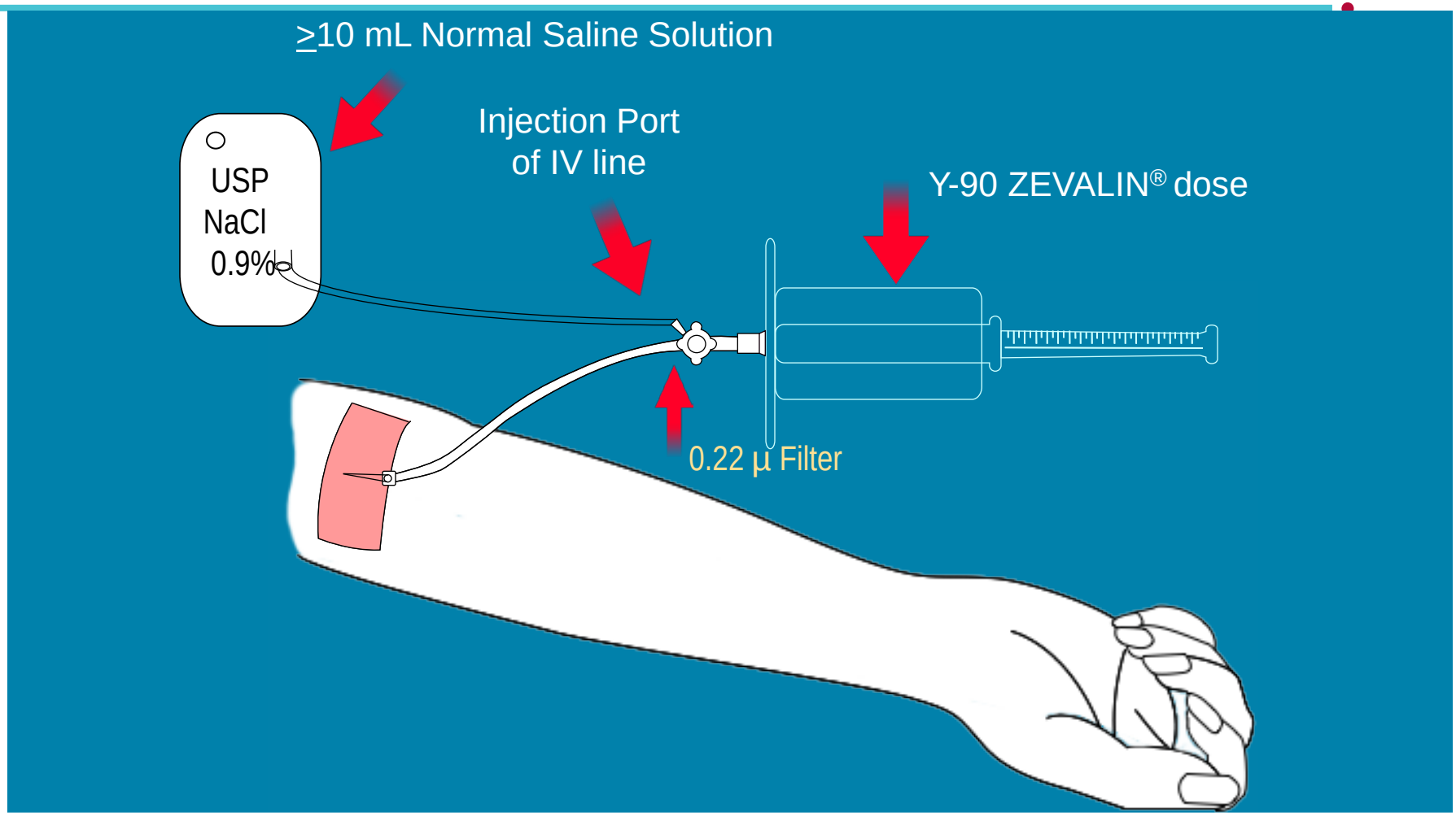
# ZEVALIN® Injection

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE




**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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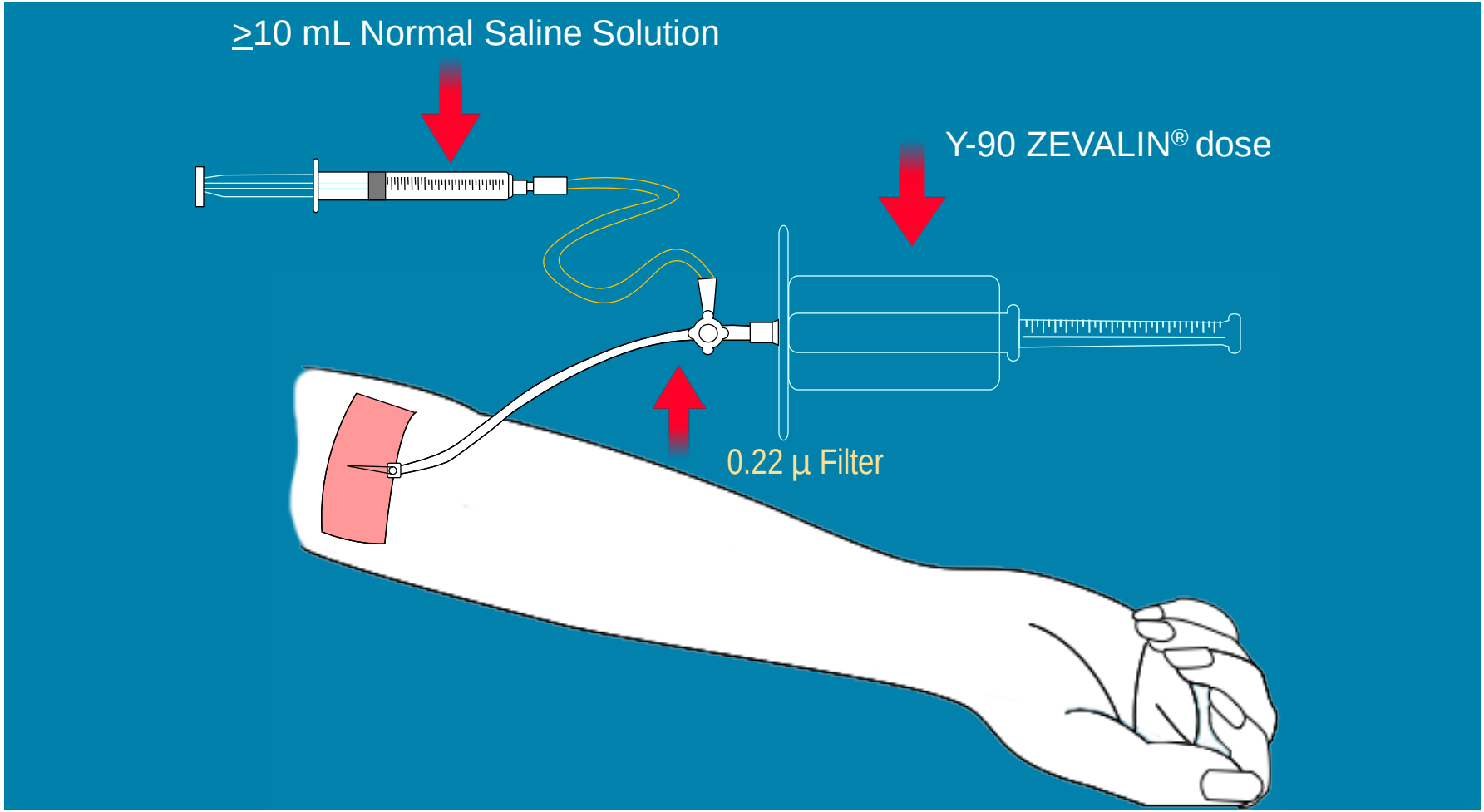
# ZEVALIN® Injection, con't

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

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# Y-90 Ibritumomab Tiuxetan

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

Acrylic
(or Acrylic
combination)
Syringe Shield

Use a 0.22 micron low-protein-binding in-line filter

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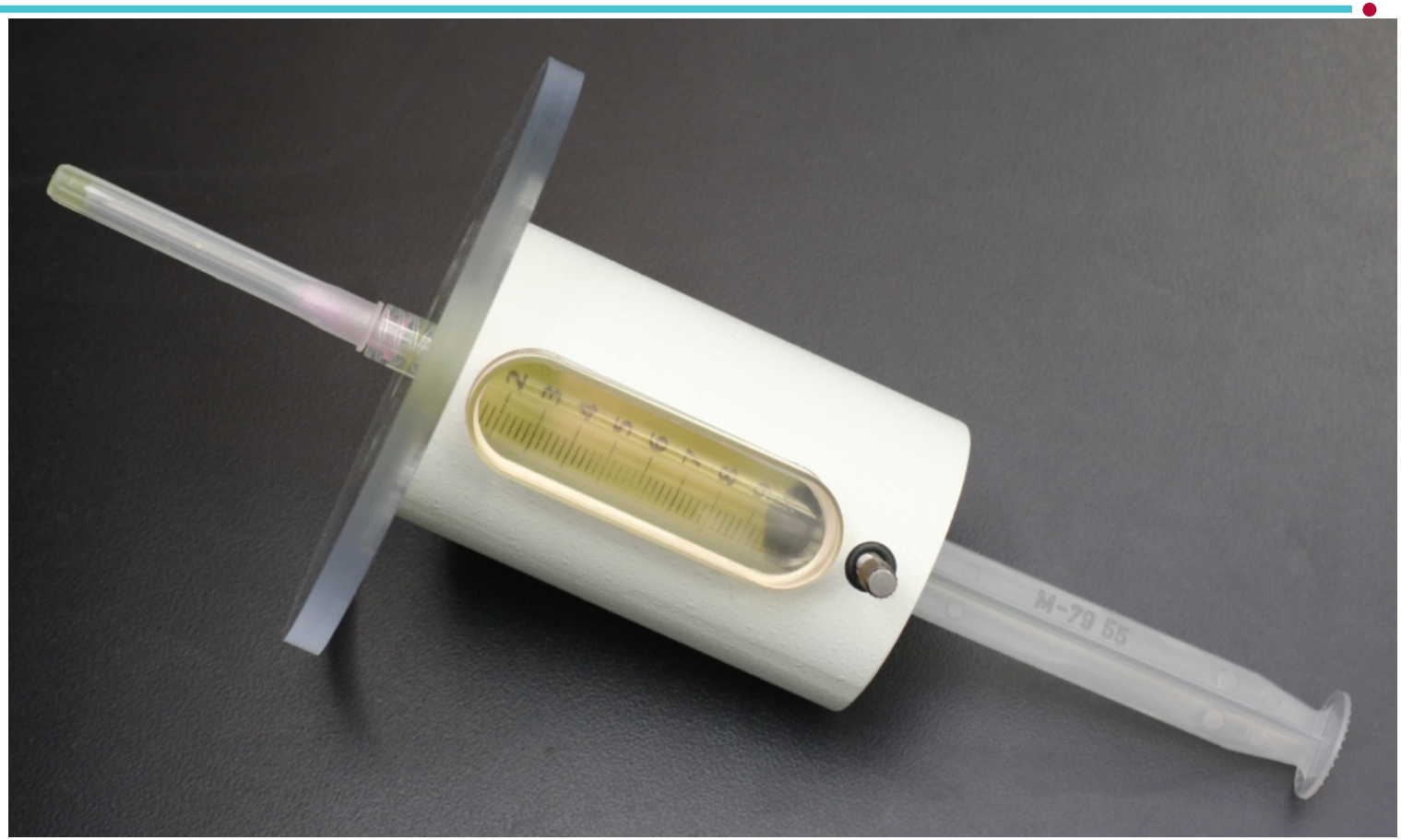
# Syringe Shield

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE



# ZEVALIN® Kit Prior to Radiolabeling

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE



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# Storage

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- Store ZEVALIN® at 2–8° C (36–46° F) until use
- Administer within:
  - 8 Hours of radiolabeling for Y-90 ZEVALIN
- Do not freeze

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
**Please see full Prescribing Information available with this program, or Click Here.**

# Straightforward Logistics

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Clinical Logistics Specialists manage ZEVALIN treatment logistics

Available to facilitate scheduling and pre- and post-treatment processes, helping ensure that every patient who is prescribed ZEVALIN gets ZEVALIN.

## ZEVALIN is delivered as a patient-ready dose

A radiopharmacy will supply a unit dose of Y-90 ZEVALIN in a 10 cc pre-filled syringe, ready for patient administration.* Beyond the acrylic syringe shield, no additional protection is needed.

## Following the second rituximab dose, patients receive the ZEVALIN injection in a single, 10-minute IV push - in the outpatient setting

ZEVALIN treatment uses beta-radiation, a form of radiation that requires only standard precautions to minimize radiation exposure. After ZEVALIN treatment, patients do not have to avoid contact with loved ones.

Healthcare professionals should advise patients to use effective contraceptive methods during treatment and for a minimum of 12 months following ZEVALIN therapy.

*Dose assay verification may be required based on local, state, and NRC regulation and licensing.

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Drug Ordering Overview

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

## Step 1 Treating Site

Place order to the radiopharmacy
Specify treatment date (must be ordered 8 business days prior to the treatment with ZEVALIN)
Obtain Spectrum Purchase Order Number
Notify radiopharmacy **immediately** in the event of a cancellation or delay

## Step 2 Radiopharmacy

Place order with ZEVALIN Support Services
Provide to ZEVALIN Support Services:
- Treatment date
- Name and Location of treating site
- Provide “Bill to” information of treating site(s) and PO #

## Step 3 ZEVALIN Support Services

Receive order from radiopharmacy
Ship the cold kit directly to the radiopharmacy
Order the Y-90 isotope from vendor and schedule shipment to the radiopharmacy
Invoice the end user(s)

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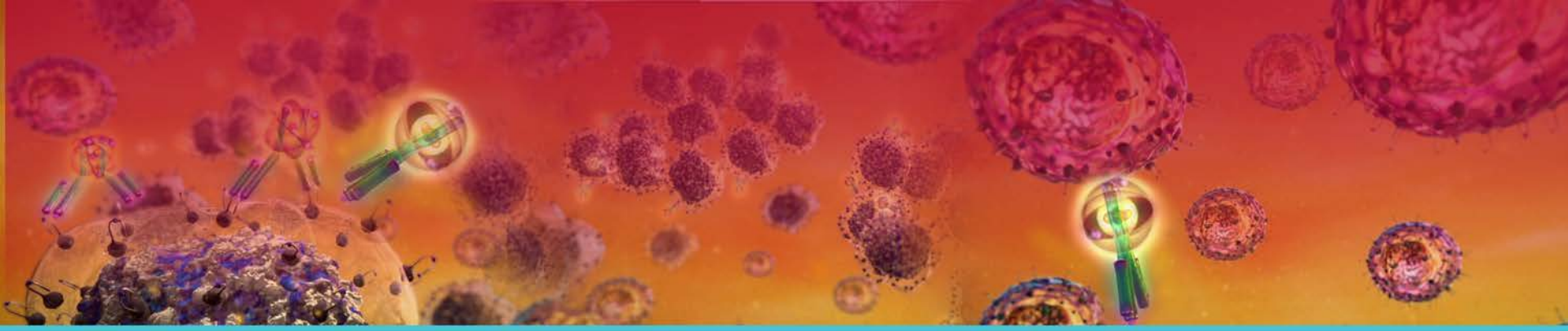

# RADIATION SAFETY

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
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# Risk of Radiation Exposure to Others Following ZEVALIN® Treatment Is Minimal

ZEVALIN
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

- Most activity is retained
  - Urinary excretion = 7.3% ± 3.2% over 7 days
- Assuming maximum 32.0 mCi dose and excretion of 7.3% over a week, total urinary excretion over a week is 2.3 mCi
  - Activity per urination = microcuries
- For the majority of patients, ordinary amounts of blood (e.g., menstruation, bad cuts, hemorrhoids) will contain inconsequential levels of radioactivity

**• ZEVALIN is a pure beta emitter. It can affect healthy cells within a 5mm radius around CD20 expressing B-cells**
**• ZEVALIN treatment has been shown to cause severe and prolonged cytopenias**
**• Other potential side effects related to ZEVALIN are secondary malignancies or radiation injury to tissues near areas of lymphomatous involvement**

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
**Please see full Prescribing Information available with this program, or Click Here.**

Wagner et al. *J Nucl Med*. 2002;43:267-272.

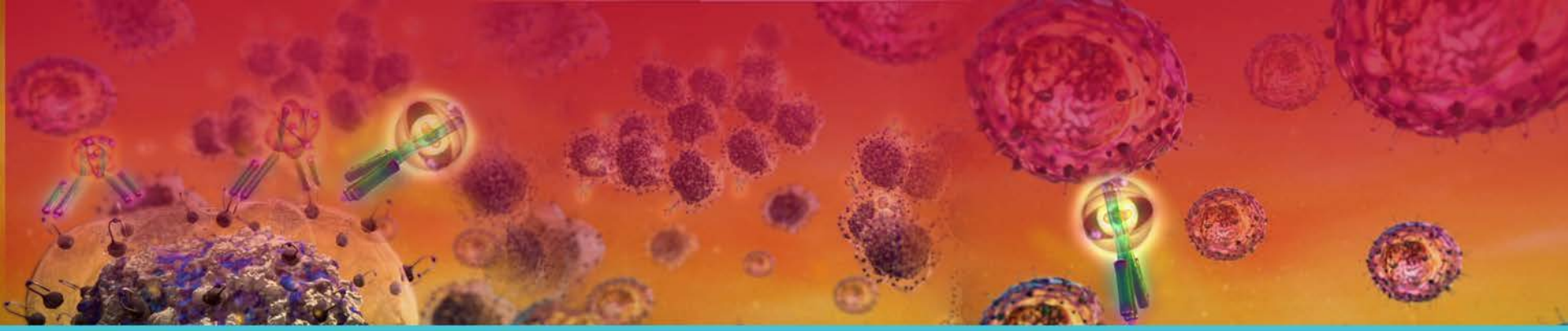
# Risk of Radiation Exposure to Others

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

- Prospective study in 13 family members of patients treated with ZEVALIN®
  - Family members with closest contact wore DoseGUARD Plus personal dosimeter for 7 days
  - Family was instructed to avoid body wastes, but no other precautions were given
  - Median deep dose equivalent over 7 days = **3.5 mrem** (range 1.4-7.9 mrem)
- Conclusion: exposure to others is negligible, in the range of background radiation

**Please see slides 35-39 for Important Safety Information, including BOXED WARNINGS.**
**Please see full Prescribing Information available with this program, or Click Here.**

**Wiseman GA, et al. Eur J Nucl Med 2001;28:1198**



# IMPORTANT SAFETY INFORMATION

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**Please see slides 58-62 for Important Safety Information, including BOXED WARNINGS.**
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# Boxed Warnings

ZEVALIN®
(ibritumomab tiuxetan)
INJECTION FOR INTRAVENOUS USE

**WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS**

- **Serious Infusion Reactions:** Deaths have occurred within 24 hours of rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most (80%) fatalities occurred with the first rituximab infusion. Discontinue rituximab and Y-90 ZEVALIN infusions in patients who develop severe infusion reactions.
- **Prolonged and Severe Cytopenias:** Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. Do not administer Y-90 ZEVALIN to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve.
- **Severe Cutaneous and Mucocutaneous Reactions:** Severe cutaneous and mucocutaneous reactions, some fatal, can occur with the ZEVALIN therapeutic regimen. Discontinue rituximab and Y-90 ZEVALIN infusions in patients experiencing severe cutaneous or mucocutaneous reactions.
- **Dosing:** The dose of Y-90 ZEVALIN should not exceed 32.0 mCi (1184 MBq).

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Warnings and Precautions

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## Risk of Developing Myelodysplastic Syndrome, Leukemia and Other Malignancies:

- The radiation dose resulting from therapeutic exposure to Y-90 radiolabeled ZEVALIN may result in secondary malignancies.
- Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to diagnosis of MDS or AML was 1.9 years following treatment with the ZEVALIN therapeutic regimen; however, the cumulative incidence continues to increase.
- Among 204 patients receiving Y-90-ZEVALIN following first-line chemotherapy, 26 (12.7%) patients in the ZEVALIN arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving ZEVALIN, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the ZEVALIN arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the ZEVALIN arm compared to no patients in the control arm.

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# Warnings and Precautions, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Extravasation:** Monitor for extravasation and terminate infusion if it occurs. Resume infusion in another limb.

**Immunization:** Do not administer live viral vaccines to patients who have recently received ZEVALIN.

**Radionuclide Precautions:** During and after radiolabeling ZEVALIN with Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

**Embryo-fetal Toxicity:** May cause fetal harm if given during pregnancy.

**Impairment of Fertility:** There is a potential risk that the ZEVALIN® therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

**Nursing Mothers:** Patients should be advised to discontinue nursing during and after ZEVALIN treatment.

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# Additional Important Safety Information

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**Adverse Reactions:**

**The most common adverse reactions of ZEVALIN are:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**Common adverse reactions (≥10%) in clinical trials:** cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

**The most serious adverse reactions of ZEVALIN are:** prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

**Adverse Reactions for First-Line Patients:**

When administered following first-line chemotherapy, grade 3/4 adverse reactions of ZEVALIN include prolonged and severe cytopenias (thrombocytopenia [51%], neutropenia [41%], leukopenia [36%], lymphopenia [18%], and anemia [5%]) and secondary malignancies (12.7%).

Cytopenias were more severe and more prolonged among eleven (5%) patients who received ZEVALIN after first-line fludarabine or a fludarabine-containing chemotherapy regimen as compared to patients receiving non-fludarabine-containing regimens.

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# Additional Important Safety Information, cont.

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

**Adverse Reactions for First-Line Patients (Continued):**

Grade 3/4 infections occurred in 8% of ZEVALIN-treated patients and in 2% of controls and included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, lower respiratory tract infection, sinusitis, and upper respiratory tract infection.

**Adverse Reactions for Relapsed or Refractory NHL Patients:**

Grade 3/4 adverse reactions of ZEVALIN in relapsed or refractory NHL patients include prolonged and severe cytopenias (thrombocytopenia [63%], neutropenia [60%], anemia [17%], and ecchymosis [<1%]) and secondary malignancies (5.2%).

Serious infections occurred in 3% of patients (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection).

Life-threatening infections were reported in 2% of patients (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis).

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ZEVALIN® [Prescribing Information]. Spectrum Pharmaceuticals, Inc.; 2013.

# Support and Ordering

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# Spectrum Therapy Access Resources: Reimbursement Support

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- Before, during, and after treatment, STAR has your practice and your patients supported
  - Verification of patient-specific insurance benefits
  - Pre-submission claims review and support
  - Prior authorization assistance
  - Coding and billing guidance
  - Payer research
  - Denied and underpaid claims assistance
  - Alternate funding research
  - Patient Assistance Program for eligible patients
  - Co-pay Assistance Program for privately-insured

**Use STAR**

**Call 1-888-537-8277**

**www.SpectrumPatientAccess.com**

STAR reimbursement counselors are available Monday-Friday 9:00 am-5:00 pm Eastern

Spectrum Pharmaceuticals, Inc. does not guarantee coverage and/or reimbursement for its products. Coverage, coding, and reimbursement policies vary significantly by payer, patient, and setting of care. Actual coverage and reimbursement decisions are made by individual payers following the receipt of claims. Healthcare professionals should always verify coverage, coding, and reimbursement guidelines on a payer and patient-specific basis. Spectrum Pharmaceuticals, Inc. reserves the right to change eligibility guidelines, terminate, or modify the STAR program at any time for any reason.

# Prior to Initiating Treatment

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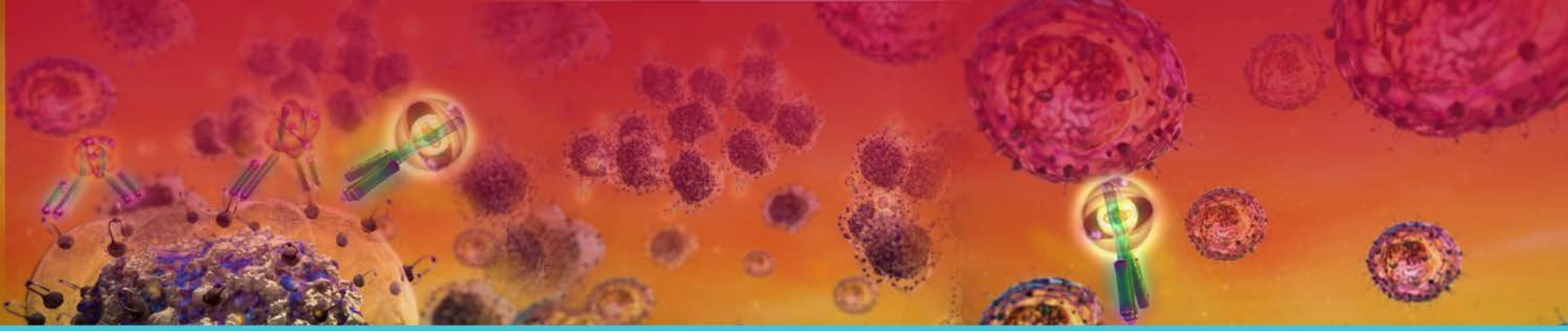
- Contact your ZEVALIN® administration facility to coordinate treatment and scheduling
- Authorized ZEVALIN administration facilities can be found at www.ZEVALIN.com
- Spectrum Clinical Logistics Specialists (CLS) are dedicated to managing all logistical aspects to ensure patients receive their ZEVALIN treatment

**Please see slides 58-62 for Important Safety Information, including BOXED WARNINGS.**
**Please see full Prescribing Information available with this program, or Click Here.**



# ZEVALIN® Support Services

**TEL: 866-298-8433**

**FAX: 877-264-8483**

**zevalinsupport@sppirx.com**

**Monday–Friday**
**8:30 am–8:00 pm EST**

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# Appendix Slides (optional if time allows)

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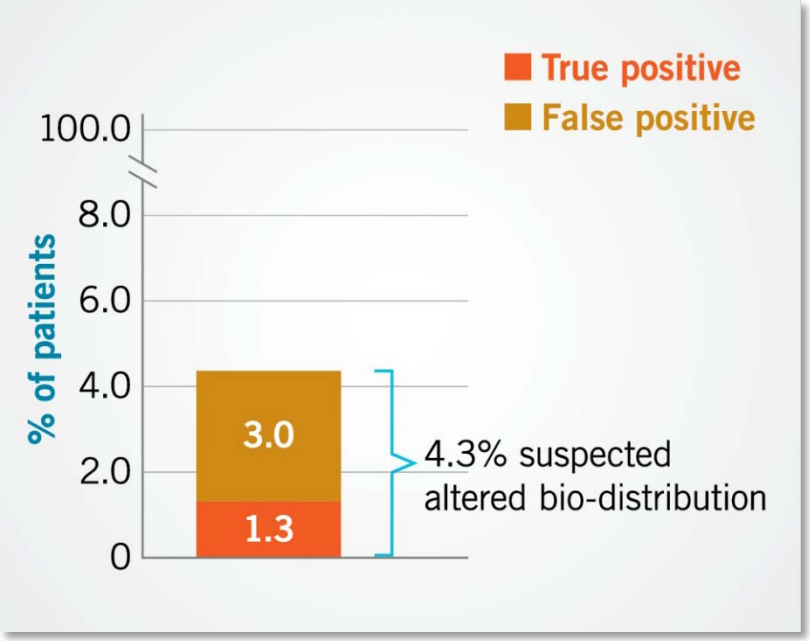
# Data Supporting Removal of the Indium-111 Bioscan Requirement

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## In-111 bioscan was not a reliable predictor of altered Y-90 bio-distribution

**Analysis of data from 253 patients who underwent the In-111 bioscan in 5 company-sponsored clinical trials showed:**




- 4.3% of patients were suspected to have altered bio-distribution
- 1.3% of patients were true positives based on expert review
- 3% of patients were found to be false positives based on expert review

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Data on File. Spectrum Pharmaceuticals, Inc.

# Data Supporting Removal of the Indium-111 Bioscan Requirement

ZEVALIN® (ibritumomab tiuxetan) INJECTION FOR INTRAVENOUS USE

## Global post-marketing surveillance showed no additional safety risk in patients receiving ZEVALIN® treatment without In-111 bioscan

- From 2002–2010, approximately 16,000 patients worldwide received ZEVALIN in routine clinical practice
  - ~9,000 in countries with the In-111 bioscan requirement
  - ~7,000 in countries WITHOUT the In-111 bioscan requirement
- Overall incidence of serious anaphylactoid reactions were similar in regions that do and do not require the In-111 bioscan (0.4% in both groups)
- Overall incidence of serious bone marrow failure were similar in regions that do and do not require the In-111 bioscan (3.3% versus 3.8%)

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**Data on File. Spectrum Pharmaceuticals, Inc.**