Clinical trial results:
Multicenter European pilot study of 90Yttrium-ibritumomab tiuxetan as first line therapy for stage III – IV follicular lymphoma (and selected patients with extended stage II) followed by consolidation Rituximab for patients in complete remission but with persistent molecular disease

Summary

EudraCT number	2006-005778-34
Trial protocol	DE SE AT
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	Zevalin first line in FL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00772655
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Hindenburgdamm 30, Berlin, Germany, 12200
Public contact	Antonio Pezzutto, Department of Hematology, Oncology and Tumor Immunology,CBF, +49 30 450 513631, antonio.pezzutto@charite.de
Scientific contact	Antonio Pezzutto, Department of Hematology, Oncology and Tumor Immunology,CBF, +49 30 450 513631, antonio.pezzutto@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2010
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary end point of this prospective, nonrandomized phase II trial is the clinical and molecular remission rate in response to 90Y-ibritumomab tiuxetan.

Protection of trial subjects:

Because of safety concerns at the time of protocol writing, the local radiation safety authority suggested limiting recruitment to patients age 50 years or older. Eligible patients had to have untreated, histologically confirmed, CD20FL grade 1 to 3a,10 stage II, III, or IV, bidimensionally measurable disease. In case of stage II, only patients requiring extensive radiation fields were eligible. For treatment, at least one of the following was required: presence of "B" symptoms, tumor progression more than 50% in 6 months, organ compression by tumor, bulky disease (lesions5 cm on at least one axis) or grade 3a FL. Patients were not eligible in case of bone marrow infiltration more than 25%, leukocytopenia less than 2,500/L, thrombocytopenia less than 100,000/µL, bulky disease exceeding 10 cm in the largest diameter, CNS lymphoma manifestation, circulating tumor cells more than 500/µL, pleural effusion, or ascites above 1,000 mL.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Italy: 17
Worldwide total number of subjects	59
EEA total number of subjects	59

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 2007 and June 2010, 35 females and 24 males were included in the trial

Pre-assignment

Screening details:

72 Patients were screened
13 patients were exluded due to criteria
59 were randomized

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	90YIT RIT - Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	90Yttrium-Ibritumomab tiuxetan
Investigational medicinal product code	Therapeutic Radiopharmaceutical
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients received rituximab 250 mg/m2 on day 1 followed by 185 MBq indium for dosimetry. On day 8 or 9, patients were given a second infusion of rituximab 250mg/m2 followed by 15 MBq/kg 90YIT up to amaximumdose
of 1,200 MBq.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	Antineoplastic agents, Monoclonal antibodies
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received rituximab 250 mg/m2 on day 1 followed by 185 MBq 111indium for dosimetry. On day 8 or 9, patients were given a second infusion of rituximab 250mg/m2 followed by 15 MBq/kg 90YIT up to amaximumdose of 1,200 MBq.
Patients who attained clinical CR but had evidence of molecular MRD received a consolidation treatment with rituximab 375 mg/m2 once per week for 4 weeks followed by four courses of rituximab 375 mg/m2 given at 8-week intervals.

Number of subjects in period 1	90YIT RIT - Group
Started	59
Completed	59

Baseline characteristics

Reporting groups	
Reporting group title	90YIT RIT - Group

Reporting group description: -

Reporting group values	90YIT RIT - Group	Total	
Number of subjects	59	59	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	66		
full range (min-max)	51 to 83	-	
Gender categorical Units: Subjects			
Female	35	35	
Male	24	24	
ECOG performance score			
ECOG, Eastern Cooperative Oncology Group			
Units: Subjects			
score 0	45	45	
score 1	14	14	
Ann Arbor stage Units: Subjects			
stage I	0	0	
stage II	12	12	
stage III	26	26	
stage IV	21	21	
REAL/WHO grade			
REAL, Revised European-American Lymphoma classification;			
Units: Subjects			
grade 1	22	22	
grade 2	22	22	
grade 2/3a	3	3	
grade 3a	11	11	
grade 3b	0	0	
Not gradable	1	1	

Bone marrow infiltration Units: Subjects			
Percentage:0	37	37	
Percentage: 1-10	6	6	
Percentage: 11-25	16	16	
Bulky disease Units: Subjects			
at least 5 cm	18	18	
less than 5 cm	41	41	
LDH			
LDH, lactate dehydrogenase			
Units: Subjects			
>normal	15	15	
≤ normal	44	44	
FLIPI			
FLIPI, Follicular Lymphoma International Prognostic Index			
Units: Subjects			
Low (zero-one factors)	18	18	
Intermediate (two factors)	25	25	
High (three-five factors)	16	16	
Time from initial diagnosis Units: months			
median	2		
full range (min-max)	0 to 70	-	

End points

End points reporting groups

Reporting group title	90YIT RIT - Group
Reporting group description: -	
Subject analysis set title	Molecular Response Group
Subject analysis set type	Intention-to-treat
Subject analysis set description: CR(u), (unconfirmed) complete response;	

Primary: Response After Therapy With 90YIT

End point title	Response After Therapy With 90YIT
End point description: CR, complete response; CRu, unconfirmed complete response; PD, progressive disease; PR, partial response; SD, stable disease	
End point type	Primary
End point timeframe: at 6 Months	

End point values	90YIT RIT - Group	Molecular Response Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	59	13		
Units: Patients				
CR	24	10		
CRu	9	3		
PR	18	0		
SD	2	0		
PD	6	0		
Deaths	0	0		
off study	0	0		

Statistical analyses

Statistical analysis title	Change of the clinical and molecular Reponse
Comparison groups	90YIT RIT - Group v Molecular Response Group
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Toxicity grade 3

End point title	Toxicity grade 3

End point description:

Hematologic

End point type	Secondary

End point timeframe:

12 months after 90Yttriumibritumomab- tiuxetan (90YIT)

End point values	90YIT RIT - Group			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Patients				
Thrombocytopenia	24			
Leukopenia	19			
Neutropenia	9			
Lymphopenia	12			
Anemia	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity Grade 4

End point title	Toxicity Grade 4

End point description:

End point type	Secondary

End point timeframe:

12 months after 90YIT

End point values	90YIT RIT - Group			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Patients				
Thrombocytopenia	4			
Leukopenia	1			
Neutropenia	10			
Lymphopenia	0			
Anemia	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity Grade 2

End point title	Toxicity Grade 2

End point description:

Nonhematologic toxicities never reached grade 3 or 4. Grade 2 toxicities included infections, gastrointestinal and cardiovascular adverse events, and skin irritations and mucositis.

End point type	Secondary

End point timeframe:

12 months after 90YIT

End point values	90YIT RIT - Group			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: Patients				
Infections	12			
Gastrointestinal	6			
Cardiovascular	3			
Vegetative	3			
Skin irritation	2			
Mucositis	1			
Other	10			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS

End point title	PFS

End point description:

End point type	Secondary

End point timeframe:

After a median follow-up of 30.6 months

End point values	90YIT RIT - Group			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: months				
median (confidence interval 95%)	25.9 (18.2 to 33.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	90YIT RIT - Group

Reporting group description: -

Serious adverse events	90YIT RIT - Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 59 (16.95%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
cerebellar tumor			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Thrombocytopenia Grade 4			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Leukopenia Grad 4			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anemia Grade 4			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia Grade 4			

subjects affected / exposed	10 / 59 (16.95%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Lymphoma			
subjects affected / exposed	4 / 59 (6.78%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Adenocarcinoma cecum			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
oral cancer (Upper gastrointestinal)			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
adenocarcinoma			
subjects affected / exposed	1 / 59 (1.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
renal cell cancer			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	90YIT RIT - Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 59 (40.68%)		

Blood and lymphatic system disorders			
Anemie			
subjects affected / exposed	24 / 59 (40.68%)		
occurrences (all)	24		
Leukocytopenia			
subjects affected / exposed	19 / 59 (32.20%)		
occurrences (all)	19		
Neutropenia			
subjects affected / exposed	21 / 59 (35.59%)		
occurrences (all)	26		
Thrombocytopenia			
subjects affected / exposed	21 / 59 (35.59%)		
occurrences (all)	29		
Infections and infestations			
Skin Herpes Zoster			
subjects affected / exposed	2 / 59 (3.39%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2009	Request for prolongation of the recruitment period of the study until 30.06.2010. Change of co-PI

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/2323371