Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	91459 (307940)	NCT00322218
Study Phase:	III	
Official Study Title:	A phase III, open-label, prospective, two-armed, multicenter, randomized, group sequential study to evaluate the efficacy and safety of subsequent treatment with the Zevalin (ibritumomab tiuxetan) study regimen versus observation in patients with diffuse large B-cell lymphoma who are in complete remission after first-line CHOP-rituximab (CHOP-R) therapy	
Therapeutic Area:	Oncology	
Test Product		
Name of Test Product:	[^{90}Y]-ibritumomab tiuxetan (Zevalin, ZK 240974)	
Name of Active Ingredient:	[^{90}Y]-ibritumomab tiuxetan	
Dose and Mode of Administration:	The combination regimen with rituximab was designed in 2 steps as follows: Day 1: Initial administration of 250 mg/m^2 rituximab, followed immediately by administration of 185 MBq (5mCi) of [^{111}In]-ibritumomab tiuxetan (the latter one only in centers where bio distribution imaging or dosimetry was compulsory according to local law). In centers where bio distribution imaging or dosimetry was not required, the first rituximab infusion was given alone. Days 7-9: Rituximab 250 mg/m^2, followed immediately by [^{90}Y]-ibritumomab tiuxetan 14.8 MBq/kg (0.4 mCi/kg) (maximum dose 1184 MBq) given as a slow intravenous (IV) push over 10 minutes. Mode of Administration: Intravenous	
Reference Therapy/Placebo		
Reference Therapy:	No reference therapy was employed; subjects in the control group remained free of any anti-lymphoma therapy and were observed for relapse.	
Dose and Mode of Administration:	Not applicable	
Duration of Treatment:	Two treatment days one week apart followed by a 12-week safety period. Due to the sequential design, the total duration of this study was not fixed.	
Studied period:	Date of first subjects' first visit:	15 MAY 2006
	Date of last subjects' last visit:	05 DEC 2008
Premature Study Suspension / Termination:	Since the recruitment rate was unacceptably low, it was decided to terminate the study prematurely (even before the first interim look) after 68 of 151 initially screened subjects had been randomized.	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 18 JUN 2007) was applicable to Poland. The amendment introduced the performance of additional computerized tomography (CT) imaging prior to study inclusion in Poland. This was	

	done to ensure proper inclusion of study subjects, since the gathering of a full set of CT images (to confirm radiological complete remission/Complete remission unconfirmed [CR/CRu] after cyclophosphamide, vincristine, prednisone, doxorubicin plus rituximab [CHOP-R] treatment) was not a standard procedure in Poland.
Study Centre(s):	The study was conducted at 40 centers in 18 countries: USA (1), France (6), Italy (5), Canada (3), Germany (3), Poland (3), Portugal (3), Sweden (3), Finland (2), Hungary (2), South Korea (2), Austria (1), Belgium (1), Ireland (1), Singapore (1), Spain (1), Switzerland (1), and, Thailand (1).
Methodology:	The study was divided into an interventional Stage 1 and a non-interventional Stage 2. Due to the premature study termination, Stage 2 was not initiated. Stage 1 of the study was structured as follows: All Screening/baseline, treatment period (starting with the first day [Day 1] of study drug administration), safety period (starting after the last day of study drug administration), follow-up period (until relapse), and post-relapse period. Assessments of health related quality of life (HRQL) measured with Functional Assessment of Cancer Therapy-General (FACT-G) and European Quality of Life 5 dimensions (EuroQoL EQ-5D) standard questionnaires were performed within 1 week of randomization and at Week 7 and Week 13. During the follow-up period, HRQL was assessed at Month 12, Month 24, Month 36, and at the final examination (upon relapse or at the end of Stage 1 of the study in subjects not having relapsed). For safety assessments adverse events (AEs), clinical laboratory variables (hematological laboratory tests, serum chemistry, and immunoglobulin, urinalysis) were assessed.
Indication/ Main Inclusion Criteria:	Indication: Diffuse large B-cell lymphoma (DLBCL) Main Inclusion Criteria: DLBCL subjects at the age of at least 60 years and in CR or CRu after 6 or 8 cycles of a first-line treatment with cyclophosphamide, vincristine, prednisone, doxorubicin plus rituximab.
Study Objectives:	<u>Overall:</u> The objectives of this study were to evaluate the efficacy and safety of the Zevalin study regimen compared with observation alone in subjects with CR or CRu after first-line cyclophosphamide, vincristine, prednisone, doxorubicin plus rituximab. Primary endpoint: Overall survival (OS) Secondary endpoints: Disease-free survival (DFS), HRQL as assessed by the subject using standard questionnaires (FACT-G and EuroQoL EQ-5D).
Evaluation Criteria:	<u>Efficacy (Primary):</u> Overall survival was defined as the time interval (in months) from randomization to death from any cause. <u>Efficacy (Secondary):</u> • Disease-free survival was defined as the time interval (in months) from randomization to the date of relapse (as assessed by the investigator) or death from any cause. • HRQL (FACT-G, EQ- 5D)

	Safety: Vital signs, AEs, hematology, blood chemistry, and immunoglobulin levels.
Statistical Methods:	Efficacy (Primary): Originally, the study was planned in a randomized, parallel-group, group-sequential design. The primary objective of this study was an inferential comparison between the 2 randomized groups in terms of overall survival using a group sequential triangular test with a two-sided α=0.009. As the study was prematurely terminated due to insufficient recruitment (even before the first preplanned interim analysis after the occurrence of 40 deaths), the group-sequential nature of the study design was not applicable for the statistical analyses. Actually, the prominent efficacy variables OS and DFS were analyzed in the full analysis set ([FAS] identical to the safety analysis set [SAF]) and per-protocol set (PPS) using Kaplan-Meier estimates by treatment group. OS which is a time-to-event variable was censored at the date of the last known follow-up visit (provided that the subject was still alive at that time). The null hypothesis H_0 (survival distributions are equal between groups) vs the alternative hypothesis H_1 (survival distributions not equal) was tested using stratified log-rank statistics with stratification factors "age-adjusted International Prognostic Index" (categories low or high) and "number of prior CHOP-R treatment cycles" (categories 6 or 8). Generally, all variables measured on a metric scale were presented by descriptive statistics, displaying n, missing n, mean, standard deviation (SD), minimum, median, maximum as well as by single case graphics, where appropriate. Categorical and binary variables were displayed using frequency tables showing the number of subjects, number of missing observations and number of subjects within each category as well as their percentage relative to the total number of subjects displayed. Changes from Baseline were displayed where appropriate. Tabulations were produced for each treatment group as well as pooled for all subjects. Efficacy (Secondary): DFS was analyzed similarly to primary efficacy variable OS. HRQoL data was summarized for each of the instruments at scheduled visits in Stage 1 by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for the FAS of subjects. Safety: Safety variables were tabulated by common descriptive statistics on the safety analysis set of subjects.

Number of Subjects:	Planned: A total of 400 subjects (200 per arm) were planned to be enrolled. Analyzed: 68 randomized subjects (FAS) were analyzed; 34 subjects per each arm. The PPS (65 subjects) comprised of 33 subjects allocated to the Zevalin arm and 32 subjects allocated to the observation control arm.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 151 subjects screened, 68 subjects were assigned to treatment (FAS/SAF). Thirty-four subjects were assigned to the Zevalin treatment regimen and 34 subjects to observation. Three subjects showed major protocol deviations and thus were excluded from the PPS. The PPS comprised of 65 subjects (33 in the Zevalin arm and 32 in the observation arm).

Mean age of subjects (females [58.8%]) was 69.5 years (range: 59 to 83), mean height was 164.4 cm (range: 141 to 181 cm), and mean body weight was 69.0 kg (range: 45.3 to 129.0). Majority of the subjects were Caucasians (83.8%), followed by (16.2%) Asians.

Results Summary — Efficacy

Primary analysis: Overall survival

The primary analysis was based on the FAS. A total of 9 FAS subjects died in the study (3 in the Zevalin arm and 6 under observation). The observed 2-sided p-value from the stratified log-rank test was p=0.39. Although the Zevalin group showed an advantage in the estimated survival rate (2 years: 0.83 vs 0.74) this positive trend did not lead to a rejection of the null hypothesis due to the limited sample size. Median survival times could not be estimated since the estimated survival rates remained greater than 50% until the end of the maximum observation time in this discontinued study.

Similar results were found in the PPS analysis.

Secondary analysis: Disease free survival

A total of 13 FAS subjects experienced a relapse or died during the course of the study (7 in the Zevalin arm and 6 under observation). Kaplan-Meier estimates at Month 24 were 0.71 in the Zevalin group and 0.80 in the observation group. The corresponding 2-sided p-value from the log-rank test was p=0.86. All 6 subjects who died in the observation arm had previously experienced relapse, whereas 4 of the 7 relapsing Zevalin subjects did not die within the study period. Of note, one subject in the Zevalin group died without having experienced a relapse (completed suicide). Again, median times could not be estimated since DFS rates remained above 50% during the study period.

Similar results were found in the PPS analysis.

Results Summary — Safety

Extent of exposure

All 34 subjects randomized to the Zevalin arm were given 2 rituximab infusions (with a median dose of 425.0 mg at each of the 2 infusion time points). Three subjects underwent radioimaging studies/dosimetry and therefore were administered [^{111}In]-ibritumomab tiuxetan at Day 1. All but 1 subject received an infusion with [^{90}Y]-ibritumomab tiuxetan following the second infusion of rituximab. The mean dose was 984.2 ± 118.8 MBq (range: 765.9-1197.0 MBq).

Adverse Events

Hematological laboratory tests were performed throughout the study for both study arms. During the safety period (up to Week 13), abnormal hematology values were recorded as AEs only if the investigator felt they were clinically significant and required therapy. During the follow-up period (after Week 13), abnormal hematology values were recorded as AEs if the

investigator felt they were clinically significant.

A total of 63 subjects (92.6%) reported at least 1 AE during the study; 33 subjects (97.1%) in the Zevalin arm and 30 subjects (88.2%) in the observation arm. The 3 most commonly specified system organ class (SOCs) in the total population were "Infections and infestations" (41.2%), "Blood and lymphatic system disorders" (35.3%), and "Musculoskeletal and connective tissue disorders" (32.4%). An obvious group difference was noted in the SOC "Blood and lymphatic system disorders", where the incidence was 61.8% on treatment with Zevalin vs 8.8% in the observation group. Further group differences (incidence difference by more than 10%) were seen in the SOCs "General disorders/administration site conditions" (35.3% on Zevalin vs 17.6% in the observation group), "Musculoskeletal and connective tissue disorders" (41.2% on Zevalin vs 23.5% in the observation group), and "Nervous system disorders" (26.5% on Zevalin vs 14.7% in the observation group). The striking group difference in the SOC "Blood and lymphatic system disorders" was due to the eminently higher occurrence of any cytopenia on treatment with Zevalin.

A total of 8 subjects (11.8%) experienced AEs that were considered study conduct-related. More subjects in the Zevalin group (7 subjects) than subjects in the observation arm (one subject) were reported to have experienced study conduct-related AEs. Study conduct-related AEs included neutropenia, thrombocytopenia, myocardial infarction, fatigue, sinusitis, dizziness, pruritus, and hematoma in the Zevalin group and one subject in the observation group with diarrhea, nausea, vomiting chills feeling abnormal, hypersensitivity, and loss of consciousness.

Adverse events reported by the investigator to be at least possibly related to rituximab, [^{111}In]-Zevalin, or [^{90}Y]-Zevalin were noted in 35.3% (12 subjects), 2.9% (1 subject), and 67.6% (23 subjects) of the subjects. As expected, most of these events were associated with leuko-, neutro-, or thrombocytopenia, and - due to the overlapping side effect profile of the study drugs – many of these events were related to both rituximab and [^{90}Y]-Zevalin. Non-hematological AEs regarded as being at least possibly drug-related to [^{90}Y]-Zevalin by the investigators included myocardial infarction, vomiting, asthenia, fatigue, mucosal inflammation, peripheral edema, rhinitis, sinusitis, joint effusion, muscular weakness, dizziness, and insomnia.

Altogether 11 subjects in the study had at least one AE that was of Common Terminology Criteria (CTC) grade 1 intensity (Zevalin: 3, observation: 8), 22 subjects had CTC grade 2 events (Zevalin 8, observation 14), 14 subjects had CTC grade 3 events (Zevalin: 8, observation: 6), 15 subjects had CTC grade 4 events (Zevalin: 13, observation: 2; mostly cytopenic events as these were reported as serious adverse events (SAEs) and 1 subject in the Zevalin arm experienced a CTC grade 5 event (this subject had committed suicide; this event was not considered drug-related).

The most common AEs regardless of relationship to study treatment that occurred during this study (defined as those with an incidence of ≥5.0% at preferred term level) involved "neutropenia" (14 subjects in the Zevalin arm vs 3 subjects in the observation arm) and thrombocytopenia (12 vs 0), followed by "nasopharyngitis" (6 vs 5) and "asthenia" (5 vs 0).

Deaths
Nine subjects died during the study observation period; 3 subjects in the Zevalin arm and 6 subjects in the observation arm. Apart from subject 150103 in the Zevalin group who committed suicide, all subjects had died of disease progression.

Serious Adverse Events (SAEs)
Overall, 14 subjects (41.2%) in the Zevalin arm and 5 subjects (14.7%) in the observation arm had experienced 24 and 6 serious adverse events, respectively.

The SAEs in the observation arm were: "basal cell carcinoma" and "intestinal obstruction" (1 Subject), "cardiac failure" (1 subject), "loss of consciousness" (1 subject) and "neutropenia" (2 subjects). Apart from the unresolved "cardiac failure" (1 subject) all of these SAEs were resolved by the end of the study period.

Since (as per study protocol) all cases of CTC grade 4 thrombocytopenia, leukopenia, anemia, and neutropenia had to be reported as an SAE irrespective of their clinical manifestations, these hematological findings were the prevailing events in the SAE pattern observed in the Zevalin group (altogether 12 subjects: 9 subjects with thrombocytopenia, 5 subjects with neutropenia, 1 subject with lymphopenia, and 1 subject with leukopenia; all these cases of cytopenia were considered drug-related). Almost all of these hematologic events had completely resolved by the end of the study observation period (apart from one case of thrombocytopenia which was reported to have at least improved to CTC grade 2 by the last visit).

Non-hematological SAEs among subjects treated with Zevalin occurred in 5 subjects and were "adenocarcinoma" (non-small cell carcinoma), "myocardial infarction" plus "catheter thrombosis" (same subject), "humerus fracture", "syncope", and "completed suicide". Apart from the episode of myocardial infarction ("possibly" related to both rituximab and [^{90}Y]-Zevalin), these events were not regarded as drug-related.

In summary, the analysis of the drug-related and non-drug related SAEs occurring in the Zevalin group did not point to any unexpected relevant safety findings associated with the administration of Zevalin.

Other significant AEs
No AEs leading to premature discontinuation of study medication were reported in this study.

Clinical laboratory findings
Generally, most of the laboratory values reported over the course of the study were within normal ranges or of CTC grade 1 or grade 2 toxicity.

CTC grade 3/4 laboratory toxicities mostly occurred during the safety period and were associated with a low platelet count and low white blood count/differential blood count induced by the Zevalin treatment. Most of these events were of grade 3 toxicity. For all hematological parameters, the peak cumulating point with respect to the occurrence of grade 3/4 toxicities seemed to be the period between Week 7 (Day 49) and Week 8 (Day 56), since most of these events were noted in this period. Afterwards, the incidence of CTC grade 3/4 toxicities decreased rapidly.

The incidence of CTC grade 3/4 toxicities not associated with any cytopenia (i.e., related to leukocytes, neutrophils, thrombocytes, lymphocytes) was rather low in the 2 study arms both in the safety phase and the follow-up phase. CTC grade 4 toxicities not associated to myelosuppression were noted 2 times only: at Month 6 (glucose; one subject in the Zevalin arm) and at the final visit (potassium, one subject in the observation arm).

Nadir analyses showed a median time to nadir of 51.0 days for platelets (thrombocytopenia), 54.5 days for leukocytes (leukopenia), 58.0 days for neutrophils (neutropenia), 24.0 days for lymphocytes (lymphopenia), and 72.0 days for hemoglobin (anemia).

Vital signs and ECG
There were no clinically relevant findings related to vital signs or the ECG examinations.

Conclusion(s)

This study was prematurely terminated after 68 subjects had been randomized because of an unacceptably low recruitment rate that would have led to an unacceptably long study duration. Notably, no safety concerns or lack of efficacy had led to the decision to cancel the study.

Due to the premature study termination, the planned primary efficacy analysis was strongly underpowered. The analysis of overall survival showed results that were in favor of the Zevalin regimen, but the observed differences were based on a rather small sample size, and the related log-rank test showed a non-significant result.

Basically, this study confirmed the established safety profile of Zevalin given in combination with rituximab as subsequent treatment in DLBCL subjects in complete remission after first-line CHOP-R therapy. The primary toxicity in the Zevalin arm compared to the untreated observation arm was reversible myelosuppression. Accordingly, almost all SAEs occurring in the Zevalin group were associated with bone marrow depletion, and were fully reversible (or at least improved to grade 2 by the end of the observation period in one subject). All of the non-hematological SAEs documented in the Zevalin group were not considered related to study drug treatment apart from myocardial infarction, for which a "possible" relationship to rituximab and Zevalin was suspected by the investigator. However, since the event had occurred not until after approximately 30 weeks following the study drug administration and alternative explanations potentially contributing to the development of coronary heart disease had been found in the subject's medical history, this causality assessment was reasonably revised by the Sponsor.

In conclusion, no relevant differences in the safety experience were found in the comparison of Zevalin-treated subjects with those allocated to the untreated observation arm apart from the expected and reversible effects of Zevalin on platelets and white blood cells, suggesting that radioimmunotherapy with Zevalin given shortly after chemotherapy with CHOP-R to subjects with complete remission does not put these subjects at a higher risk compared to those with no consolidation therapy.

Publication(s):	None		
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Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Pharma AG
Postal Address	D-13342 Berlin Deutschland
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D-51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
1	Universitätsklinikum Innsbruck	LKH Innsbruck Univ.-Klinik fuer Innere Medizin Abt. fuer Haematologie und Onkologie Anichstr. 35 6020 Innsbruck	6020	Innsbruck	AUSTRIA
2	UZ Gent	Dienst hematologie K12 De Pintelaan 185 9000 Gent	9000	Gent	BELGIUM
3	CHUM - Hopital Notre-Dame	1560 Sherbrooke est Montreal, Quebec H2L 4M1	H2L 4M1	Montreal	CANADA
4	Cross Cancer Institute	11560 University Avenue NW	T6G 1Z2	Edmonton	CANADA
5	Sunnybrook Health Sciences Centre	2075 Bayview Avenue	M4N 3M5	Toronto	CANADA

6	HUS, Meilahden sairaala	Syopatautien klinikka PL 180 00029 HUS	00029	Helsinki	FINLAND
7	Oulun yliopistollinen sairaala	PL 10 90029 OYS	90029	Oulu	FINLAND
8	Centre hospitalier du Bocage	Service d'hematologie 2, boulevard du marechal de lattre de tassigny BP 1542	21034	Dijon	FRANCE
9	Centre Hospitalier Regional Henri Mondor	Service d'hematologie 51, avenue du Marechal de Lattre de Tassigny 94010 Creteil	94010	Creteil	FRANCE
10	Centre Léon Bérard	28 Rue Laennec	69003	Lyon	FRANCE
11	Hopital Claude-Huriez CHRU	Hpital claude huriez 6eme ouest F - 59037 Lille Cedex	59037	Lille Cedex	FRANCE
12	Hôpital de la Pitié-Salpétrière - Paris	Hopital de la Pitie salpetriere 47, boulevard de l'hopital 75013 Paris	75013	Paris	FRANCE
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14	Johannes-Gutenberg-Universität Mainz	III. Medizinische Klinik und Poliklinik Bereich Hämatologie und Onkologie Langenbeckstr. 1	55131	Mainz	GERMANY

15	Klinikum Chemnitz gGmbH	Krankenhaus Küchwald Klinik für Innere Medizin III Hämatologie, Onkologie, Stammzelltransplantation BürgerStr. 2	09113	Chemnitz	GERMANY
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17	National Institute of Oncology	Orszagos Onkologiai Intezet - National Institute of Oncology Rath Gy. u. 7-9 1122 Budapest	1122	Budapest	HUNGARY
18	University of Debrecen Medical&Health Science Center	Debreceni Egyetem Orvos es Egeszsegtudomanyi Centrum 2 Belklinika Nagyerdei krt. 98 4032 Debrecen	4032	Debrecen	HUNGARY
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20	IRCCS Ist Europeo Oncologia	Via Ripamonti, 435	20141	Milano	ITALY
21	Ospedale Le Molinette	Ematologia 2 Corso Bramante, 88/90	10126	Torino	ITALY
22	Ospedale Niguarda Ca'Granda	Ematologia Talamona Piazza Ospedale Maggiore, 3	20122	Milano	ITALY
23	Ospedale Silvestrini	Ematologia e Immunologia Clinica Via Brunamonti, 51	06122	Perugia	ITALY

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27	Centrum Onkologii - Instytut im. M.Sklodowskiej-Curie	Klinika Nowotworow Ukladu Chlonnego ul. Roentgena 5	02-781	Warszawa	POLAND
28	Szpital Uniwersytecki w Krakowie	Oddzial Kliniczny Kliniki Hematologii ul. Kopernika 17	31-501	Krakow	POLAND
29	Uniwersyteckie Centrum Kliniczne	Klinika Hematologii i Transplantologii ul. Debinki 7	80-952	Gdansk	POLAND
30	Centro Hospitalar de Lisboa Norte - Hospital Santa Maria	Avenida Professor Egas Moniz	1649-035	Lisboa	PORTUGAL
31	Instituto Portugues de Oncologia de Francisco Gentil	Rua Dr. Antonio Bernardino de Almeida	4200-072	Porto	PORTUGAL
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