CLINICAL STUDY REPORT

NAME OF SPONSOR/COMPANY: VU Medical Center NAME OF STUDY TREATMENT: obinutuzumab TRADENAME: Gazyvaro	

TITLE OF THE STUDY	**A phase II study of obinutuzumab monotherapy in rituximab-refractory follicular lymphoma**
Protocol number (ToetsingOnline) EUDRACT number METC protocol number	NL48577.029.14 2013-004635-69 2014.153
DATE OF REPORT	18th of May, 2022
NUMBER OF STUDY CENTERS AND COUNTRIES	This study was conducted at 1 center in 1 country: the Netherlands
PUBLICATIONS	**^{89}Zr-Immuno-PET: Toward a Noninvasive Clinical Tool to Measure Target Engagement of Therapeutic Antibodies In Vivo.** Jauw YWS, O'Donoghue JA, Zijlstra JM, Hoekstra OS, Menke-van der Houven van Oordt CW, Morschhauser F, Carrasquillo JA, Zweegman S, Pandit-Taskar N, Lammertsma AA, van Dongen GAMS, Boellaard R, Weber WA, Huisman MC.J Nucl Med. 2019 Dec;60(12):1825-1832. doi: 10.2967/jnumed.118.224568. Epub 2019 May 30. PMID: 31147401 **First-in-human in-vivo biodistribution of a glyco-engineered antibody: ^{89}Zirconium-labeled obinutuzumab in patients with non-Hodgkin lymphoma** Yvonne Jauw, Josee Zijlstra, Otto Hoekstra, Sonja Zweegman, Pascal Odou, Danielle Vugts, Damien Huglo, Franck Morschhauser and Marc Huisman Journal of Nuclear Medicine May 2017, 58 (supplement 1) Abstract 387; Oral presentation SNMMI Annual Meeting 2017 **Beyond SUV: from false-positive to true positive tumor uptake measures of ^{89}Zr-labeled CD20 monoclonal antibody** Marc Huisman, Ronald Boellaard, Josee Zijlstra, Daphne de Jong, Danielle Vugts, Sonja Zweegman, Otto Hoekstra, Guus Van Dongen and Yvonne Jauw Journal of Nuclear Medicine May 2019, 60 (supplement 1) Abstract 125;

	Oral presentation SNMMI Annual Meeting 2019 **^{89}Zr-Immuno-PET: Toward a Noninvasive Clinical Tool to Measure Target Engagement of Therapeutic Antibodies In Vivo.** Jauw YWS, O'Donoghue JA, Zijlstra JM, Hoekstra OS, Menke-van der Houven van Oordt CW, Morschhauser F, Carrasquillo JA, Zweegman S, Pandit-Taskar N, Lammertsma AA, van Dongen GAMS, Boellaard R, Weber WA, Huisman MC. Journal of Nuclear Medicine May 2019, 60 (supplement 1) Abstract 1407; Poster presentation SNMMI Annual Meeting 2019
STUDY PHASE	II
STUDY PERIOD	First Patient Enrolled: 19-08-2014 Early termination date: 25-10-2019
METHODOLOGY	Study design: Phase II, single-cohort, non-blinded, single-agent, interventional single center study. The Simon two-stage design will be used: 12 to 25 eligible patients will be included in the study, according to the number of responses observed in the first 12 patients. The maximum study duration is 2.5 years per patient, consisting of a maximum of 6 months for the treatment phase (Induction I and II) and a maximum of 2 years for the maintenance phase. Study population: Patients with biopsy-proven rituximab-refractory follicular lymphoma, will be included. Upon enrollment of this study, a baseline FDG-PET-CT scan will be obtained. Patients are scheduled for 5 treatment visits, where obinutuzumab will be administered intravenously. During therapy and follow-up, patients are scheduled for standard laboratory analysis and PET/CT scans on visits to the outpatient clinic. The exposure to ionizing radiation is non-negligible, but patient may have clinical benefit by study treatment. Patients do not require shielding after injection of ^{89}Zr-labeled obinutuzumab. Patients with clinical benefit (defined as CR, PR or SD) measured with FDG-PET at week 10-12 are eligible for continuation of obinutuzumab monotherapy with 4 monthly infusions (Induction II). Responding patients (defined as CR, PR or SD) measured with FDG-PET at month 6, will receive a bimonthly maintenance treatment with obinutuzumab for up to 2 years, as tolerated or until disease progression.

	All adverse events will be reported during the study period up to 28 days after the last drug administration regardless of the relationship with study drug and after this period if the event is related to the study drug. Before obinutuzumab dosing: After Informed Consent, but prior to any study medication, only SAEs caused by protocol-mandated intervention needs to be reported (e.g. SAE related to invasive procedures) During obinutuzumab dosing: All AEs / SAEs needs to be reported during use of the obinutuzumab. After obinutuzumab dosing: All SAEs from the last dose of the IMP up to 28 days need to be reported. All SAEs considered of having a causal relationship to the obinutuzumab (as considered by the investigator) need to be reported, regardless of time elapsed since last obinutuzumab dose even if the study has stopped.
NUMBER OF PATIENTS (PLANNED AND ANALYZED)	A total of 12 to 25 eligible patients was planned to be included in the study, according to the number of responses observed in the first 12 patients. A total of 6 patients were included. One patient was a screen failure due to transformation to aggressive lymphoma in the biopsy at screening. Data of the other 5 patients have been analyzed. The study was terminated early due to insufficient inclusion of patients.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	♦ Biopsy-proven rituximab refractory follicular lymphoma (defined as a relapse or disease progression within 6 months after discontinuation of rituximab containing treatment). ♦ No clinical or pathological evidence of transformation to high-grade or diffuse large B-cell lymphoma (e.g. B symptoms, fast-growing tumour, or increasing lactate dehydrogenase level) ♦ Patients must have radiographically documented measurable disease, defined as 2 or more clearly demarcated lesions with a largest diameter of at least 1.5 cm or 1 clearly demarcated lesion with a largest diameter of at least 2.0 cm by computed tomography scan. All radiology studies must be performed within 14 days prior to registration. ♦ Adult patients, >=18 years of age ♦ Clinical indication for treatment as determined by the “treating physician” ♦ ECOG performance status of 0, 1 or 2.

	♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial ♦ Before patient registration, written informed consent must be given according to GCP, and national regulations.
STUDY TREATMENTS, DOSE, MODE OF ADMINISTRATION	Four weekly infusions of obinutuzumab (Induction I) were given intravenously in a dose of 1000mg as induction therapy, with the exception of the first infusions in week 1 (100mg on day 0 and 900mg on day 1, followed by 10mg of ^{89}Zr-obinutuzumab (37MBq), as a bolus of 20ml with flushing (10ml physiologic saline). Patients with clinical benefit of Induction I, consisting of 4 weekly infusions of obinutuzumab, (defined as CR, PR or SD) are eligible for continuation of treatment with 4 monthly infusions of 1000mg obinutuzumab monotherapy (Induction II). Patients with responding disease on FDG-PET at month 6 are eligible for obinutuzumab maintenance therapy in a bimonthly schedule for a maximum of 2 years or until disease progression
DURATION OF STUDY TREATMENT	The maximum study duration was 2.5 years per patient, consisting of a maximum of 6 months for the treatment phase (Induction I and II) and a maximum of 2 years for the maintenance phase.

SUMMARY OF OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Statistical Analyses
Primary • To determine the overall response rate (ORR) of 4 weekly infusions of obinutuzumab monotherapy (Induction I) in patients with rituximab-refractory follicular lymphoma.	• Overall response rate using the Lugano Response Classification 2014 for disease assessment.	Not analyzed: early study termination due to insufficient inclusion
Secondary • To determine the efficacy (defined as progression free survival, overall survival, duration of response, duration of stable disease, time to next treatment) of obinutuzumab monotherapy given as 4 weekly infusions (Induction I) to rituximab-refractory follicular lymphoma patients • To determine the efficacy (defined as ORR, progression free survival, overall survival, duration of response, duration of stable disease, time to next treatment) of obinutuzumab monotherapy given as 4 monthly infusions (Induction II) to rituximab-refractory follicular lymphoma patients responding to 4 weekly infusions of obinutuzumab monotherapy	• Progression-free survival • Overall survival • Duration of response, in responders • Duration of stable disease • Time to next treatment • The detection of tumour lesions employing contrast enhanced CT-scan • The detection of tumour lesions employing ^{18}F-FDG-PET • The detection of tumour lesions employing ^{89}Zr-obinutuzumab-PET • The detection of ^{89}Zr-obinutuzumab in normal tissue • The description of safety data: all adverse and serious adverse events according to the NCICTCAE v.4.	Due to the limited number of patients included the secondary objectives: progression free survival, overall survival, duration of response, duration of stable disease and time to next treatment were not analyzed. For the imaging objectives, descriptive data analysis on tumor uptake and biodistribution of ^{89}Zr-obinutuzumab is provided. The number of patients included is too limited for comparisons or to determine relationships/value of imaging techniques.

• To determine the efficacy (defined as progression free survival, overall survival, duration of response, duration of stable disease, time to next treatment) of obinutuzumab maintenance given as bimonthly infusions (up to a maximum of 2 years) to rituximab-refractory follicular lymphoma patients responding to 4 weekly infusions of obinutuzumab monotherapy (Induction I), followed by 4 monthly infusions of obinutuzumab monotherapy (Induction II). • To investigate the relationship between tumour uptake on immuno-PET and tumour response to obinutuzumab • To compare tumour uptake using immuno-PET as a novel imaging biomarker to “standard imaging technique” (18F-FDG-PET/CT) • To determine the value of 18F-FDG-PET-CT scanning in response assessment of follicular lymphoma patients • To investigate the biodistribution and dosimetry in normal tissue of 89Zr-obinutuzumab • To assess safety data by monitoring all adverse and serious adverse events (AEs/SAEs) according to the NCI CTCAE v.4.		

SUMMARY OF RESULTS AND CONCLUSIONS

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Patient	Gender	Age	Biopsy at screening	Stage	Weight (kg)	Height (cm)	Previous treatment lines
1	Male	50	FL	IV	106	187	1
2	Male	75	FL	IV	85	172	2
3	Female	60	FL	IV	61	164	2
4	Male	67	FL	IV	65	186	1
5	Female	45	FL	IV	78	174	1
6	Male	66	Transformed *				

*screen failure

EXPOSURE

Patient	Induction I (1000mg, 4, weekly)	Induction II (1000mg, 4, monthly)	Maintenance (1000mg, bimonthly, maximum of 2 years)
1	Completed	Completed	-
2	Completed	-	-
3	Completed	Up to C3D1	-
4	Completed	-	-
5	Completed	-	-
6	-	-	-

EFFICACY RESULTS

Patient	Response after Induction I	Response after Induction II
1	PR	PD
2	PD	-
3	PR	PD
4	PD	-

5	PD	-
6	-	-

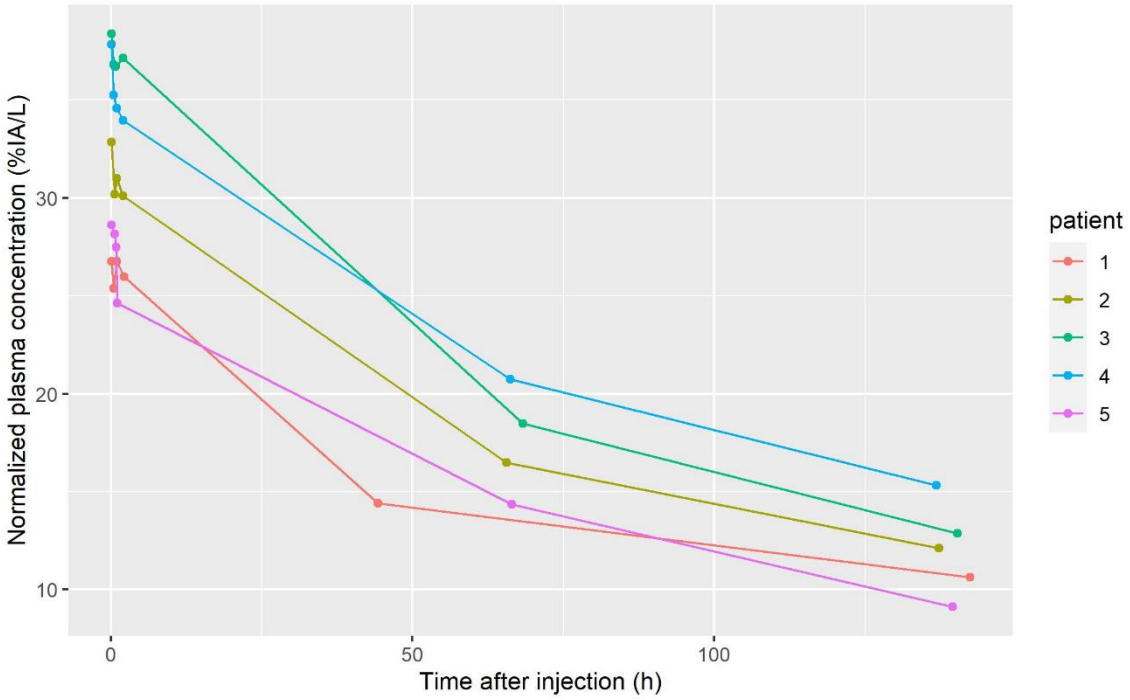
Due to the limited number of patients included the secondary objectives: progression free survival, overall survival, duration of response, duration of stable disease and time to next treatment were not analyzed.

SAFETY RESULTS

Patient	SAE	AE
1	No	No
2	No	No
3	No	Yes, urine tract infection, grade 2 (oral antibiotics)
4	No	No
5	No	No
6	-	-

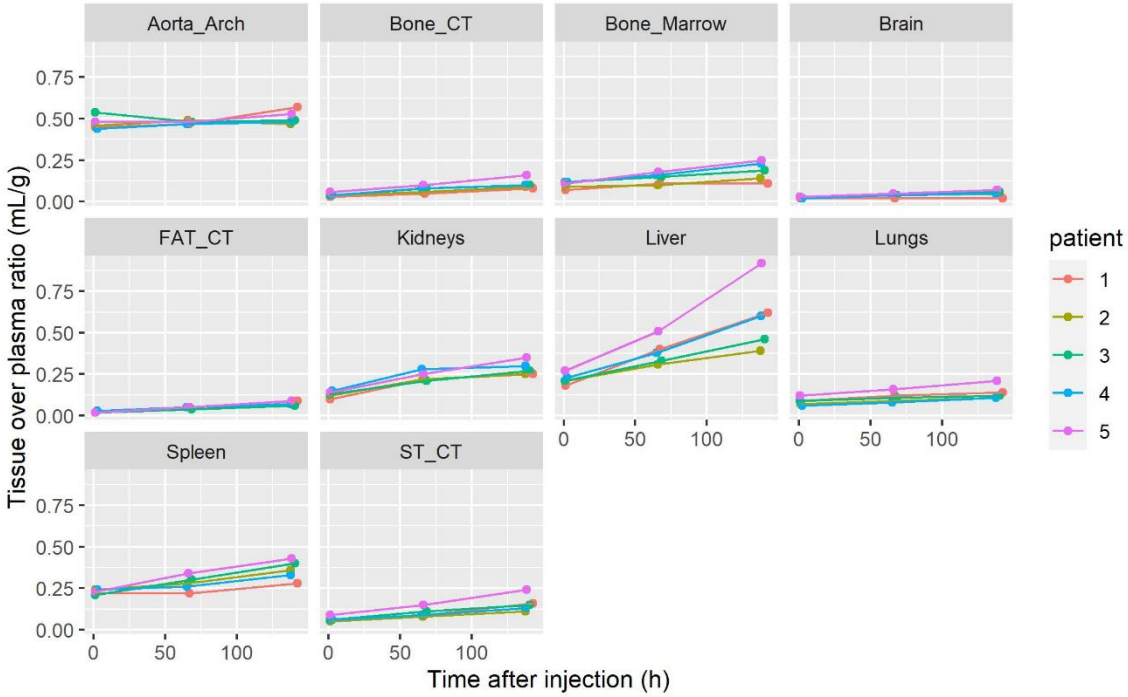
PHARMACOKINETICS RESULTS

PK of ^{89}Zr-obinutuzumab



OTHER RESULTS

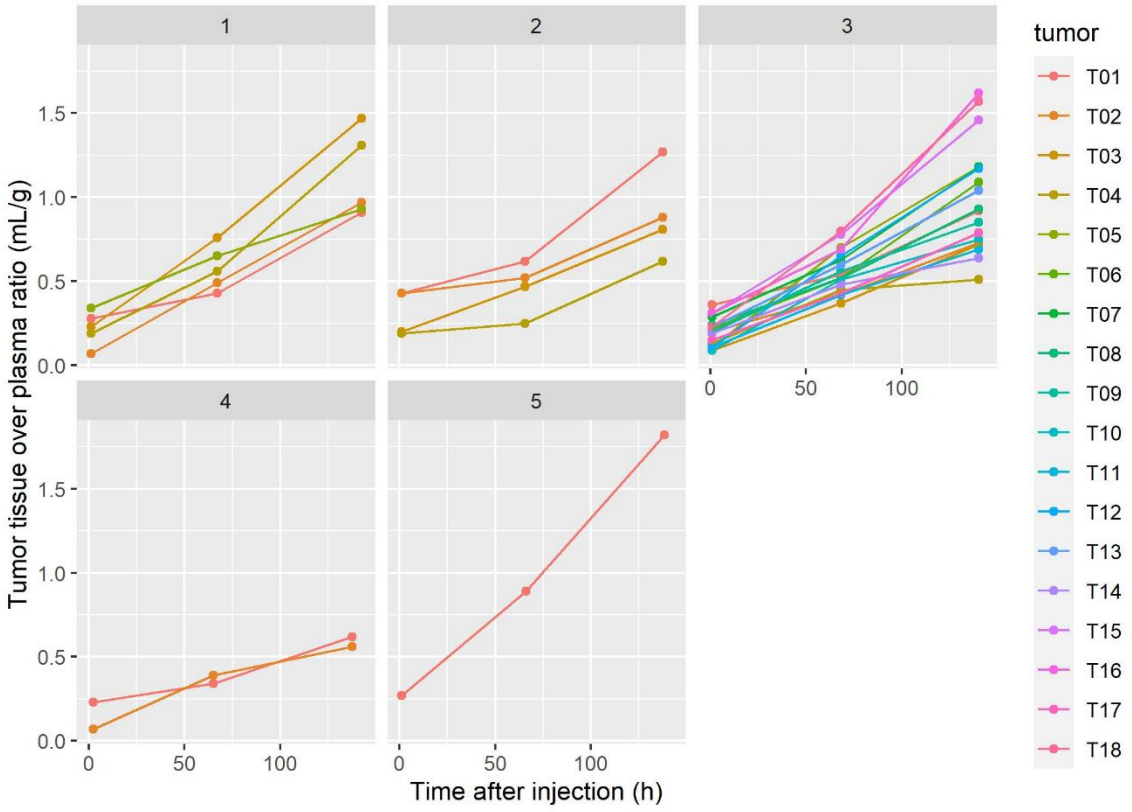
Biodistribution of ^{89}Zr-obinutuzumab in normal tissue



Dosimetry of ^{89}Zr-obinutuzumab

The effective whole body radiation dose of ^{89}Zr-obinutuzumab was 0.49 mSv/MBq (based on the first three patients; two males and one female).

Tumor uptake of ^{89}Zr-obinutuzumab



CONCLUSIONS

- Monotherapy with obinutuzumab in patients with rituximab-refractory follicular lymphoma was safe and well tolerated.
- Efficacy of obinutuzumab monotherapy in patients with rituximab-refractory follicular lymphoma could not be evaluated due to the limited number of patients included.
- ^{89}Zr-immuno-PET provides a non-invasive clinical tool to assess biodistribution and tumor uptake of ^{89}Zr-obinutuzumab.