CLINICAL STUDY REPORT

Title:	Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström Macroglobulinemia. A Multicenter Open Label, Two-Arm Randomized European Phase III Study
Study number:	ECWM-1
EudraCT number:	2013-000506-37
Test drug:	Bortezomib s.c. Rituximab i.v. and s.c.
Development phase:	Phase III
Sponsor's name and address:	University Hospital Ulm, Ulm, Germany; represented by the Chairman of the board
Co-ordinating Investigator:	Prof. Dr. Christian Buske University Hospital of Ulm Department of Internal Medicine III Albert-Einstein-Allee 23, D-89081 Ulm Phone: +49 / 731 / 500-65801 E-mail: christian.buske@uni-ulm.de
Responsible Statistician:	Prof Pierre Morel and Dr Caroline Skrypczak Service d'Hématologie Clinique et Thérapie Cellulaire CHU Amiens Picardie, Rondd Point du Pr Cabroln 80054 Amiens; Cedex1
Study dates:	Study initiation date (first patient enrolled): 28-JAN-2014 Date of early recruitment termination: 21-SEP-2018 Last patient last treatment: 17-APR-2019 Study completion date (last patient completed): 16-APR-2024
Version/date:	Version: Final 1.0, date: 08-Apr-2025

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2 SIGNATURE PAGE

PRINCIPAL OR COORDINATING INVESTIGATOR'S SIGNATURE OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström Macroglobulinemia.
A Multicenter Open Label, Two-Arm Randomized European Phase III Study

STUDY AUTHORS: Prof. Dr. Christian Buske; Principal Coordinating Investigator and Sponsor's responsible Medical Officer
Dr. Pierre Morel, Statistician

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

INVESTIGATOR/SPONSOR: Prof. Dr. Christian Buske

AFFILIATON: University Hospital of Ulm
Department of Internal Medicine III
Albert-Einstein-Allee 23
D-89081 Ulm

DATE: 08.04.2025 SIGNATURE: 

3 STUDY SYNOPSIS

Name of Sponsor: University Hospital of Ulm	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product:	Volume:	
Name of Active Ingredient:	Report:	

Title of the study:	Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström Macroglobulinemia. A Multicenter Open Label, Two-Arm Randomized European Phase III Study Study number: ECWM-1
Investigator(s):	Coordinating Investigator, *Leiter der klinischen Prüfung* according to German law: Prof. Dr. Christian Buske, Comprehensive Cancer Center / Department of Internal Medicine III, University of Ulm, Albert-Einstein-Allee 11, 89081 Ulm Co-coordinating investigators: Dr. Pierre Morel (France) Prof. Dr. Meletios A. Dimopoulos, (Greece) Lena Brandefors (Sweden) Prof. Dr. R. Garcia Sanz (Spain) Prof. Dr. M. Gomes da Silva (Portugal) Prof. Dr. Roman Hajek (Czech Republic)
Study centre(s):	Total number of centers recruiting in the study: 54 Number of centers in: France 27 Germany 22 Greece 1 Sweden 1 Spain 1 Portugal 1 Czech Republic 1
Publications (references):	J Clin Oncol. 2023 May 10;41(14):2607-2616
Period of study:	Study initiation date (first patient enrolled): 28-JAN-2014 Date of early recruitment termination: 21-SEP-2018 Last patient last treatment: 17-APR-2019 Study completion date (last patient completed): 16.04.2024
Clinical phase:	Phase III
Objectives:	Primary study objectives: Progression Free Survival Secondary study objectives: Response rates (CR, VGPR, PR, MR) and overall response rate (ORR) four weeks after the end of induction therapy, best response, time to best response, time to first response, time to treatment failure, remission duration, cause specific survival, overall survival

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Methodology (design of study):

European phase III trial, multicenter, two–arm, open label, and randomized

Treatment phase:

- WM patients in need of treatment.
- Randomization between Arm A & Arm B

Induction standard arm (Arm A)

Cycle 1:

- Dexamethasone 20 mg p.o. Day 1
- Rituximab 375 mg/m^2 i.v. Day 1
- Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5

Cycle 2-6:

- Dexamethasone 20 mg p.o. Day 1
- Rituximab 1400 mg absolute s.c. Day 1
- Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5

Repeat day 29.

Induction experimental arm (Arm B):

Cycle 1:

- Bortezomib 1.6 mg/m^2 s.c. Day 1,8,15
- Dexamethasone 20 mg p.o. Day 1
- Rituximab 375 mg/m^2 i.v. Day 1
- Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5

Cycle 2-6:

- Bortezomib 1.6 mg/m^2 s.c. Day 1,8,15
- Dexamethasone 20 mg p.o. Day 1
- Rituximab 1400 mg absolute s.c. Day 1
- Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5

Repeat day 29.

Patients were stratified according to: country, ISSWM

Follow-up Phase

All subjects who entered the trial were continued to be followed every 3 months for disease progression, subsequent treatment, and survival for two years after completion/discontinuation of the induction treatment. Subsequently, patients were monitored every 6 months for three additional years.

Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) was installed and composed of 3 members, including a statistician, who were not involved in the execution of the trial. The DSMC reviewed data regarding safety including the three safety analyses (see below) as planned according to the DSMC Charter.

Path Reference

Archival lymph node or bone marrow biopsy specimen obtained at the time of initial diagnosis with representative stained slides, were submitted to the national pathology of the participating study group for confirmation of WM. The investigative site submitted a bone marrow biopsy as well as aspirate slides and tumour/lymph node biopsy slides (if available) as part of the baseline screening (preferentially whole tumour blocks, and both unstained and HE stained slides).

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Number of patients:	384 patients were planned. Recruitment was stopped after 202 patients were enrolled.
Diagnosis and main criteria for inclusion:	• Clinicopathological diagnosis of WM as defined by consensus panel one of the Second International Workshop on WM. Pathological diagnosis had to occur before study inclusion and randomization. In addition, pathological specimens had to be sent to the national pathological reference center at study inclusion and randomization. The positivity for CD20 could be assumed from any previous bone marrow immunohistochemistry or flow cytometry analysis performed up to 6 months prior to enrollment. Inclusion in the study was based on morphological and immunological criteria. Immunophenotyping was performed in each center and saved locally. Flow cytometry of bone marrow and blood cells included at least one double staining and assessed the expression of the following antigens: surface immunoglobulin, CD19, CD20, CD5, CD10 and CD23. Patients were eligible if tumor cells expressed the following antigens: CD19, CD20, and if they were negative for CD5, CD10 and CD23 expression. Patients with tumor cells positive for CD5 and/or CD23 and morphologically similar to WM cells might have been included after ruling out other low-grade B-cell malignancies. • Presence of at least one criterion for initiation of therapy, according to the 2nd Workshop on WM: - Recurrent fever, night sweats, weight loss, fatigue - Hyperviscosity - Lympadenopathy which is either symptomatic or bulky (≥5 cm in maximum diameter) - Symptomatic hepatomegaly and/or splenomegaly - Symptomatic organomegaly and/or organ or tissue infiltration - Peripheral neuropathy due to WM - Symptomatic cryoglobulinemia - Cold agglutinin anemia - IgM related immune hemolytic anemia and/or thrombocytopenia - Nephropathy related to WM - Amyloidosis related to WM - Hemoglobin ≤10g/dL - Platelet count <100x10^9/L - Serum monoclonal protein >5g/dL, even with no overt clinical symptoms • Cumulative illness rating scale (CIRS) score less than 6 • World Health Organization (WHO)/ECOG performance status 0 to 2. • Other criteria: - Age ≥ than 18 years - Life expectancy >3 months. - Baseline platelet count ≥ 50 x 10^9/L, absolute neutrophil count ≥ 0.75 x 10^9/L (if not due to BM infiltration by the lymphoma). - Meet the following pre-treatment laboratory criteria at the Screening visit conducted within 28 days of study enrollment: o ASAT (SGOT): ≤3 times the upper limit of institutional laboratory normal value o ALAT (SGPT): ≤3 times the upper limit of institutional laboratory normal value

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- o Total Bilirubin: ≤20 mg/L or 2 times the upper limit of institutional laboratory normal value, unless clearly related to the disease (except if due to Gilbert's syndrome)
- o Serum creatinine: ≤ 2mg/dl

- Premenopausal fertile females had to agree to use a highly effective method of birth control for the duration of the therapy up to 6 months after end of therapy. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.
- Men had to agree not to father a child for the duration of therapy and 6 months after and had to agree to advice a female partner to use a highly effective method of birth control.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent might have been withdrawn by the subject at any time without prejudice to future medical care.
- Prior systemic treatment of the WM (plasmapheresis and short–term administration of corticosteroids < 4 weeks administered at a dose equivalent to < 20 mg/day prednisone is allowed)
- Patient with hypersensitivity to dexamethasone.
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Uncontrolled bacterial, viral or fungal infection
- Active HIV, HBV or HCV infection
- Known interstitial lung disease
- Prior allergic reaction or severe anaphylactic reaction related to humanized or murine monoclonal antibody.
- Central Nervous System involvement by lymphoma
- Prior history of malignancies unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
  - o Basal cell carcinoma of the skin,
  - o Squamous cell carcinoma of the skin,
  - o Carcinoma in situ of the cervix,
  - o Carcinoma in situ of the breast,
  - o Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
- Uncontrolled illness including, but not limited to:
  - o Uncontrolled diabetes mellitus (as indicated by metabolic derangements and/or severe diabetes mellitus related uncontrolled organ complications)
  - o Chronic symptomatic congestive heart failure (Class NYHA III or IV).
  - o Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months
  - o Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
  - o Known pericardial disease
- Subjects with ≥ Grade 2 neuropathy.
- Women who are pregnant as well as women who are breast feeding and did not consent to discontinue breast-feeding.

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	• Participation in another clinical trial within four weeks before randomization in this study • No consent for registration, storage and processing of the individual disease-characteristics and course as well as information of the family physician about study participation.
Test product, dose and mode of administration, batch number:	The Induction experimental arm (Arm B) is considered the test treatment in this study. It consisted of the administration of study drug as follows: Cycle 1: • Bortezomib 1.6 mg/m^2 s.c. Day 1,8,15 • Dexamethasone 20 mg p.o. Day 1 • Rituximab 375 mg/m^2 i.v. Day 1 • Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5 Cycle 2-6: • Bortezomib 1.6 mg/m^2 s.c. Day 1,8,15 • Dexamethasone 20 mg p.o. Day 1 • Rituximab 1400 mg absolute s.c. Day 1 • Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5
Duration of treatment:	Each patient receives treatment over a period of 6 28-day-cycles, i.e. treatment duration is 6 months
Reference therapy, dose and mode of administration, batch number:	The Induction standard arm (Arm A) is considered the reference therapy. It consisted of the administration of study drug as follows: Cycle 1: • Dexamethasone 20 mg p.o. Day 1 • Rituximab 375 mg/m^2 i.v. Day 1 • Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5 Cycle 2-6: • Dexamethasone 20 mg p.o. Day 1 • Rituximab 1400 mg absolute s.c. Day 1 • Cyclophosphamide 100 mg/m^2 x 2 p.o. Day 1-5
Criteria of evaluation:	The aim of this study was to compare the progression free survival (PFS) of previously untreated WM patients with WHO/ECOG performance between 0 and 2, after combination therapy with either DRC or DRC plus Bortezomib (B-DRC). **Parameters for the comparison of the treatment groups:** PFS as the interval between time from randomization to the first documented progression or death due to any cause. **Expected improvement for the experimental arm (arm BR)** Using the results of the update of the Greek DRC trial as baseline, the improvement of the 2-year progression free survival from 65 to 80% seems to be a clinical plausible improvement.

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Statistical methods:

Efficacy:

Summary statistics are provided for all relevant efficacy endpoints by treatment group.

The primary efficacy analyses are based on the intent-to-treat population (ITT) which includes all randomized subjects. PFS, the primary endpoint of this study, was defined as the interval between time from randomization to the first documented progression or death due to any cause.

Patients in ongoing remission at the time of analysis are censored on the date of their last follow-up.

Kaplan-Meier estimates of PFS function are provided. Hazard ratios with 95% confidence intervals are estimated using the Cox proportional hazards model. Subgroup analysis for PFS is performed.

Secondary endpoints are analyzed to further assess treatment.

For efficacy including response rates, duration of response, overall survival etc. Fisher's exact test are used to compare response rates between the two treatment groups.

Safety:

Data from all subjects who received at least one dose of study drug are included in the safety analyses.

Safety analyses were planned to be performed on all included patients at 17, 32 and 48 months after the inclusion of the first patient. With the anticipated inclusion rate as outlined above this corresponded to safety analyses 6 months after the inclusion of at least 100 randomized patients. The first DSMC was held when 177 patients were randomized in the trial.

Summary and conclusions:

Efficacy: Differences between both treatment groups in the primary endpoint and in all secondary endpoints could not be shown with this trial. The additional treatment with bortezomib (arm B) results in a numerically earlier response.

Safety: The number of patients with any AE and patients with any AE of grade ≥ 3 is similar in both treatment groups. The number of patients with serious AEs and serious AE of grade ≥ 3 is equal in both arms.

Conclusions: This analysis also demonstrated that with longer follow-up there is no significant difference in PFS or OS between the two treatment arms. This illustrates that DRC on its own is highly effective in controlling the disease and that it is still justified to consider DRC as one of the standard treatments in WM. There was a numerical difference in the time to major response in favor of Bortezomib-DRC, which underlines that particularly in patients with a highly dynamic disease and higher tumor burden, adding of Bortezomib to DRC may have a clinical benefit.

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5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AL(A)T (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
AMG	Arzneimittelgesetz (German Drug Law)
AS(A)T (SGOT	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area under the concentration-time curve
B-DRC	Bortezomib/Dexamethasone/Rituximab/Cyclophosphamide
BMI	Body mass index
BSA	Body surface area
C1D1	Cycle 1, Day 1
CA	Competent authority
CBC	Complete blood count
CD20	Antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	Cyclophosphamide/Doxorubicin/Vincristine/Prednisone
CI	Confidence interval
CIRS	Cumulative illness rating scale
CLL	Chronic lymphatic leukemia
CR	Complete remission/response
CRF	Case report form
CRO	Contract research organization
CSS	Cause-specific survival
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
DNA	Deoxyribonucleic acid
DRC	Dexamethasone/Rituximab/Cyclophosphamide
DSMC	Data safety monitoring committee
DSUR	Development safety update report
EC	Ethics committee
ECOG	Eastern cooperative oncology group
GCP	Good Clinical Practice
HBV	Hepatitis-B-virus
HCV	Hepatitis-C-virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISSWM	International Prognostic Index WM
ITT	Intention-to-treat
i.v.	Intravenous

LDH	Lactic Dehydrogenas
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor response
NCI	National cancer institute
ORR	Overall response ratio
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PP	Per-protocol
PR	Partial remission
RD	Remission duration
RNA	Ribonucleic acid
SAE	Serious adverse event
s.c.	subcutaneous
SD	Stable disease
SmPC	Summary of product characteristics
TTF	Time to treatment failure
VGPR	Very good partial response
WHO	World Health Organization
WM	Waldenström’s macroglobulinemia

6 ETHICS

6.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The sponsor submitted this study to country central ethics review committees and to competent authorities and forwarded a copy of written approvals / advices to the investigators.

A list of IECs or IRBs is given in Appendix 15.1.

6.2 ETHICAL CONDUCT OF THE STUDY

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989), the 48th (Somerset West, 1996), the 52nd (Edinburg, 2000) World Medical Assemblies, notes for clarification added by the WMA General Assembly on paragraph 29 (Washington 2002) and on Paragraph 30 (Tokyo 2004) and amendment laid down by the 59th (Seoul, October 2008) World Medical Assemblies.

This study is also in accordance with laws and regulations of the countries in which the trial was performed, as well as any applicable guidelines.

6.3 PATIENT INFORMATION AND CONSENT

The investigator obtained informed consent in compliance with national requirements from each subject prior to any study related procedure or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent was reviewed and approved by the sponsor prior to Ethics Review Committee submission.

The investigator explained to a potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it might entail. Patients were informed that they are free not to participate in the trial and that they might withdraw consent to participate at any time. They were told which alternative treatments are available if they refused to take part and that such refusal would not prejudice future treatment.

If the withdrawal was caused by any adverse drug events, the patient should have informed the investigator about this fact. All data collected before the time point of withdrawal remained within the study database (according to AMG §40 (2a) 3). Consent was sought from the patient, in order to be allowed to

- report further major outcome information (e.g. efficacy data)
- guarantee the safety of a patient

- comply with requirements to submit complete documents for authorisation.

Documentation that informed consent had occurred prior to the study subject's entry into the study and of the informed consent process should have been recorded in the study subject's source documents including the date.

The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, is maintained in the Investigator's study files and a copy was given to the study subject. In addition, if the protocol was amended and it had impact on the content of the informed consent, the informed consent document was revised. Study patients participating in the study when the amended protocol was implemented had to re-consent with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject are maintained in the investigator's study files and a copy given to the study subject.

No compensation was paid to the patients.

7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator, Leiter der klinischen Prüfung according to German law:

Prof. Dr. Christian Buske, Comprehensive Cancer Center / Department of Internal Medicine III, University of Ulm, Albert-Einstein-Allee 11, 89081 Ulm

Co-coordinating investigators:

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Lena Brandefors, Sunderby Sjukhus, Medicinklinken, Hematologiska dagvarden, avd 62, 97180 Lulea, Sweden

Prof. Dr. R. Garcia Sanz, University Hospital of Salamanca, Paseo de San Vicente, 58-182, 37007 Salamanca, Spain

Prof. Dr. M. Gomes da Silva, Instituto Portugues de Oncologia de Lisboa Francisco Gentil – EPE (IPOLFG-EPE), Department of Hematology, Rua Prof. Lima Basto, 1099-023 Lisboa, Portugal

Prof. Dr. Roman Hajek, Fakultni nemocnice Ostrava, Klinka hematoonkolgie, 17. Listopadu 1790, 70852 Ostrava, Czech Republic

A list of all recruiting study centers with addresses is provided in Appendix 15.2.

A Data Safety Monitoring Board was constituted by the following persons:

Prof. Dr. Michele Ghielmini, Istituto Oncologico della Svizzera Italiana, Ospedale Regionale Bellinzona e Valli, 6500 Bellinzona, Switzerland

Prof. Tadeusz Robak, Department of Hematology, Medical University of Lodz, Copernicus Memorial Hospital, 93-510 Lodz, Ul. Ciolkowskiego 2, Poland

Prof. Dr. Stefano Suciu, EORTC, Senior Statistician, Avenue E. Mounier 83/11, 1200 Brussels, Belgium

8 INTRODUCTION

Waldenström's macroglobulinemia (WM) is defined by a bone marrow infiltration by lymphoplasmacytic cells and the presence of a monoclonal immunoglobulin (Ig) M gammopathy in the peripheral blood[1]. The clinical understanding of the disease has been greatly improved by the identification of internationally recognized criteria for initiating therapy[2], the description of an international prognostic index for patients requiring a first-line therapy[3] and the definition of response criteria. These criteria are mainly based on the evolution of serum IgM concentration[4]. However, delayed IgM monoclonal protein responses may cause important difficulties in response assessment. In addition, discrepancies between the kinetics of serum M protein reduction and the clearance of monoclonal B-cells from the bone marrow have been reported[5].

Despite continuing advances in the therapy of WM, the disease remains incurable with a median survival of 5 to 8 years from the time of diagnosis thereby necessitating the development and evaluation of novel treatment approaches.

During the last 10 years, many biological studies demonstrated a large heterogeneity among WM patients, whereas other papers reported some abnormalities frequently observed in WM patients. Moreover, several studies supported the role of several pathways in regulation of survival and homing in WM.

Improvements of therapeutic results have been attempted by evaluating numerous combinations of the currently available agents. Nevertheless, it is especially important to take the side effects of these regimens into account, because of the age of onset of the disease (median 65 years). Such regimens should be avoided in patients who will more likely experience damage than benefit due to their frailty, either related to a poor performance status or a significant number of comorbidities as assessed by the use of currently available comorbidity scores.

Single agent regimen based on alkylating agent, purine analogs, and bortezomib demonstrated significant activity in symptomatic patients.

The use of rituximab as single agent regimen is associated with response rates 27 to 48% [6] [7] [8] [9] [10] [11] around 30%. The delivery of this regimen can be associated with a flare syndrome defined by an unexpected rise of the level of the monoclonal component within 4 to 8 weeks following treatment initiation[12].

Faced with many effective regimens and few comparative studies, a consensus panel of experts recommended combination therapies such as rituximab with nucleoside analogues with or without alkylating agents or with cyclophosphamide-based therapies (eg, cyclophosphamide, doxorubicin, vincristine, and prednisone or cyclophosphamide and dexamethasone) or combinations of rituximab with thalidomide. However, the guidelines did not recommend a specific first-line regimen. Because of the long natural history of WM, the choice of initial treatment is critical so that agents are not used that

limit future treatment options. The prior use of purine nucleoside analogues has been associated with difficulty in mobilizing stem cells and should therefore be avoided in patients who may be eligible for autologous transplant. Furthermore, a recent report has indicated that nucleoside analogue–based combinations may be associated with an increased risk of transformation or myelodysplasia[13]. Alkylating agent–based regimens in combination with rituximab may be preferable as initial therapy for Waldenström macroglobulinemia. Although there are no data from randomized clinical trials showing that the DRC regimen is superior to combinations containing purine nucleoside analogues, anthracyclines, or proteasome inhibitors, this effective regimen is associated with a modest toxicity profile and a low likelihood of limiting future stem cell collections. Therefore, the opinion of many groups is that this regimen is the combination of choice as initial treatment of patients with symptomatic or bulky disease, hematologic compromise, or hyperviscosity.

For other monoclonal antibodies in other clinical settings the conversion from intravenous (i.v.) to subcutaneous (s.v.) administration has resulted in an improved tolerability with less infusion-related reactions, shorter administration times, an increased patient-convenience and an improved cost-effectiveness. For example, alemtuzumab (an anti-CD52 monoclonal antibody approved for the treatment of patients with CLL) administered s.c. has shown better tolerability with similar efficacy compared to i.v. administration[14]. These advantages are anticipated for the s.c. administration of rituximab as well. It is therefore envisaged that a s.c. application of rituximab would bring significant and clinically meaningful benefits to patients. Subcutaneous administration of rituximab is expected to occur over up to 10 minutes. Subcutaneous administration could thus significantly reduce the time a patient spends in the hospital and eliminate hospital burden associated with i.v. administration. Until now, the relatively large volume of the established rituximab dose has hindered the s.c. administration of rituximab. These hurdles have been overcome by concentrating the i.v. rituximab formulation 12-fold and by adding rHuPH20 as an excipient and a permeation enhancer. As a recombinant human hyaluronidase rHuPH20 hydrolyses hyaluronic acid fibers and thereby reversibly opens the interstitial space in the subcutaneous tissue allowing the installation of volumes larger than 2-3 ml.

Therefore, this study was conducted with a fixed rituximab s.c. dose of 1400 mg on Day 1 of each 28-day cycle after introductory i.v. application of 375 mg/m^2 rituximab on Day 1 in Cycle 1 as authorized dosage in induction therapy for non-Hodgkin's lymphoma. The fixed s.c. dose was calculated from the pharmacokinectic results of the dose finding stage of study BP22333[15]. In this stage of the study, patients were dosed on a body surface are adjusted basis both for the s.c. and i.v. administration of rituximab. Preliminary i.v. and s.c. pharmacokinetic data from 75 patients in study BP22333[15] were integrated into a pharmakokinetic model and model-based simulations had then been used to predict serum C_{trough} and AUC for various s.c. rituximab doses. The simulations showed that using a fixed s.c. dose of 1400 mg for a total of 8 cycles of induction treatment followed by q2m

maintenance was expected to achieve non-inferior rituximab C_{trough} values to the i.v. regimen (375 mg/m^2 i.v. for total of 8 cycles followed by q2m or q3m maintenance).

In BP22333[15] the highest s.c. dose was 1800 mg (total dose) and was well tolerated as well. For a dose of 1400 mg, a patient received a s.c. dosing volume of approximately 11.7 mL. Rituximab SC is approved for NHL at a dose of 1400mg.

9 STUDY OBJECTIVES

The **primary objective** of the trial was to evaluate whether the addition of Bortezomib to the combination regimen Dexamethasone/Rituximab/Cyclophosphamide (B-DRC) improves progression free survival (PFS) compared to Dexamethasone/ Rituximab/Cyclophosphamide (DRC) alone. Therefore, the PFS of previously untreated WM patients with WHO/ECOG performance status between 0 and 2 and CIRS score less than 6, after combination therapy with either DRC or B-DRC should be compared.

The **secondary objective** was to compare the efficacy and safety of bortezomib in combination with DRC using the following parameters of efficacy:

- Response rate (CR, VGPR, PR, MR) and overall response (ORR) four weeks after the end of induction therapy
- Best response
- Time to best response
- Time to first response
- Time to treatment failure
- Remission Duration
- Cause specific survival
- Overall survival

10 INVESTIGATIONAL PLAN

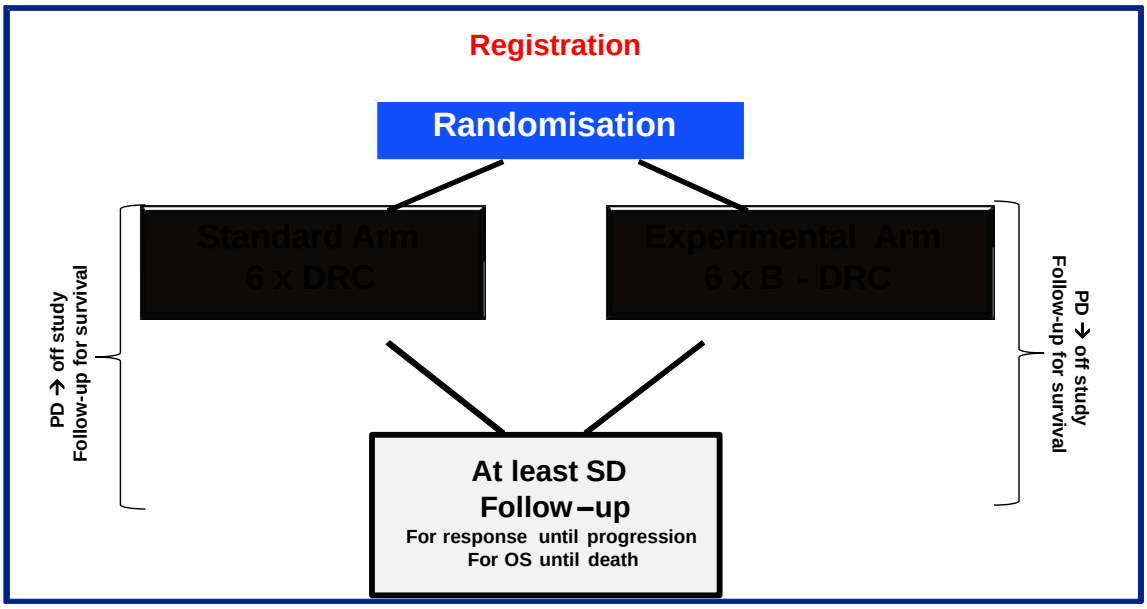
10.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This study is an international, multicenter, randomized phase III trial of 6 cycles of B-DRC versus 6 cycles of DRC in patients aged ≥ 18 years with previously untreated Waldenström's macroglobulinemia (WM) in need of treatment.

The study flow was as follows:

- Previously untreated patients were screened for eligibility for the trial. If the patient was eligible for the study, the patient has been registered and randomized between B-DRC versus DRC before the first cycle of induction treatment.
- Patients who progressed at any time point during induction were considered as treatment failure. They were followed up for development of secondary neoplasias and overall survival until death, however no longer than LPLV.
- Patients, who achieved at least a SD after induction treatment were followed up for response until progression/relapse and for overall survival until death, however no longer than LPLV.

Figure 1: Study Flow



All patients were followed up to 5 years after the end of induction.

It was planned that a total of 384 patients at approximately 100 investigator sites were randomized at 1:1 ratio to receive either experimental or standard induction. Every patient received treatment over a time period of 6 x 4 weeks, followed by a follow-up period of 5 years.

After finishing all study relevant procedures, therapy and follow-up period, the patient is followed in terms of routine aftercare and treated if necessary by the primary responsible hematologic-oncologic center.

An independent external Data Safety Monitoring Committee (DSMC) reviewed ongoing safety data throughout the study. The Data Safety Monitoring Board included at least three independent members (2 experts in WM and one independent statistician). Review of the safety data by the DSMC took place based on the safety analyses, which were planned to be performed on all included patients at 17, 32 and 48 months after the inclusion of the first patient. With the anticipated inclusion rate, this corresponded to safety analyses 6 months after the inclusion of at least 100 randomized patients. The first DSMC was held when 177 patients were randomized in the trial. All data presented at the meeting was considered confidential. Following each meeting the DSMC prepared a report and recommended changes in the conduct of the trial, if necessary. Details on the work of the board was described in a specific DSMC charter, jointly agreed upon the board and the sponsor.

10.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This was a randomized European phase III, multicenter, two–arm, open label trial to compare first line DRC with and without Bortezomib in patients with WM.

Guidelines do not yet recommend a specific first-line regimen. Because of the long natural history of WM, the choice of initial treatment is critical so that agents are not used that limit future treatment options. Although there are no data from randomized clinical trials showing that the DRC regimen is superior to combinations containing purine nucleoside analogues, anthracyclines, or proteasome inhibitors, this effective regimen is associated with a modest toxicity profile and a low likelihood of limiting future stem cell collections. Therefore, this regimen is the combination of choice as initial treatment of patients with symptomatic or bulky disease, hematologic compromise, or hyperviscosity.

Single agent regimen based on alkylating agent, purine analogs, and bortezomib demonstrated significant activity in symptomatic patients.

Therefore, it was the choice in this study to compare the combination therapy with either DRC or DRC plus Bortezomib (B-DRC) in patients with WM.

10.3 SELECTION OF STUDY POPULATION

Patients had a proven clinicopathological diagnosis of WM as defined by consensus panel of the Second International Workshop on WM[16]. Furthermore, patients were in need of treatment as defined by “Consensus Panel Two” recommendations from the Second International Workshop on Waldenström’s Macroglobulinemia[2].

10.3.1 Inclusion criteria

Each patient had to meet all of the following inclusion criteria to be enrolled in this study:

- Clinicopathological diagnosis of WM as defined by consensus panel one of the Second International Workshop on WM[15]. Pathological diagnosis had to occur before study inclusion and randomization. In addition, pathological specimens had to be sent to the national pathological reference center at study inclusion and randomization. The positivity for CD20 positive could be assumed from any previous bone marrow immunohistochemistry or flow cytometry analysis performed up to 6 months prior to enrollment. Inclusion in the protocol was based on morphological and immunological criteria. Immunophenotyping was performed in each center and saved locally. Flow cytometry of bone marrow and blood cells included at least one double staining and assessed the expression of the following antigens: surface immunoglobulin, CD19, CD20, CD5, CD10 and CD23. Patients were eligible if tumor cells expressed the following antigens: CD19, CD20, and if they were negative for CD5, CD10 and CD23 expressions. Patients with tumor cells positive for CD5 and/or CD23 and morphologically similar to WM cells might be included after ruling out other low-grade B-cell malignancies.
- Patients had to have at least one of the following critera to initiate treatment as defined by "Consensus Panel Two" recommendations from the Second International Workshop on Waldenström Macroglobulinemia[2].
    - Recurrent fever, night sweats, weight loss, fatigue
    - Hyperviscosity
    - Lymphadenopathy which was either symptomatic or bulky (≥5cm in maximum diameter)
    - Symptomatic hepatomegaly and/or splenomegaly
    - Symptomatic organomegaly and/or organ or tissue infiltration
    - Peripheral neuropathy due to WM
    - Symptomatic cryoglobulinemia
    - Cold agglutinin anemia
    - IgM related immune hemolytic anemia and/or thrombocytopenia
    - Nephropathy related to WM
    - Amyloidosis related to WM
    - Hemoglobin ≤10g/dL
    - Platelet count $<100x10^9$/L
    - Serum monoclonal protein >5g/dL, even with no overt clinical symptoms

- Cumulative illness rating scale (CIRS) score less than 6.
- World Health Organization (WHO)/ECOG performance status 0 to 2.
- Other criteria
  - Age ≥ 18 years
  - Life expectancy >3 months.
  - Baseline platelet count ≥$50x10^9$/L (if not due to BM infiltration by the lymphoma), absolute neutrophil count ≥$0.75x10^9$/L.
  - Meet the following pre-treatment laboratory criteria at the Screening visit conducted within 28 days of study enrollment:
    - ASAT (SGOT): ≤3 times the upper limit of institutional laboratory normal value
    - ALAT (SGPT): ≤3 times the upper limit of institutional laboratory normal value
    - Total Bilirubin: ≤20 mg/L or 2 times the upper limit of institutional laboratory normal value, unless clearly related to the disease (except if due to Gilbert's syndrome)
    - Serum creatinine ≤ 2mg/dL
- Premenopausal fertile females had to agree to use a highly effective method of birth control for the duration of the therapy up to 6 months after end of therapy. A highly effective method of birth control was defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.
- Men had to agree not to father a child for the duration of therapy and 6 months after and must agree to advice a female partner to use a highly effective method of birth control.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent might be withdrawn by the subject at any time without prejudice to future medical care.

10.3.2 Exclusion criteria

The presence of any of the following excluded a subject from enrollment:

- Prior systemic treatment of the WM (plasmapheresis and short–term administration of corticosteroids < 4 weeks administered at a dose equivalent to < 20 mg/day prednisone is allowed)
- Patient with hypersensitivity to dexamethasone.

- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Uncontrolled bacterial, viral or fungal infection
- Active HIV, HBV or HCV infection
- Known interstitial lung disease
- Prior allergic reaction or severe anaphylactic reaction related to humanized or murine monoclonal antibody.
- Central Nervous System involvement by lymphoma
- Prior history of malignancies unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
  - Basal cell carcinoma of the skin,
  - Squamous cell carcinoma of the skin,
  - Carcinoma in situ of the cervix,
  - Carcinoma in situ of the breast,
  - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
- Uncontrolled illness including, but not limited to:
  - Uncontrolled diabetes mellitus (as indicated by metabolic derangements and/or severe diabetes mellitus related uncontrolled organ complications)
  - Chronic symptomatic congestive heart failure (Class NYHA III or IV).
  - Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months
  - Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
  - Known pericardial disease
- Subjects with ≥ Grade 2 neuropathy.
- Women who are pregnant as well as women who are breast-feeding and do not consent to discontinue breast-feeding.
- Participation in another clinical trial within 4 weeks before randomization in this study
- No consent for registration, storage and processing of the individual disease characteristics and course as well as information of the family physician about study participation.

10.3.3 Removal of patients from therapy or assessment

The only reason for the exclusion of a patient from the study was his or her withdrawal of consent. Patients could withdraw their informed consent to this study at any time and this did not interfere with their right of treatment by the local investigator (physician). In case of cessation of the study-treatment a final statement concerning the treatment effect and the causes of premature study-termination were given by the local investigator.

In case it became evident ex post that a patient did not qualify for the study (e. g. did not fulfil all inclusion criteria nor had an exclusion criterion at the time of randomization) the patient was not excluded from the study because the analysis of the trial is performed according to the intention-to-treat principle. The physician treating a patient with ex-post non-qualification was informed by the Scientific Study Coordinator or his delegate on the ex post non-qualification of a patient. In case that the patient did not complete the therapy according to the protocol of this study it is up to the treating physician to decide whether the patient should have continued with the per-protocol therapy or not. However, the documentation of patients with ex post non-qualification was continued as planned in the protocol, because the documentation of such patients is not different from the documentation of qualified patients.

In contrast to the continuing documentation, per-protocol treatment of the patient might have been stopped for the following reasons:

- no response of the lymphoma to the per-protocol therapy
- disease progression at any time
- intercurrent illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree
- repeated clinically relevant violation of the protocol
- non-compliance by the patient with protocol requirements
- excessive and unexpected toxicity of the treatment
- patient’s decision to stop her/his participation in the trial
- decision by the treating physician for medical reasons, in particular when it becomes evident ex post that the patient did not qualify for the study
- discontinuation of the study at the request of sponsor
- Patient was lost to follow-up. If a patient did not return for scheduled visits, every effort should have been made to re-establish contact. In any circumstance, every effort should have been made to document patient outcome, if possible.

In summary, a patient should have been withdrawn from the trial treatment if, in the opinion of the investigator, it was medically necessary, or if it was the wish of the patient.

The reason for the early termination of the per-protocol treatment was documented and the 'Coordinating Investigator' and the 'National Co-coordinating Investigator' were informed in written form e.g. on the respective CRF. Patients who stopped per-protocol therapy early were documented and followed-up according to protocol. Early termination should be avoided. In case of an early termination of therapy, reasons/ circumstances and if applicable the final disease status of the patient was documented. If the patient did not withdraw the consent for further follow-up, he or she should be followed-up as planned.

Furthermore, patients with grade 3 or 4 IRR after the second rituximab infusion were withdrawn from the study.

10.4 TREATMENTS

10.4.1 Treatments administered

In this trial, **bortezomib** as s.c. formulation is considered as investigational medicinal product (IMP) and was provided by Johnson & Johnson. Bortezomib is approved for s.c. application as monotherapy in adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation or in combination with melphalan and prednisone for adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

Rituximab as s.c. formulation is considered also as IMP and was provided by Roche as the s.c. application form and had not received marketing authorization at time of study start (marketing authorization was received in the EU shortly thereafter on 21 March 2014). As rituximab i.v. is part of the treatment strategy with rituximab s.c. (rituximab i.v. in Cycle 1 followed by rituximab s.c. in Cycle 2-6) rituximab i.v. is considered likewise as IMP and was provided by Roche, too.

With regard to non-Hodgkin's lymphoma rituximab rituximab i.v. has a marketing authorization

- for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy
- as maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy
- monotherapy for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

The other drugs are standard of care. For induction, commercially available oral formulation of **cyclophosphamide** and **dexamethasone** will be used. Standard of care

chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated WM patients at the center.

Cyclophosphamide and dexamethasone are to be used according to the respective summary of product characteristics (SmPC).

10.4.2 Identity of investigational product(s)

Bortezomib for injection is a sterile lyophilized powder for reconstitution and was supplied in vials containing bortezomib and mannitol at a 1:10 ratio. For s.c. application only vials containing 3.5 mg of bortezomib with 35 mg of mannitol were used. Bortezomib (VELCADE®) was provided by Johnson & Johnson.

Rituximab was applied i.v. in the first induction cycle and s.c. in induction cycle 2-6. In this trial rituximab i.v. and s.c. was supplied by Roche.

Any authorized merchandise with the active ingredient **dexamethasone** as oral application form e.g. Fortecortin® tablets was allowed. Dexamethasone was not provided for this study.

Any authorized merchandise with the active ingredient **cyclophosphamide** in tablet form was allowed. Cyclophosphamide was not provided for this study.

10.4.3 Method of assigning patients to treatment groups

The Informed Consent was signed before starting of any trial related procedures.

Patients were registered and randomized through the web-based patient registration system. Randomization was only accepted from authorized investigators.

Registration occurred prior to initiation of treatment: the eligibility criteria were confirmed and the Registration Worksheet was completed.

After registration the unique trial identification number and randomization result was generated and sent out by E-Mail to the investigator.

Eligible patients were randomized at 1:1 ratio to receive either experimental (B-DRC) or standard (DRC) treatment. Patients were stratified according to countries and the risk group according to the International Prognostic Index (ISSWM)[3] which was calculated by investigators.

An overview of the distribution of the ISSWM and other baseline characteristics is given in Figure 2 as well Table 1 and Table 2, respectively.

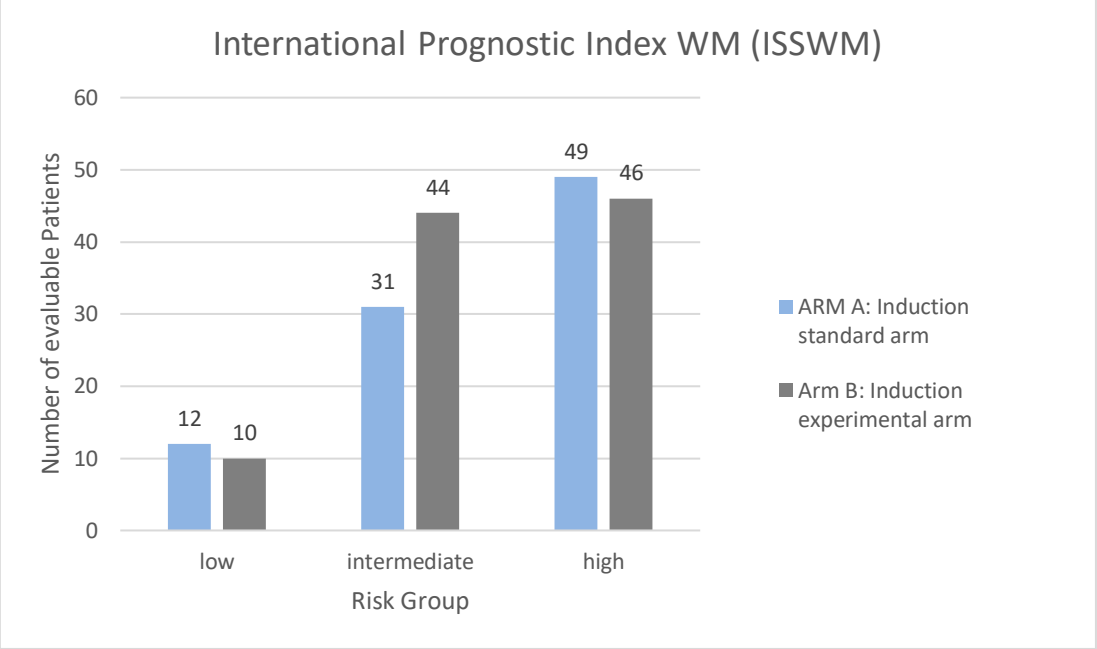


Figure 2: International Prognostic Index WM (ISSWM)

Table 1: International Prognostic Index WM (ISSWM)

Number of evaluable Patients			
ISSWM	Arm A: Induction standard arm	Arm B: Induction experimental arm	Grand Total
Low	12	10	22
Intermediate	31	44	75
High	49	46	95
Grand Total	**92**	**100**	**192**

Table 2: Baseline Characteristics at time of randomization

Characteristic (n=202)	Arm A %	Arm B %	TOTAL %
Age > 65	61	60	60.4
Hemoglobin ≤11.5 g/dl	82.3	76.7	79.5
Platelets < 100 x 10^9/l	14.4	17.8	16.1
ß2-Mikroglobulin > 3 mg/l	74.4	75.5	75.0
Serum IgM >70 g/l	11.6	4.0	7.8

ß2-Mikroglobulin is only measured during Screening visit. For Serum IgM, Hemoglobin and Platelets we use the values measured on Cycle 1 Day 1 (C1D1) because these values are closer to the start of treatment.

The randomization method is provided in Appendix 15.3

10.4.4 Selection of doses in the study

Patients receiving **bortezomib s.c.** were administered a dose of 1.6 mg/m^2. The total amount (in mg) of bortezomib to be administered was determined based on body surface area. Body surface area was calculated based on body weight using a standard nomogram. The dose was calculated on Day 1 of each cycle; the dose administered remained the same throughout each cycle but was recalculated at the start of the next cycle. If a patient experienced a notable change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose could be re-calculated at that time. The total calculated dose of bortezomib was rounded to the nearest decimal point (e.g., a calculated dose of 2.47 mg can be rounded to 2.5 mg).

Patients receiving **rituximab i.v.** were administered a dose of 375 mg/m^2. The appropriate amount of solution was withdrawn from the vial from the following calculation:

Volume (mL) = BSA (m²) * dose (375 mg/m²) / concentration of reconstituted solution mg/mL

Patients receiving rituximab s.c. were administered at a dose of 1400 mg absolute. 11.7 mL amount of solution were withdrawn from the vial.

Each oral administration of **dexamethasone** contained 20 mg.

Each oral administration of **cyclophosphamide** (anhydrous) contained 50 mg.

10.4.5 Selection and timing of dose for each patient

Eligible patients were registered and had a 1:1 randomization to receive B-DRC or DRC. In general, study treatment occurred on the scheduled day (± 4 days), with the exception of delays resulting from toxicities.

The induction consisted of 6 cycles. Treatment courses were administered in 28-day cycles.

Cycle 1:

Components	Dose	Standard Arm DRC	Experimental Arm B-DRC
Bortezomib:	1.6 mg/m^2 s.c.	-	Day 1,8,15
Dexamethasone:	20 mg p.o.	Day 1	Day 1
Rituximab:	375 mg/m² i.v.	Day 1	Day 1
Cyclophosphamide:	100 mg/m² x 2 p.o.	Day 1-5	Day 1-5

Cycle 2-6:

Components	Dose	Standard Arm DRC	Experimental Arm B-DRC
Bortezomib:	1.6 mg/m^2 s.c.	-	Day 1,8,15
Dexamethasone:	20 mg p.o.	Day 1	Day 1
Rituximab:	1400 mg absolute s.c.	Day 1	Day 1
Cyclophosphamide:	100 mg/m^2 x 2 p.o.	Day 1-5	Day 1-5

Repeat day 29.

10.4.6 Blinding

Not applicable.

10.4.7 Prior and concomitant therapy

Prophylaxis for Herpes Zoster reactivation was obligatory for all patients treated with bortezomib during the treatment phase. Acceptable antiviral therapy included acyclovir (e.g. 400mg p.o. 3 times-a-day), famcyclovir (e.g. 125mg p.o. twice-a-day) or valacyclovir (e.g. 500mg p.o. twice-a-day).

All medications, procedures and supportive therapies administered from Day 1 of Cycle 1 through the first follow-up visit were recorded in the source documents and the subject's CRF. Supportive therapy for WM that is ongoing at baseline was permitted during the treatment period of the study. Any anti-neoplastic treatment for WM other than bortezomib, cyclophosphamide, dexamethasone or rituximab was not permitted.

Concomitant medications for other medical conditions were permitted, as clinically indicated. The following medications and supportive therapies are examples of support therapies that could be used if needed during this study:

- Platelet, and packed red blood cell transfusions were permitted, as necessary;
- Granulocyte-Colony Stimulating Factor, Erythropoietin;
- Medications to prevent and treat rituximab related infusion reactions (i.e. acetaminophen, diphenhydramine, glucocorticoids, ranitidine or cimetidine).
- Prophylaxis antiemetics were not routinely recommended but were left to the investigator's discretion. Systemic corticosteroids could not be used in the prophylaxis or therapy of emesis.
- Plasmapheresis could be considered in all patients with signs of hyperviscosity before start of the induction regimen to avoid an 'IgM flare'.

Any treatment responsible for lymphocyte depletion and live-attenuated vaccines were not permitted.

10.4.8 Treatment compliance

The infusions respectively s.c. injections of bortezomib and rituximab were administered by medical staff at the site and therefore supervised accordingly. The oral administration of dexamethasone and cyclophosphamide was done also under supervision of the site staff and intake is captured in the CRF accordingly.

10.5 EFFICACY AND SAFETY VARIABLES

10.5.1 Efficacy and safety measurements assessed and flow chart

Screening procedures

The following procedures were conducted at the screening visit (after obtaining informed consent). All screening evaluations were completed before the patient was registered into the study and received study drug (within 4 weeks prior to the first administration of therapy).

- Medical History, complete physical examination and immunization status
- Determination of WHO/ECOG performance status
- Determination of CIRS
- Concomitant medication
- The initial staging procedures listed below will be performed

Once screening examinations were completed and patient eligibility for this study was established, the provided randomization checklist form was completed for registration of the patient.

The initial staging included the following assessments:

- A bone marrow biopsy and aspiration within 6 months prior to enrollment demonstrating CD20+ disease. Biopsy material from an excisional or core biopsy was submitted for retrospective central confirmation to the national pathological reference center.
- Serum protein electrophoresis
- Serum immunofixation
- Quantitative immunoglobulins (IgM, IgG, IgA)
- CBC with differential

- Coagulation tests (prothrombin ratio and activated partial thromboplastin time) with Von Willebrand factor antigen and functional test in case of abnormal activated partial thromboplastin time before bone marrow biopsy
- Chemistry panel (electrolytes, total bilirubin, SGOT, SGPT, LDH, urea, creatinine, total protein and albumin)
- Serology for hepatitis B, C and HIV. Testing for HbsAg and anti-Hbc was obligatory for the Hepatitis B serology. In case the patient was positive for either HbsAg and/or anti-Hbc, patients could be included only if HBV-DNA was negative. In this case Hepatitis B prophylaxis was initiated and HBV-DNA in these patients were re-evaluated in regular intervals according to local guidelines. HBV-DNA positive patients might not be included into the trial.
- β_2-microglobulin, LDH
- Cryoglobulinemia (in case of positivity, CBC and/or serum protein electrophoresis should be collected at 37°C), cold agglutinin, direct antiglobulin test, Coombs test
- Proteinuria, urine protein electrophoresis and immunofixation
- Free light chain assay
- CT scans of chest, abdomen and pelvis within 3 months of study enrollment. If there are contraindications against performing CT scans, MRT imaging was also accepted.
- Fundoscopy, if hyperviscosity syndrome was suspected
- 12–lead ECG
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) had a serum pregnancy test at screening, which had to be repeated 2 weeks after the first test to confirm results.
  Urine pregnancy tests was performed at specified subsequent visits and might be performed more frequently if required by local legislation. If a urine pregnancy test was positive, dosing was delayed until the patient's status was determined by a serum pregnancy test.

Assessments during induction treatment

Assessments during induction treatment were performed before start of each new cycle and are summarized in Table 3. Study assessments during treatment occurred on the scheduled day (± 4 days), with the exception of delays resulting from toxicities. Response to treatment was evaluated before each cycle with a serum protein electrophoresis and quantitative IgM serum assessment. In case of response or stable disease, the next cycle was delivered. Progression at the end of the previous cycle or after end of induction was considered as treatment failure. In this case the patients discontinued treatment and

entered follow-up. Modified response criteria as recently defined[4] was used for evaluating responses, identifying stable or progressive disease (see Appendix A of the protocol[17]). Response after end of induction was assessed 4 weeks after the end of the last induction cycle. A CT scan in case of initial lymph node enlargement or splenomegaly, bone marrow trephine biopsy, bone marrow smear and aspirate was repeated at that time (bone marrow evaluation only for confirmation of complete response or documentation of delayed response). Best response within the time period between the beginning of treatment and end of follow–up was documented for every patient. Patients who benefit from the study treatment were observed only. It was not planned to offer these patients any further therapy such as consolidation or maintenance therapy.

Therefore:

1) Changes in the serum concentration of monoclonal immunoglobulin was monitored with serum protein densitometry tracing (electrophoresis) (in particular if IgM monoclonal protein exceeded 5g/dL) or by nephelometry. Sequential analyses of serum IgM should have been performed using the same methodology in the same laboratory.

2) During the subsequent follow-up bone marrow trephine biopsy and bone marrow smears and aspirate was only mandatory to confirm complete response and CT scan (if contraindications MRT) only in case of abnormalities related to WM before initiation of therapy.

3) Serum protein electrophoresis, nephelometry and immunofixation was repeated at least 6 weeks later in case of complete response to confirm CR.

At the end of each cycle, efficacy and safety was assessed. Concomitant therapy and supportive cares including hematopoietic stimulating factors and transfusion were recorded. Free light chain assay was evaluated at the end of therapy.

The details of evaluations are summarized in Table 3.

If **progression** occurred at any timepoint of the study (i.e. during induction therapy or during Follow up), the following examinations were performed as also summarized in Table 3:

- Physical examination and performance status
- Serum protein electrophoresis and serum immunofixation
- Quantitative immunoglobulins (IgM, IgG, IgA)
- CBC with differential
- Chemistry panel (electrolytes, total bilirubin, SGOT, SGPT, LDH, urea, creatinine, total protein and albumin, coagulation tests)
- β_2-microglobulin

- Cryoglobulinemia (in case of positivity, CBC and/or serum protein electrophoresis should be collected at 37°C), cold agglutinin, direct antiglobulin test, Coombs test
- Proteinuria, urine protein electrophoresis and immunofixation
- Free light chain assay
- CT scans of chest, abdomen and pelvis (if contraindications MRT)
- Bone marrow biopsy and aspiration with flow cytometry
- If agreed by the patient biological sampling of bone marrow, blood, serum and plasma

Follow-up assessments

Patients with complete, partial, minor response or stable disease were surveyed without therapy until progression of the disease. Patients were clinically evaluated every 3 months after the last cycle for 2 years and then every 6 months for 3 years. At these times, physical examination, WHO performance status, results of serum protein electrophoresis, nephelometry, immunofixation (in case of normal values of previous tests) and beta-2-microglobulin were recorded. Blood cell counts with differential, chemistry panel (electrolytes, total bilirubin, SGOT, SGPT, urea, creatinine, LDH, total protein and albumin) were monitored, too. CT scan were repeated every 6 months in case of initial lymph node enlargement or splenomegaly (if contraindications for CT, MRT was accepted).

Patients with failure to induction therapy or progression were followed up only for survival data and data with regard to further treatment of WM (if applicable). At the time point of progression the examinations listed in Table 3 and above will be performed and documented.

Table 3: Time schedule of diagnostic assessments

Examination	**Baseline[1]**	**Before each cycle**	**After 3rd cycle**	**Four weeks after end of 6th cycle**	**FU[12] Every 3 months for 2 years after induction therapy**	**FU[12] Every 6 months for further 3 years**	**At progression**
Inclusion/exclusion criteria, informed consent	**X**						
Medical history, demographics, comorbidity index (CIRS),	**X[1]**						
Pregnancy test (to be repeated after 2 wks)	**X**						
Fundoscopy in case of hyperviscosity	**X**						
12-lead ECG	**X**						
Performance status (WHO/ECOG)	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Physical examination including vital signs	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CT scan[2]	**X**		**X[3]**	**X[3]**	**X[3,4]**	**X[3]**	**X**
Bone marrow aspiration and - biopsy with flow cytometry[5]	**X**			**X[6]**	**X[6]**	**X[6]**	**X**
Bone marrow cells storage, DNA and RNA[7]	**X**			**X[11]**			**X**
Blood cells, serum plasma storage[7]	**X**			**X**			**X**
Laboratory tests[8]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serum immunofixation, quantitative immunoglobulins (IgM, IgG, IgA)[9]	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Examination	Baseline[1]	Before each cycle	After 3rd cycle	Four weeks after end of 6th cycle	FU[12] Every 3 months for 2 years after induction therapy	FU[12] Every 6 months for further 3 years	At progression
β_2-microglobulin, LDH	X		X	X	X	X	X
Urine analysis: Bence Jones proteinuria and other proteinuria assays	X			X[10]			X
Direct antiglobulin test, cryoglobulinemia, cold agglutinin test, Coombs test	X						X
Anti-HIV, HBV[13], HCV	X						
Free light chain	X			X			X
Concomitant therapy and supportive cares		Continuously					X
Adverse events		Continuously					X

1- Within 4 weeks prior to the first administration of therapy.
2- All tumour lesions at baseline, follow target lesions accordingly. At baseline within 3 months of study enrollment, if contraindications MRT is accepted.
3- If clinically indicated or in case of initial lymph node/splenogemagly
4- Every 6 months
5- Within 3 weeks prior to enrollment
6- As confirmation of complete response (histology) or documentation of delayed response.
7- Study specific diagnostics
8- Serum protein electrophoresis, CBC with differential, coagulation tests, chemistry panel (electrolytes, glucose, total bilirubin, SGOT, SGPT, urea, creatinine, total protein and albumin)
9- In the case of CR repeat at least 6 weeks later for confirmation of CR
10- If positive at diagnosis
11- Only in those patients in whom bone marrow aspiration has been performed.
12- Follow up examinations in the indicated intervals until progression. Patient with failure to induction therapy or progression will be followed up only for survival data and data with regard to further treatment of M. Waldenström (if applicable).
13- Testing for HbsAg and anti-Hbc is obligatory for the Hepatitis B serology. In case the patient is positive for either HbsAg and/or anti-Hbc, patients can be only included if HBV - DNA is negative. In this case Hepatitis B prophylaxis has to be initiated and HBV DNA in these patients needs to be re-evaluated in regular intervals according to local guidelines. HBV DNA positive patients may not be included into the trial

Progression/relapse

Relapse/progression was determined by the modified response criteria as recently published[4] (see Appendix A of the protocol[16]). A pathological confirmation by biopsy of the bone marrow or lesion if present should have been done if possible. New anti-lymphoma therapy and response to salvage therapy was collected in the CRF.

Histological material

The histological examination of bone marrow biopsy was performed within 6 months prior to therapy onset. The pathological assessment was performed by the local as well as the national pathology reference center. The pathological review of bone marrow was requested at randomization and it was strongly recommended that the diagnostic genetic analysis performed by the reference pathology included

- MYD88 Mutations
- CXCR4 Mutations

Biological material

If the patient agreed to, biological sampling was performed at defined time points.

If any patients withdrew his/her consent to further biological sampling and storage during study participation, no further collection of biological samples took place and already stored samples were destroyed if possible and wished by the patient. This did not affect the patient's participation in the clinical study in any other respect.

10.5.2 Appropriateness of measurements

All assessments and treatments listed in Table 3 except for the administration of the study medication bortezomib s.c. and the biosampling (see [7]study specific diagnostics) and rituximab i.v. and s.c. were performed within therapy and diagnostic routine on standard WM therapy. During routine bone marrow aspiration and routine peripheral blood collection, additional material was collected for study purposes (additional characterization of the disease) in the case of the patient's consent.

10.5.3 Primary efficacy variables

The aim of this study is to compare the progression free survival (PFS) of previously untreated WM patients with WHO/ECOG performance status between 0 and 2 and CIRS score less than 6, after combination therapy with either DRC or B-DRC.

PFS is calculated from the date of inclusion to the following events: the date of progression and the date of death if it occurred earlier. In the absence of progression and death, PFS duration is censored at the stopping date or the date of last follow-up.

10.5.4 Drug concentration measurements

Not applicable

10.6 DATA QUALITY ASSURANCE

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it might be necessary to conduct a site audit or an inspection.

The investigators agreed to allow the sponsor and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, do not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in the CRF, review of documentation required to be maintained, and checks on drug accountability.

The sponsor does in all cases help the investigator prepare for an inspection by any regulatory agency.

Monitoring visits to the trial site were made periodically during the trial to ensure that GCP and all aspects of the protocol were followed. The CRO announced independent special trained monitors who checked on site on the basis of the patients records the fulfilment of inclusion/exclusion criteria, of diagnostic procedures at study entry, the presence of an informed consent, handling of remission criteria, performance of treatment and adverse events and correct documentation of patient's data in the CRF (Source Data Verification). The number of contacts depended on the characteristics of the respective center, e.g., the number of recruited patients. Source documents were reviewed for verification of agreement with data on case report forms. Details on the extent of data verification were described in the study specific monitoring manual. The investigator/institution guaranteed direct access to source documents by the representative of the CRO and appropriate regulatory authorities.

10.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

10.7.1 Statistical and analytical plans

The aim of this study is to compare progression free survival (PFS) of previously untreated WM patients with WHO performance between 0 and 2 and CIRS score less than 6, after combination therapy with either DRC or B-DRC.

10.7.1.1 Primary Endpoint

The primary endpoint of the trial is progression-free survival (PFS). PFS is calculated from the date of inclusion to the following events: the date of progression and the date of death if it occurred earlier. In the absence of progression and death, PFS duration is censored at the stopping date or the date of last follow-up. PFS estimates are obtained

using the Kaplan-Meier method, and then compared across baseline groups using the log-rank test, with effect measured by hazard ratio estimated from the Cox proportional hazard regression model.

10.7.1.2 Secondary Endpoints

The following secondary efficacy endpoints are evaluated:

- **Response rate**

  The response rates (CR, VGPR, PR, MR) and overall response rate (CR, VGPR, PR, MR) are evaluated 4 weeks after the end of induction treatment.

- **Best response**

  Best response is determined in the time interval from the start of induction therapy to end of follow-up.

- **Time to best response**

  Time to best response is defined as the time from the start of induction to best response the patient achieves (CR, VGPR, PR, MR).

- **Time to first response**

  Time to first response is defined as the time from the start of induction to first response (MR, PR, VGPR or CR).

- **Time to treatment failure (TTF)**

  Time to treatment failure (TTF) is defined as the time of randomization to discontinuation of therapy for any reason including death from any cause, progression, toxicity or add-on of new anti-cancer therapy. Patients alive without treatment failure are censored at the latest tumor assessment date.

- **Remission duration (RD)**

  Remission duration is calculated in patients with response (CR, VGPR, PR, MR) to induction from end of induction to the date of progression, relapse or death from any cause. Patients alive without progression and relapse is censored at the latest tumor assessment date or the stopping date.

- **Cause specific survival (CSS)**

  Cause specific survival is defined as the period from the induction randomization to death from lymphoma or lymphoma related cause; deaths unrelated to WM are censored.

- **Overall survival (OS)**

  Overall survival is defined as the period from the induction randomization to death from any cause. Patients who have not died until the time of the analysis are censored at their last contact date.

10.7.1.3 Expected improvement for the experimental arm (arm B-DRC)

Using the results from the Greek DRC trial[18] as baseline, the improvement of the 2-year progression free survival from 65 to 80% seems to be a clinical plausible improvement.

10.7.1.4 Safety Analyses

Safety analyses were planned to be performed on all included patients at 17, 32 and 48 months after the inclusion of the first patient. With the anticipated inclusion rate as outlined above this corresponded to safety analyses 6 months after the inclusion of at least 100 randomized patients. The first DSMC was held when 177 patients were randomized in the trial. Furthermore, safety is evaluated by monitoring dose delays and dose intensity, adverse events, serious adverse events, and deaths.

These were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Laboratory safety assessments include regular monitoring of hematology, blood chemistry, and tests of immunologic parameters. However, laboratory abnormalities in laboratory tests that were performed for safety surveillance and were not needed for assessment of any efficacy variables were captured as adverse events, rather than capturing the raw laboratory values.

The principal investigator based on his general expertise regarding the significance of the accumulating data and in accordance with the regulatory and ethical principles, might have terminated the study for safety concerns at any time point. In addition, the DSMC assessed toxicity and safety at the time point of the pre-scheduled three safety analyses and would have terminated the trial in the case of unexpected and nonacceptable toxicity.

10.7.1.5 Analysis Populations

Intention-to-treat (ITT) population

The intention-to-treat (ITT) population includes all patients randomized for induction regardless of study drug being received or not or other protocol violations.

According to the ITT, patients from the ITT population were analysed based on assigned treatment group per induction randomization. Patients without staging during induction were excluded for the evaluation of remission rates.

Safety population

For safety analyses, patients who started treatment were evaluated according to the treatment actually received (as treated).

10.7.2 Determination of sample size

The distribution between the sexes is not relevant, because neither incidence of WM differed between sexes nor clinically outcome measures such as response, progression free and overall survival had been shown to be related to sexes. A total sample size of 384 (split equally between the two groups), or 106 events, achieved 90% power to detect a hazard rate of 0.5180 when the 2-year progression-free survival estimates in DRC and B-DRC groups are 65% (S1) and 80% (S2) respectively, at a significance level (alpha) of 0.05 using a two-sided log rank test. These results assumed that 3 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries and that the hazards are proportional. Assuming that no patients were lost to follow-up, a 3.3-year recruitment phase is anticipated (116 randomized patients per year). Sequential efficacy analyses should have been made at 17 months, 32 and 48 months after at least 100 randomized patients.

Details when Spending = O'Brien-Fleming, N = 384, d = 106, S1 = 0.6500, S2 = 0.8000

Look	Time	Lower Bndry	Upper Bndry	Nominal Alpha	Inc Alpha	Total Alpha	Inc Power	Total Power
1	17.0000	-3.58947	3.58947	0.000331	0.000331	0.000331	0.049716	0.049716
2	32.0000	-2.51265	2.51265	0.011983	0.011765	0.012097	0.511024	0.560740
3	48.0000	-1.99311	1.99311	0.046250	0.037903	0.050000	0.339625	0.900366

10.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

In this final report all evaluations are performed on all obtained data for the 202 enrolled patients including the follow-up phase.

Changes in the conduct of the study

The study was conducted as planned in the protocol until 21-SEP-2018 when the recruitment was terminated early. 202 patients (instead of 384) were recruited over a period of 4 years and 8 months before the study prematurely stopped recruitment. Planned duration of recruitment was approximately 3.3 years. The early recruitment termination was due to the fact that the treatment landscape had changed tremendously through ibrutinib. Ibrutinib is a chemotherapy-free treatment approach and was approved by the EMA for first-line therapy in patients with WM based on its excellent efficacy and tolerability.

Changes in the planned analysis

Safety analyses were planned to be performed on all included patients at 17, 32 and 48 months after the inclusion of the first patient. With the anticipated inclusion rate as outlined above this corresponded to safety analyses 6 months after the inclusion of at least 100 randomized patients. The DSMC was held when 177 patients were randomized in the trial. Other DSMC meetings did not take place as recruitment was stopped after 202 patients.

Therefore, the trial was not carried out according to the planned group sequential design. The reason was the low recruiting and the early stopping of recruitment. Instead, the trial was stopped after recruiting of 202 patients on the 21-SEP-2018.

Planned interim analyses were not performed due to the low recruiting and the early stopping of the trial recruitment.

11 STUDY PATIENTS

11.1 DISPOSITION OF PATIENTS

202 male and female patients with WM were enrolled into the study and were intended to be treated per protocol (ITT population). Seven patients did not receive any study treatment: 3 patients withdrew their consent (# 11, 17, 143), 4 patients were randomized but are a screening failure (#29, 50, 109, 177).

Table 4: Patient disposition

		Treatment A	Treatment B
No. of subjects enrolled and randomized	202	100	102
No. of subjects not receiving any medication	7	4	3
Reason for not receiving medication:			
Withdrawal of consent	3	1	2
Screening failure	4	3	1
No. of subjects for PFS analysis	171	82	89

12 EFFICACY EVALUATION

12.1 DATA SETS ANALYSED

All patients who signed the informed consent were assigned to a randomization number. These patients were considered as enrolled/randomized patients, even if they did not receive any trial treatment. Due to potential protocol violations and premature study discontinuations, the analysis of the study covered the following three sets of patients.

The intention-to-treat (ITT) population includes all patients randomized for induction regardless of study drug being received or not or other protocol violations. According to the ITT, patients from the ITT population will be analyzed based on assigned treatment group per induction randomization. Patients without staging during induction will be excluded for the evaluation of remission rates.

The per-protocol (PP) population covers all patients who fulfil the following conditions:

- All 6 cycles of induction therapy were received
- Patients were treated according to their randomization result
- Dose density: At least 80% of medication was received (for each study drug with consideration of dose reduction)

Forbidden concomitant medication (anti-neoplastic treatment) was not considered.

Safety population: For safety analyses, patients who started treatment were evaluated according to the treatment actually received (as treated).

A tabular listing of all patients excluded from PP analysis set will be provided in Appendix 15.5.

12.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline demographic data for the ITT population at time of randomization are presented in the following: age (Table 5), sex (Table 6), body weight (Table 7), body height (Table 8), BMI (Table 9), ECOG status (Table 10), ethnic origin (Table 11), body surface area (Table 12), B symptomatic, (Table 13), neuropathy (Table 14).

Furthermore, the treatment duration is presented in Table 15.

Table 5: Age (years)

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
202	0	34.9	60	68	74	89.8	66.4	10.3

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
100	0	39.6	59	68	73	83.6	65.8	10.1

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
102	0	34.9	60	68	75	89.8	67	10.5

Table 6: Sex

	Treatment group		
Frequency Percent	Arm A	Arm B	Total
Female	33 33.0	34 33.3	67 33.2
Male	67 67.0	68 66.7	135 66.8
Total	100	102	202

Table 7: Body Weight (kg)

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
198	4	40.0	64.0	73.0	84.0	125.0	74.2	14.6

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
97	3	47.0	64.0	73.0	83.0	120.0	74.3	14.4

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
101	1	40.0	65.0	73.0	84.0	125.0	74.1	14.9

Table 8: Body height (cm)

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
198	4	148.0	164.0	170.0	176.0	197.0	170.2	9.8

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
97	3	150.0	164.0	171.0	176.0	193.0	170.3	9.5

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
101	1	148.0	164.0	170.0	176.0	197.0	170.2	10.0

Table 9: BMI (kg/m²)

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
198	4	16.07	22.6	25.4	28.2	46.9	25.6	4.3

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
97	3	16.7	22.7	24.9	27.7	46.9	25.6	4.5

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
101	1	16.07	22.5	25.5	28.7	36.7	25.6	4.2

Table 10: ECOG status

	Treatment group		
Frequency Percent	Arm A	Arm B	Total
Missing	3 3.0	3 2.9	6 3.0
0	57 57.0	51 50.0	108 53.5
1	35 35.0	44 43.1	79 39.1
2	5 5.0	4 3.9	9 4.4
Total	100	102	202

Table 11: Ethnic origin

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
Missing	3 3.0	0 0	3 1.5
Caucasian	85 85.0	94 92.2	179 88.6
African	1 1.0	0 0.0	1 0.5
Other	11 11.0	8 7.8	19 9.4
Total	100	102	202

Table 12: Body Surface Area (m^2)

Whole population								
N	**N Miss**	**Minimum**	**Lower Quartile**	**Median**	**Upper Quartile**	**Maximum**	**Mean**	**Std Dev**
198	4	1.33	1.72	1.85	2.00	2.35	1.85	0.20

Treatment group: Arm A								
N	**N Miss**	**Minimum**	**Lower Quartile**	**Median**	**Upper Quartile**	**Maximum**	**Mean**	**Std Dev**
97	3	1.42	1.74	1.85	2.00	2.35	1.85	0.19

Treatment group: Arm B								
N	**N Miss**	**Minimum**	**Lower Quartile**	**Median**	**Upper Quartile**	**Maximum**	**Mean**	**Std Dev**
101	1	1.33	1.72	1.85	1.99	2.34	1.84	0.20

Table 13: B-symptoms

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
Missing	3 3.0	1 1.0	4 2.0
No	64 64.0	79 77.5	143 70.8
Yes	33 33.0	22 21.6	55 27.2
Total	100	102	202

Table 14: New or worsened Neuropathy during treatment

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
Missing	5 5.0	3 2.9	8 4.0
No	85 85.0	70 68.6	155 76.7
Yes	10 10.0	29 28.4	39 19.3
Total	100	102	202

Table 15: Treatment duration (days)

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
194	8	4	143	144	151	195	138	33,3

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
95	5	4	142	144	148	173	134	36,8

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
99	3	4	144	145	151	195	141	29

12.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Not applicable.

12.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

12.4.1 Analysis of Efficacy

Analysis of primary endpoint.

The primary endpoint of the trial is progression-free survival (PFS). The analysis of the primary endpoint is based on the ITT population and the PP population. PFS estimates were obtained using the Kaplan-Meier method, and then compared across groups using the log-rank test, with effect measured by the hazard ratio estimated from the Cox proportional hazard regression model.

The median observation time was 68.8 months (Interquartile range: 64.2-77.3).

The Kaplan-Meier plot for the ITT population resp. PP population is shown in Figure 3 resp. Figure 4.

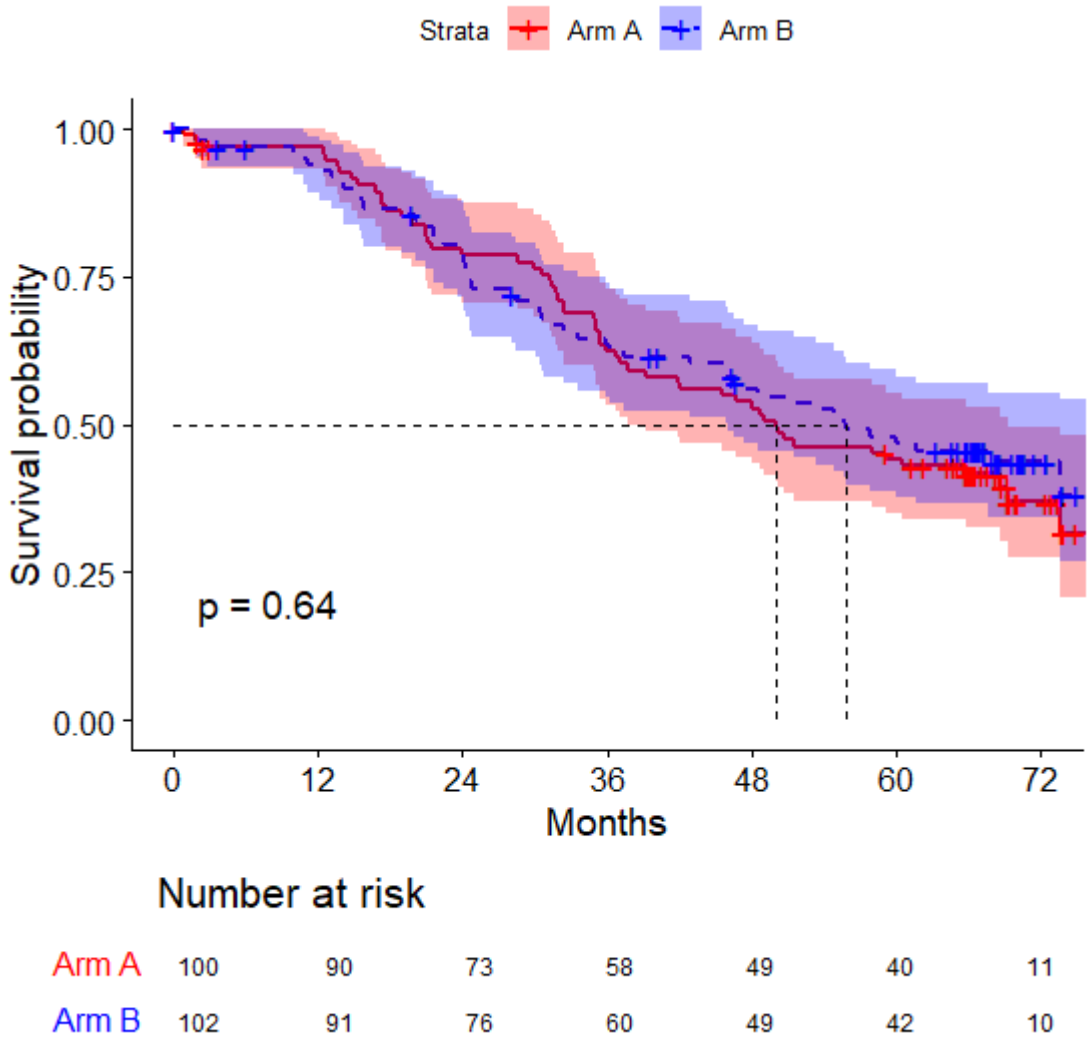


Figure 3: Kaplan-Meier plot for PFS (ITT population)

The median survival time for PFS in the ITT population is 50.1 months in Arm A (95% CI: 39.2; 69.4) and 60. in Arm B (95% CI: 46.0; n.a.). The hazard ratio in the ITT population is 0.914 (95% CI: 0.629; 1.329, p=0.64) for the comparison Arm A vs. Arm B.

n.a.: calculation was not possible because the survival curve is always greater than 0.50.

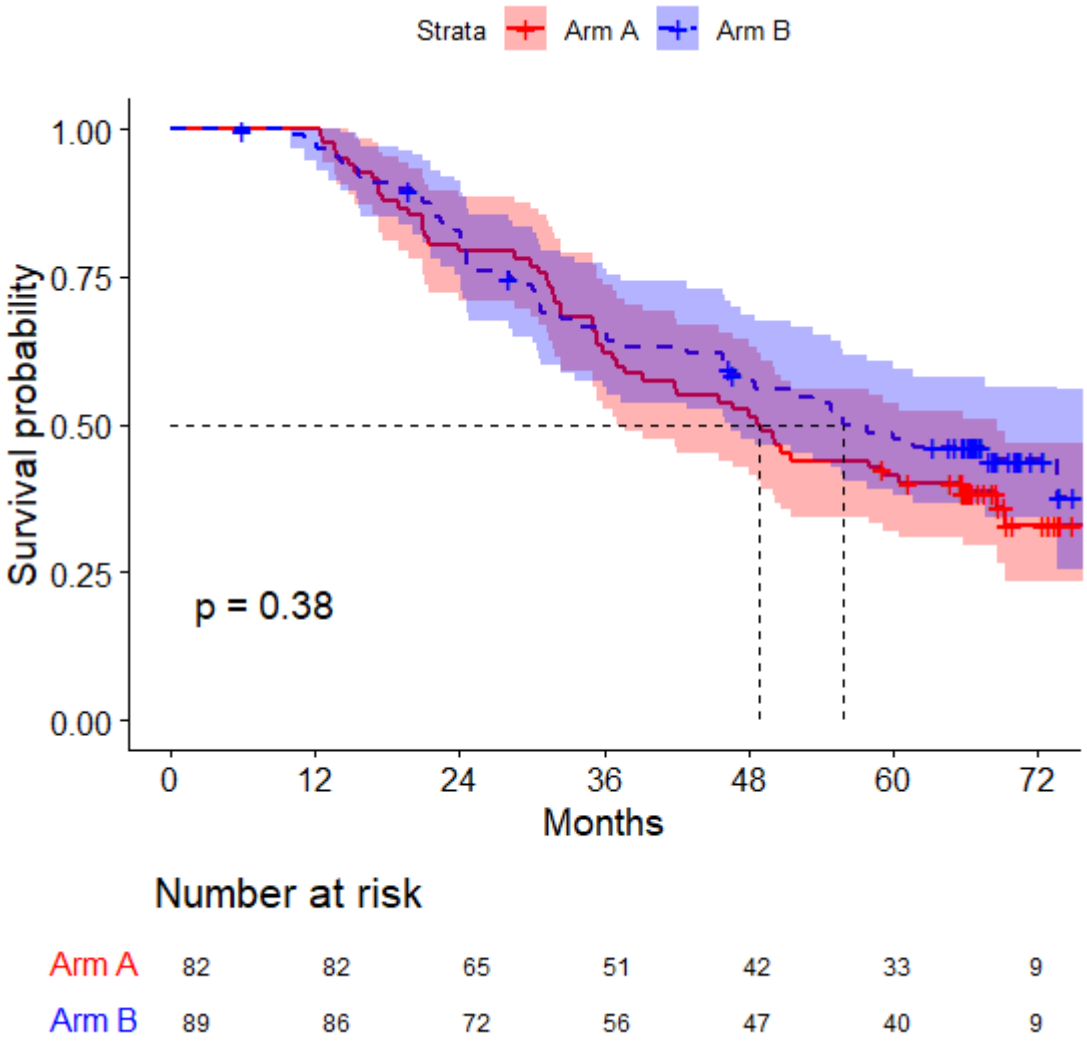


Figure 4: Kaplan-Meier plot for PFS (PP population)

The median survival time for PFS in the PP population is 48.9 months in Arm A (95% CI: 37.7; 68.7) and 55.9. in Arm B (95% CI: 46.5; n.a.). The hazard ratio in the PP population is 0.84 (95% CI: 0.57; 1.24, p=0.38) for the comparison Arm A vs. Arm B.

n.a.: calculation was not possible because the survival curve is always greater than 0.50.

Analysis of secondary endpoints.

The analysis of the secondary endpoints is performed for the ITT population. The results are presented in the following. Secondary endpoints are response rate (CR, VGPR, PR, MR) and overall response rate (ORR) four weeks after end of induction therapy, best response, time to best response, time to first response, time to treatment failure (TTF), remission duration (RD), cause specific survival (CSS) and overall survival (OS). The abbreviation n.a. means not available in case of median survival times.

Table 16 resp.
Table 17 shows the results for the response rate resp. overall response rate.

Table 16: Response rate (CR, VGPR, PR, MR), p=0.35 (Fisher test)

four weeks after end of induction therapy

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
CR	1 1.1	2 2.1	3 1.6
VGPR	8 8.9	15 15.8	23 12.4
PR	51 56.7	57 60.0	108 58.5
MR	19 21.1	15 15.8	34 18.4
SD	9 8.9	4 4.2	13 6.5
PD	2 3.3	1 2.1	3 2.7
Total (available)	90	94	184
Not assessable	10	8	18

Table 17: Overall response rate (ORR), p=0.12 (Fisher's exact test)

four weeks after end of induction therapy

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
No positive response	11 12.2	5 6.3	16 9.2
ORR (CR, VGPR, PR, MR)	79 87.8	89 93.7	168 90.8
Total	90	94	184
Frequency Missing = 18			

Table 18 shows the results for the best response.

Table 18: Best response, p=0.32 (Fisher test)

	Treatment group		
Frequency Percent	**Arm A**	**Arm B**	**Total**
CR	1 1.1	5 5.2	6 3.2
VGPR	19 21.1	29 30.2	48 25.8
PR	56 62.3	51 53.1	107 57.5
MR	10 11.1	7 7.3	17 9.2
SD	2 2.2	3 3.1	5 2.7
PD	2 2.2	1 1.1	3 1.6
Not assessable	10	6	16
Total	100	102	202

The Kalbfleish and Prentice estimate of cumulative incidence of best response occurrence is shown in Figure 5

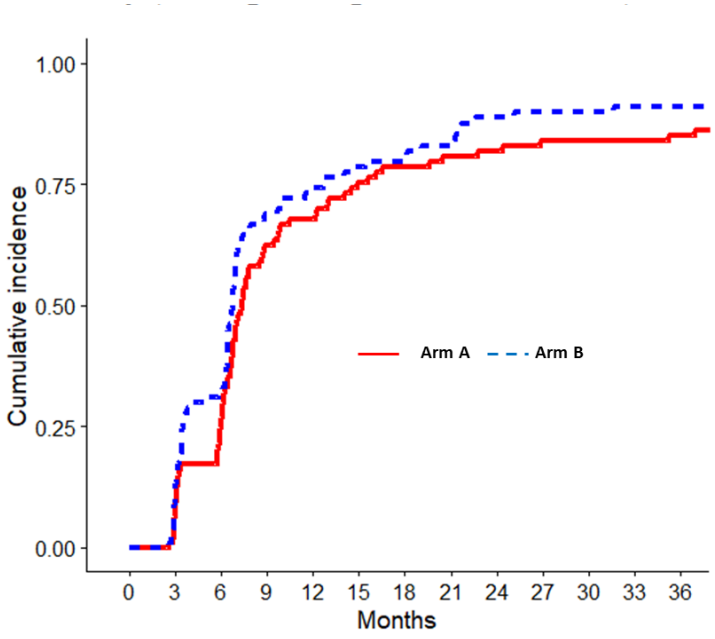


Figure 5: The Kalbfleish and Prentice estimate of cumulative incidence of best response occurence

The 12-months cumulative incidence of best response occurrence was 67% (95%CI: 58%-76%) in Arm A and 74% (95%CI: 65%-83%) in arm B. The p-value for the Fine and gray test was p=0.21.

The plot of the cumulative incidence of first response is shown in Figure 6.

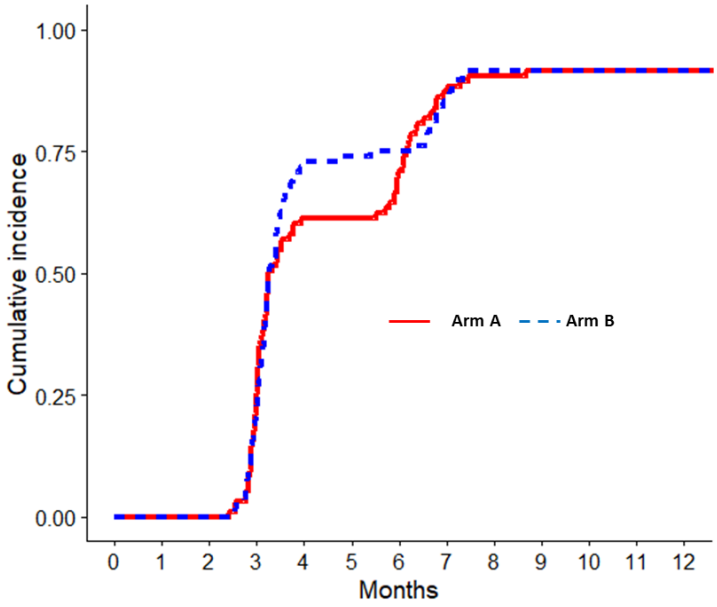


Figure 6: The Kalbfleish and Prentice estimate of cumulative incidence of first response occurrence

The 4-months cumulative incidence of first response occurrence was 61% in Arm A (95%CI: 52%-70%) and 73% (95%CI: 64%-81%) in arm B. The p-value for the Fine and gray test was p=0.83.

The Kaplan-Meier plot for time to treatment failure shows Figure 7.

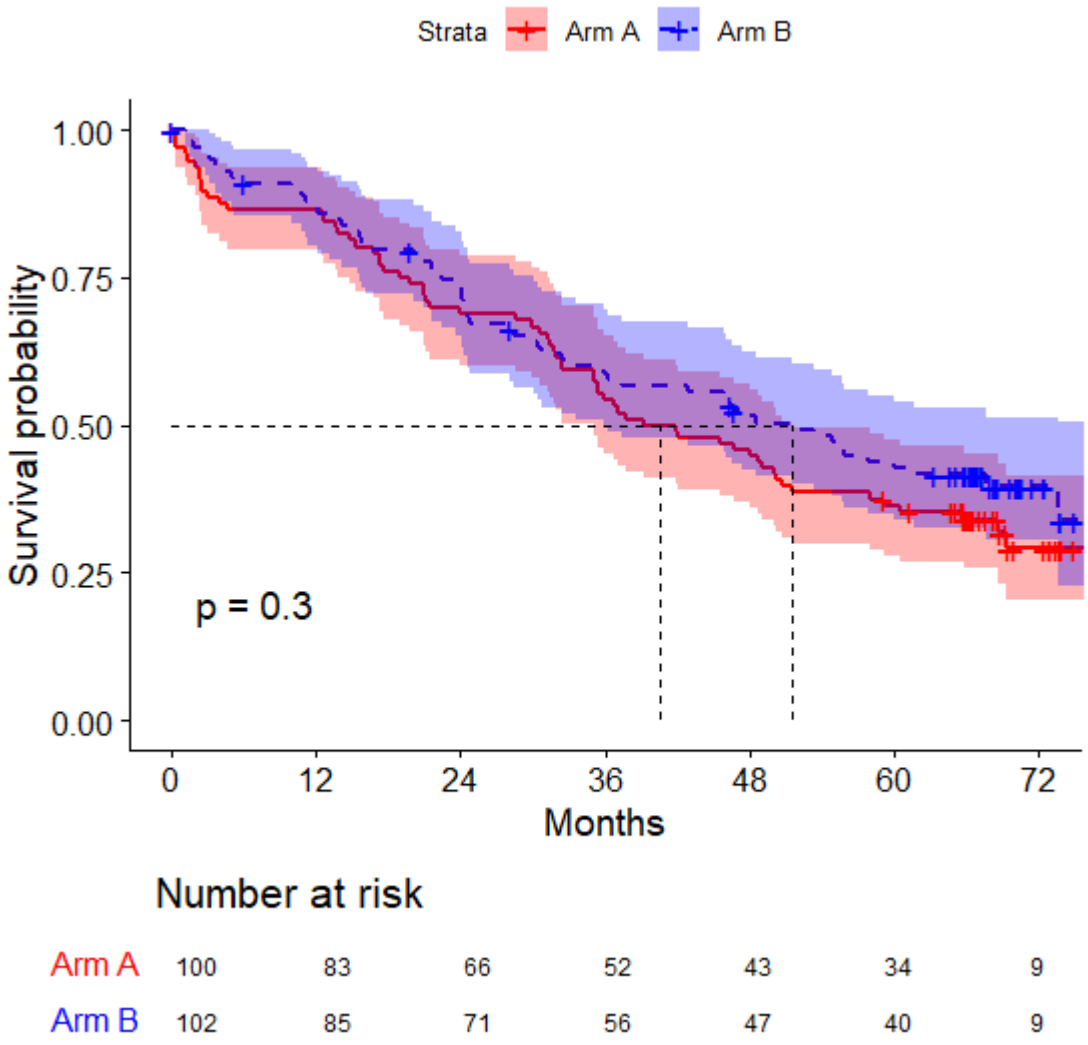


Figure 7: Kaplan-Meier plot for time to treatment failure (TTF)

The median survival time for time to treatment failure is 40.5 months in Arm A (95% CI: 35.1; 51.6) and 51.5 in Arm B (95% CI: 35.8; n.a.). The p-value for the log-rank test is p=0.3.

The Kaplan-Meier plot for time to next treatment is shown in Figure 8..

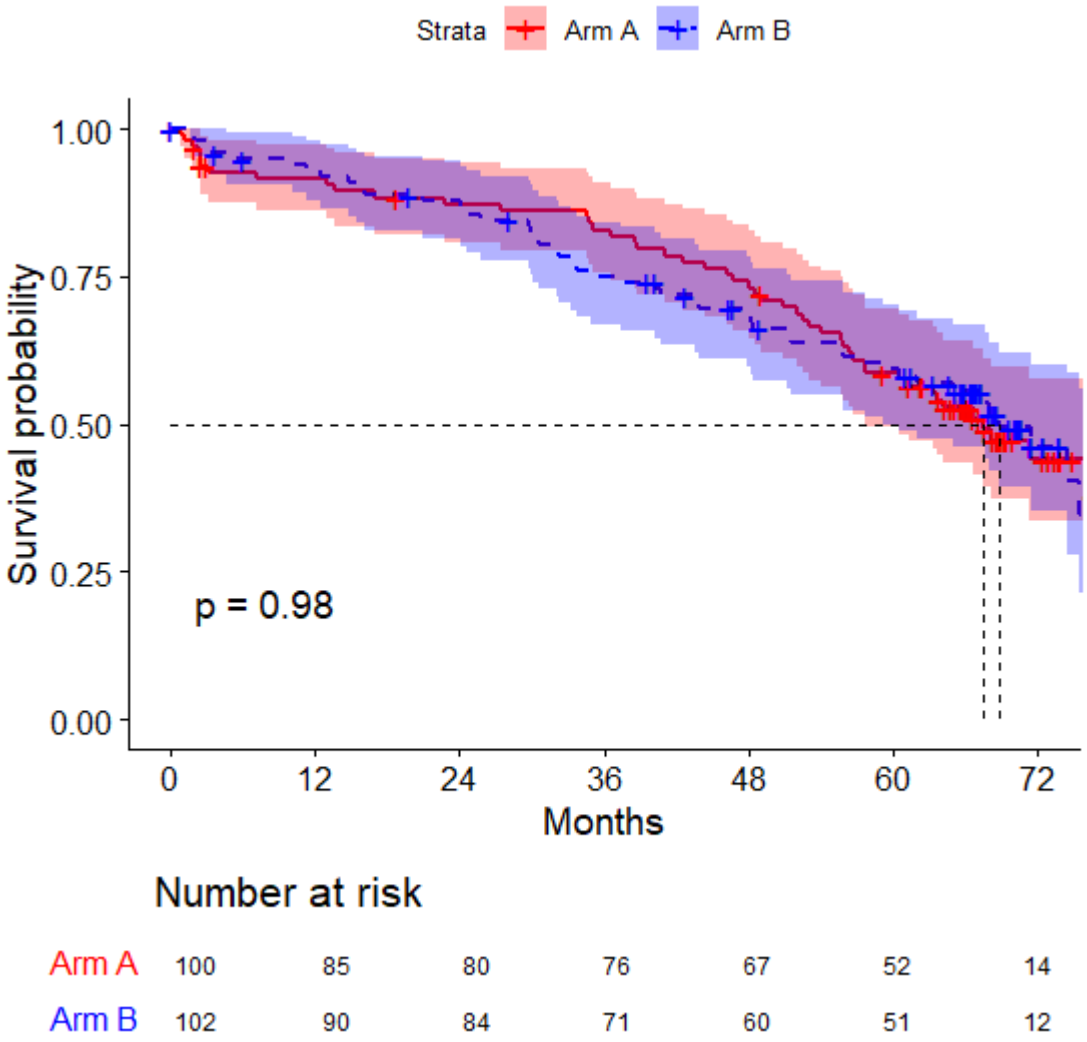


Figure 8: Kaplan-Meier plot for time to next treatment (TNT)

The median survival time for time to next treatment is 67.5 months in Arm A (95% CI: 57.8; n.a.) and 68.8 in Arm B (95% CI: 59.2 ; n.a.). The p-value for the log-rank test is p=0.98.

The Kaplan-Meier plot for remission duration shows Figure 9.

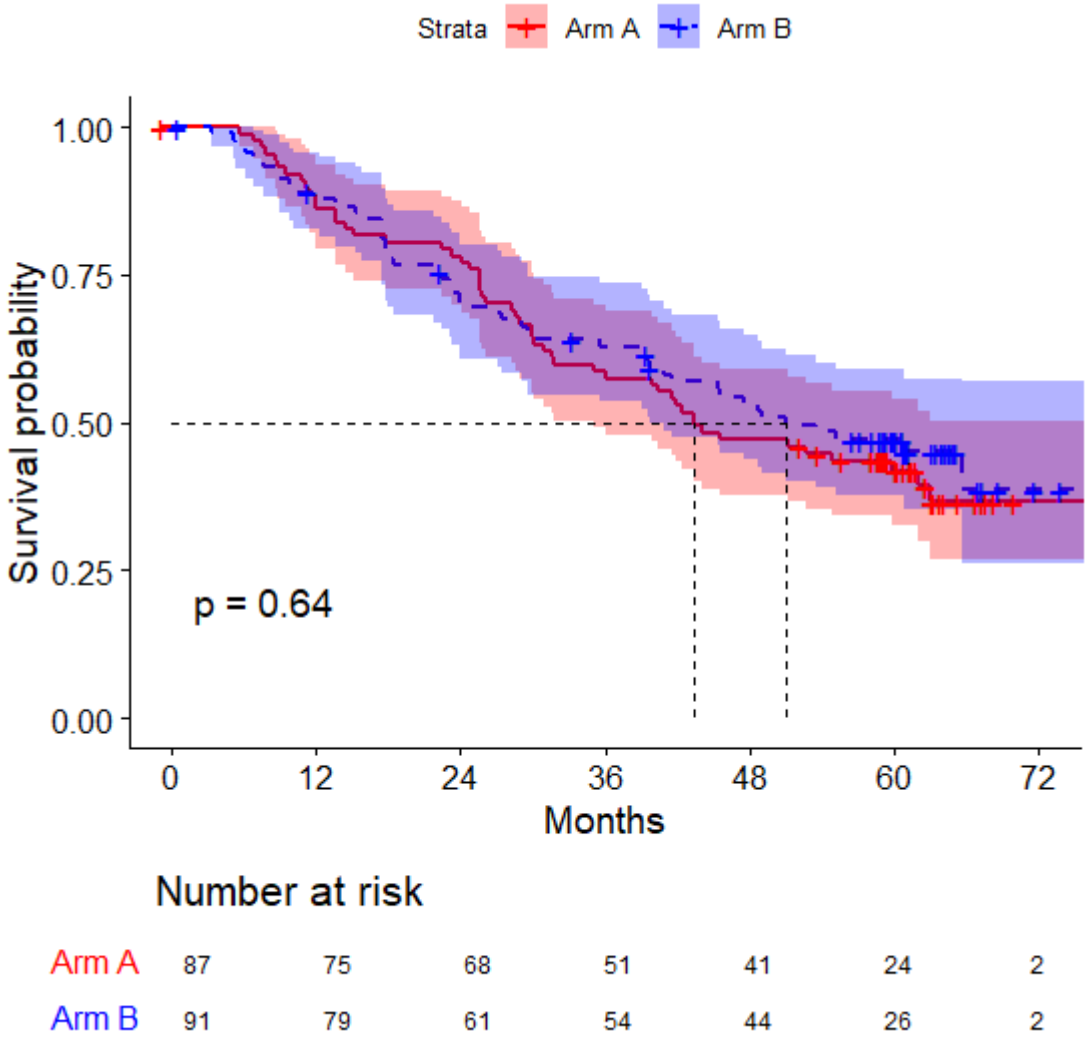


Figure 9: Kaplan-Meier plot for remission duration (RD)

The median survival time for remission duration 43.5 months in Arm A (95% CI: 35.0; 51.6) and 51.1 in Arm B (95% CI: 39.7; n.a.). The p-value for the log-rank test is p=0.64.

n.a.: calculation was not possible because the survival curve is always greater than 0.50.

The Kaplan-Meier plot for cause specific survival shows Figure 10.

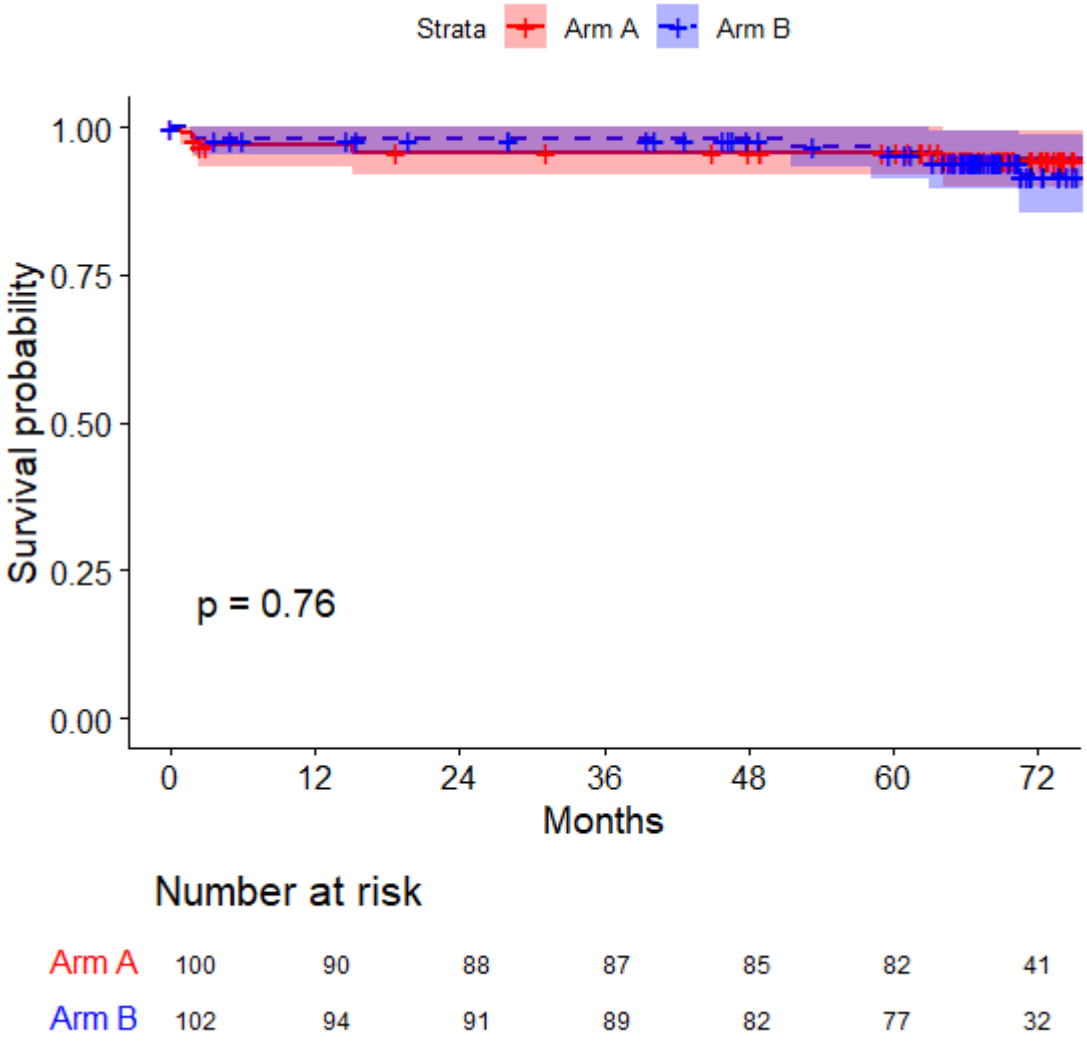


Figure 10: Kaplan-Meier plot for cause specific survival (CSS)

The median survival time for cause specific survival is n.a. both in Arm A and in Arm B. The p-value for the log-rank test is p=0.76.

n.a.: calculation was not possible because the survival curve is always greater than 0.50.

The Kaplan-Meier plot for overall survival is shown in Figure 11.

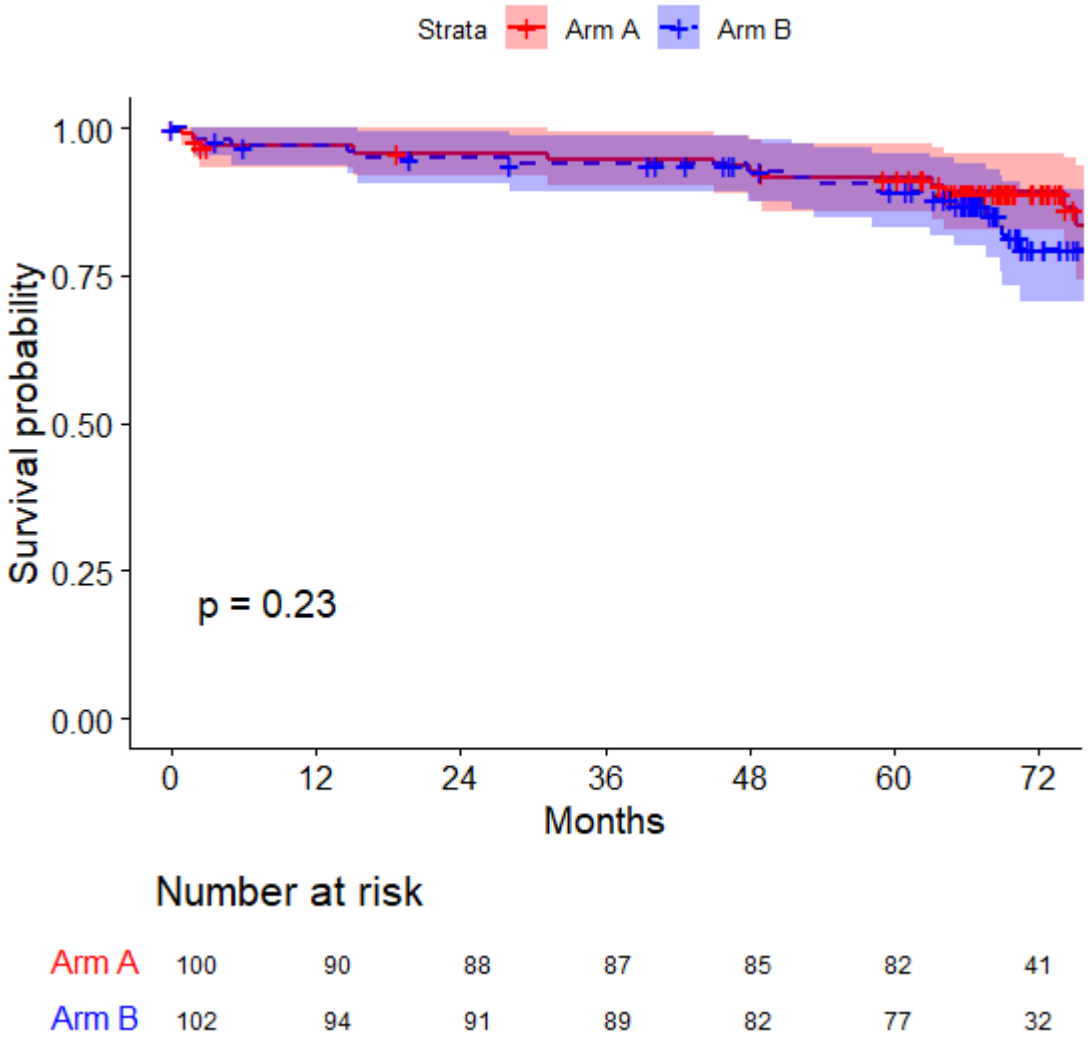


Figure 11: Kaplan-Meier plot for overall survival (OS)

The median survival time for overall survival is n.a. both in Arm A and in Arm B. The p-value for the log-rank test is p=0.23.

n.a.: calculation was not possible because the survival curve is always greater than 0.50.

12.4.2 Statistical/analytical issues

12.4.2.1 Adjustments of Covariates

Not applicable.

12.4.2.2 Handling of Dropouts or Missing Data

Handling of dropouts was not defined in the trial protocol. For the primary endpoint PFS and the secondary time to event outcomes, patients who dropped out were censored. Missing data in all other endpoints were not replaced.

12.4.2.3 Data Monitoring

At that time point of the final analysis, 204 patients were randomized in the trial (two patients were randomized twice). The trial was active in 7 European countries (Germany, France, Greece, Czech Republic, Sweden, Spain and Portugal).

Safety data were generated with the help of the company Diamond PV. All DSMC members received four DSURs (Development Safety Update Report), each covering one year of study. The last one was the DSUR covering August 2016-August 2017 (at that time point 140 patients were randomized). The report showed a summary table of all documented SAEs and it could be seen that during the study they were infrequent. There were some respiratory/thoracic disorders and only one nervous disorder event. In summary, there were 14 events (13 patients) in 140 patients with infectious and respiratory disorders with a slight increased number of events in the experimental Arm B.

After discussion of safety data, the DSMC teleconference meeting confirmed that there were no objections against continuation of the study.

12.4.2.4 Multicentre Studies

Because of the small sample size of some trial sites and the high number of trial sites, no further investigations of effects of trial sites were performed.

12.4.2.5 Multiple Comparisons/Multiplicity

No multiple comparisons were specified and done in this trial.

12.4.2.6 Use of an “Efficacy Subset” of Patients

Not applicable.

12.4.2.7 Active-Control Studies Intended to Show Equivalence

This topic is not relevant for this trial.

12.4.2.8 Examination of Subgroups

Subgroup analyses were not performed.

The international prognostic index for WM has been primarily designed for overall survival. It has not been checked because of the small number of events (death).

12.4.3 Tabulation of individual response data

Not applicable.

12.4.4 Drug dose, drug concentration, and relationships to response

Not applicable.

12.4.5 Drug-drug and drug-disease interactions

Drug-drug and drug-disease interactions were not investigated in this trial.

12.4.6 By-patient displays

Not applicable.

12.4.7 Efficacy conclusions

Primary efficacy analysis

An improvement in PFS for the addition of Bortezomib to the combination regimen Dexamethasone/Rituximab/Cyclophosphamide (B-DRC) compared to DRC alone could not be shown with this trial. The hazard ratio for the ITT population is 0.914 (95% CI: 0.629; 1.329, p=0.64) for the comparison B-DRC vs. DRC. The hazard ratio for the PP population is 0.84 (95% CI: 0.57; 1.24, p=0.38) for the comparison DRC vs. B-DRC.

Secondary efficacy analysis

An improvement in any secondary endpoint for the addition of Bortezomib to the combination regimen Dexamethasone/Rituximab/Cyclophosphamide compared to DRC alone could not be shown with this trial.

The additional treatment with bortezomib (arm B) results in a numerically earlier response.

Overall, no significant differences between both treatment arms could be shown in the primary endpoint and in all secondary endpoints.

13 SAFETY EVALUATION

13.1 EXTENT OF EXPOSURE

The per-protocol (PP) population covers 170 patients who received all 6 cycles of induction therapy and had a dose density of at least 80% of medication (for each study drug with consideration of dose reduction).

13.2 ADVERSE EVENTS (AE)

13.2.1 Brief summary of adverse events

Table 19: Overall summary of adverse events (data is presented as number of patients (%))

Number of	Arm A n=100	Arm B n=102	Total n=202
patients with any AE	91 (45%)	97 (48%)	188 (93%)
patients with any AE of grade ≥ 3	49 (48.5%)	52 (51.5%)	101 (50%)
patients with serious AEs	27 (66.9%)	14 (34.1%)	41 (20.3%)
patients with any serious AE of grade ≥ 3	17 (60.7%)	11 (39.3%)	28 (13.9%)
patients discontinued due to an AEs	6 (54.5%)	5 (45.5%)	11 (5.4%)
patients with drug-related* AEs	47 (38.2%)	76 (61.8%)	123 (60.9%)

* possibly or probably related

13.2.2 Display of adverse events

There were no unexpected AEs and most of the AEs could be categorized as hematotoxic effects of the chemotherapy as expected. Neurotoxicity occurred but is expected in the experimental Arm B because of the use of Bortezomib.

13.2.3 Analysis of adverse events

Similar to the display of adverse events also the SAEs affected mostly hematopoiesis with some neurotoxicity observed. The observed toxicity in this study was in the expected range known for the DRC and Bortezomib application.

13.2.4 Listing of adverse events by SOC and frequency

All adverse events categorized by SOC and CTC AE grade for each arm A and B are listed in Appendix 15.6.

13.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

13.3.1 Listing of deaths, other serious adverse events and other significant adverse events

13.3.1.1 Deaths

The following table provides information about the 26 patients who died.

Arm A: 9 patients / Arm B: 17 patients

Table 20: Patients who died

ID	Arm	Last visit performed	death_date	Reason
3	A	Cycle 1	13.05.2014	Tumor related
8	B	Follow-up 3	16.02.2016	Pancreas Carcinoma
9	A	Survival Follow-up 10	03.01.2018	Tumor related
15	B	Follow-up 13	26.10.2020	unknown
21	B	Survival Follow-up 10	11.04.2022	unknown
22	A	Survival Follow-up 8	29.04.2018	Bronchial Carcinoma
37	A	Cycle 1	15.02.2016	Sudden death probably due to cardiac disease.
43	B	Survival Follow-up 9	16.11.2021	unknown
46	B	Survival Follow-up 10	28.10.2019	Probably related to complications of liver cirrhosis and progression of MW.
51	B	Follow-up 11	24.06.2020	Tumor related
53	B	Survival Follow-up 7	17.02.2022	Tumor related
54	B	Survival Follow-up 5	26.06.2021	Tumor related
56	A	Survival Follow-up 8	02.08.2021	Tumor related
59	B	Cycle 3	26.09.2016	Tumor related
62	B	Cycle 2	02.07.2016	Pulmonary hypertension with congestive cardiac failure
75	A	Follow-up 8	16.03.2020	Tumor related; progressive disease
89	B	Survival Follow-up 1	17.02.2023	Unknown, probably tumor related. (Transformation of Waldenström disease into large cell B lymphoma)
95	B	Survival Follow-up 1	27.04.2022	unknown
96	A	Survival Follow-up 1	06.11.2017	Tumor related
100	A	Survival Follow-up 11	07.12.2021	unknown
120	A	Cycle 3	06.07.2017	Respiratory insufficiency, pre-existing condition
147	B	Survival Follow-up 6	19.03.2022	unknown
151	B	Survival Follow-up 3	01.03.2023	Metastatic pancreatic neuroendocrine tumor
159	B	Cycle 2	21.01.2018	Natural death
183	B	Restaging after Cycle 3, Survival Follow-up 1	19.06.2019	Pulmonary embolism
195	B	Follow-up 12	28.04.2023	Tumor related

13.3.1.2 Other serious adverse events

See Appendix 15.6.

13.3.2 Narratives of deaths, other serious adverse events and certain other significant adverse events

In total, 26 patients died during the study.

Reasons for death during reporting period which were also reported as Serious Adverse Events were: tumor related (#3), pancreas carcinoma (#8), unknown/ sudden death (#37), pulmonary hypertension with congestive cardiac failure (#62), respiratory insufficiency/pre-existing condition (#120) and natural death (#159)

The narratives of the above-mentioned six cases are provided below.

Patients # 9, 51, 53, 54, 56, 59, 75, 96 and 195 died from underlying disease or progression of WM. Patient # 46 died because of progression of WM and complications of a liver cirrhosis. Patient #22 died from bronchial carcinoma and #183 from pulmonary embolism. The death of patient # 151 is caused by a metastatic pancreatic neuroendocrine tumor. The reason for death of patients # 15, 21, 43, 95, 100 and 147 is unknown. The reason for patients' #89 death is also unknown, but probably it is because of transformation of WM into a large cell B lymphoma.

However, according to protocol signs, symptoms and physical findings indicative of progression of lymphoma were not to be reported as "Serious Adverse Events". Also all events that occurred 28 days after the last study medication and that were considered as not being related to study medication were not reported as SAEs, therefore, no narratives are available for these 5 cases.

A 56-year-old male Subject **(subject no. 003)** experienced tumor lysis syndrome, whilst participating in the above study. This event was considered serious due to prolonged hospitalisation, persisting/significant disability or incapacity, and being life threatening.

The Subject had a medical history of chronic obstructive pulmonary disease (COPD), onset date unknown.

There was no concomitant medication reported for this Subject.

On 17 April 2014, the Subject was hospitalised and administered rituximab 375 mg/m2 intravenously (i.v.).

On this day, the Subject was also administered dexamethasone 20 mg and cyclophosphamide 400 mg, orally, which are considered non-investigational medicinal products (IMPs) as defined by the study protocol.

The last dose of rituximab and dexamethasone prior to the onset of the event was on 17 April 2014.

On 19 April 2014, Subject was administered the last dose of cyclophosphamide prior to the event.

On 21 April 2014, the Subject experienced tumour lysis syndrome.

On 12 May 2014, it was the reported that there had been a worsening of the Subject's general condition. The

Subject was resuscitated and required further care on the Intensive Care Unit (ICU) but had shown no improvement.

On 13 May 2014, the Subject died. The cause of dead was reported to be hypoxic brain damage.

The Investigator reported that an autopsy was not performed.

The Investigator assessed the relationship between rituximab (i.v.) and tumour lysis syndrome as being related.

The Investigator assessed the relationship between dexamethasone and tumour lysis syndrome as being related.

The Investigator assessed the relationship between cyclophosphamide and tumour lysis syndrome as being related.

Tumour lysis syndrome is expected for rituximab (i.v.) as per the Investigator's Brochure (IB).

There was a temporal relationship between the administration of the study medication and onset of the SAE.

Pharmacovigilance comment:
Rituximab is known to mediate the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first rituximab IV infusion in patients with high numbers of circulating malignant lymphocytes.

Confounding factors included the non-IMPs of dexamethasone and cyclophosphamide which the Investigator assessed as related.

Investigator causality is assessed as related for tumour lysis syndrome with rituximab (i.v.).

Company causality is assessed as related for tumour lysis syndrome with rituximab (i.v.).

A 79-year-old male Subject **(subject no. 008)** experienced pancreatic cancer whilst participating in the above study.

The Subject was taking the following medicines concomitantly: ASS (acetylsalic acid) 100mg, furosemide 20mg, Rekewan Kps ret.(potassium chloride), ramipril 5mg, metoprolol 47.5mg, simvastatin 20mg, allopurinol 150mg, Movicol Btl

(macrogol, sodium chloride, potassium chloride). Medical history included cholangiosepsis, “enterobacter cloacae”(bacterial infection), PAVK (english translation: peripheral artery occlusive disease), stenosis kidney and nephrolithasis.

This Subject has been participating in the above study since 13 November 2014.

On 13 November 2014, bortezomib 3.2mg/m^2 (subcutaneous [s.c]) and rituximab 750mg/m^2 (intravenous [i.v]), dexamethasone 20mg (oral) and cyclophosphamide (oral) was administered.

On 09 December 2014, rituximab 1400mg was administered subcutaneously.

On 03 March 2015, the last dose of rituximab (subcutaneous) and dexamethasone was administered.

On 07 March 2015, the last dose of cyclophosphamide was administered.

On 17 March 2015, the last dose of bortezomib was administered.

At the time of the report, the event of pancreatic carcinoma was ongoing.

On 13 July 2015, the Subject experienced pancreatic carcinoma; the subject was hospitalised on the same day.

On 31 July 2015, the Subject was discharged from hospital.

A last date of administration for rituximab (i.v) is was not reported.

Follow-up information was received on 24 September 2015.

The Subject was taking the following medicines concomitantly: ASS (acetylsalicylic acid) 100mg, oral, ramipril 5mg, oral and metoprolol 47.5mg, oral for hypertonia, simvastatin 20mg, oral for cholesterol, allopurinol 150mg, oral for inflammation, Movicol Btl (macrogol, sodium chloride, potassium chloride) obstipation, and furosemide 20mg, oral and Rekewan Kps ret.(potassium chloride), oral, for an unknown indication.

Medical history included: cholangiosepsis, “enterobacter cloacae” (bacterial infection), PAVK (peripheral artery occlusive disease), kidney stenosis and nephrolithiasis.

On 27 July 2015, the Subject was diagnosed with an undifferentiated 2.5*2.8*3.5 cm pancreas head carcinoma, which was confirmed by histology.

On 12 August 2015, the Subject was hospitalised again for treatment of the malignancy. During this period the Subject received therapy with piperacillin tazobactam antibiotic, thrombocytes concentrate 2 x blood intravenously and was later discharged on 24 August 2015.

On 31 August 2015, the Subject was hospitalised for a third occasion and was then discharged on 03 September 2015.

On 08 September 2015, the Subject began chemotherapy with gemcitabine 75%. It was reported that the Subject refused treatment of an operation.

Investigator reported that the outcome of the event was unchanged and the Subject's current status was stable.

Follow up information was received 02 August 2016.

The Investigator reported that the Subject had completed all six treatment cycles prior to the onset of the SAE, but that cycle three was only the first day (06 January 2015).

On 31 March 2015, the last dose of rituximab s.c. and dexamethasone was administered. On this day, the Subject was also administered bortezomib and cyclophosphamide.

On 04 April 2015, the last dose of cyclophosphamide was administered.

On 07 April 2015 and 14 April 2015, the Subject was administered the last doses of bortezomib and cycle six was completed.

On 16 February 2016, the Subject died.

No further information was reported.

The Investigator assessed the relationship between Bortezomib and pancreatic cancer as not related.

The Investigator assessed the relationship between Rituximab (s.c.) and pancreatic cancer as not related.

The Investigator assessed the relationship between Rituximab (i.v.) and pancreatic cancer as not related.

The Investigator assessed the relationship between Dexamethasone and pancreatic cancer as not related.

Pharmacovigilance comment:
Pancreatic cancer is unexpected for bortezomib, rituximab (s.c.) and rituximab (i.v.) as per the Investigator's brochure for the IMPs.

There was no temporal relationship as the last administration of the bortezomib and rituximab (s.c.) last administered approximately three months prior to the event onset.

Investigator causality is assessed as not related for pancreatic cancer with Company causality assessed as not related for pancreatic cancer with bortezomib, rituximab (s.c.) and rituximab (i.v.).

A 69-year-old male Subject **(Subject No. 037)** died suddenly whilst participating in the above study.

The Subject had an underlying disease of cardiac amyloidosis related to Waldenström which was initially diagnosed on 23 December 2015.

The Subject was taking the following medicines concomitantly; 0.4 I.U of Clexane (enoxaparin) subcutaneously one a day for thrombo prophylaxis; 20 mg of Losec (omeprazole), orally once a day for gastro prophylaxis; 100 mg of Zyloric (allopurinol) every other day for preventing an increase of uric acid; and 50 mg of

Lopresor (metoprolol) twice a day, 200 mg of Angoran (amiodorone) daily and 40 mg of Lasix (furosemide) daily all for cardiac amyloidosis.

On 25 January 2016, the Subject was administered with 375 mg/m2 of rituximab intravenous (i.v.). On this day, the Subject was administered with the following non-IMPs orally; 20 mg of dexamethasone and 400 mg of cyclophosphamide as background therapy.

On 15 February 2016, the Investigator was informed by the Subjects daughter that the Subject had died while sleeping in this home. No autopsy was performed.

Follow up information received on 31 May 2016.

The investigator reported no autopsy was performed however the Subject's sudden death was probably due to cardiac involvement due to amyloidosis and was possibly arrhythmic related.

The Investigator assessed the relationship between rituximab (i.v.) and sudden death as not related.

The Investigator assessed the relationship between dexamethasone and cyclophosphamide as not related.

Case correction was completed on 30 October 2019: During SAE reconciliation, Subject number was added to identification field and the severity of the event was added as Severe, as the event was reported as CTCAE grade 4 – life threatening.

Pharmacovigilance comment:
Sudden death is unexpected as per the Investigators brochure for rituximab (i.v.). A confounding factor included the Subject's underlying condition of cardiac amyloidosis. The investigator reported the Subject's sudden death was probably due to cardiac involvment due to amyloidosis and was possibly arrhythmic related. No autopsy was performed so it is difficult to fully assess the case. Investigator causality is assessed as not related for sudden death and rituximab (i.v.). The sponsor causality is assessed as not related for sudden death and rituximab (i.v.).

A 77-year-old male Subject **(Subject No. 062)** experienced decompensated congestive heart failure, whilst participating in the above study. The decompensated congestive heart failure was considered serious due to requiring hospitalisation and resulting in death.

Ongoing medical history included aortic valve stenosis and mitral valve stenosis from 01 July 2015 and hypertension.

The Subject was taking the following medicines concomitantly: Zelitrex (valacyclovir) for infection prevention, Movicol (macrogol) as laxative therapy and Lasix (furosemide) as diuretic therapy.

On 23 May 2016, the Subject began his first cycle of study treatment and was administered bortezomib 16mg/m2 subcutaneously and rituximab 375 mg/m2 intravenously (i.v.).

On this day, the Subject was also administered dexamethasone 20 mg and cyclophosphamide 200 mg, orally, which are considered non-investigational medicinal products (IMPs) as defined by the study protocol.

On 20 June 2016, the Subject began his second cycle and had his first dose of rituximab 1400mg subcutaneously (s.c.).

The last administration of subcutaneous rituximab and dexamethasone prior to event onset was on 20 June 2016.

The last administration of cyclophosphamide prior to event onset was on 27 June 2016.

On 01 July 2016, the Subject was admitted to hospital due to a fall, in the context of poor general condition, dyspnoea, and oedema of the lower limbs.

The Subject was admitted to the care of the Cardiology service for decompensated congestive heart failure with pulmonary hypertension (60 mmHg). Upon admission, the Subject was noted to be dyspnoeic and tachycardic with haemodynamic retention. A clinical picture of cardiac decompensation was noted, with a Brain-Type natiuretic peptide (BNP) of 1613 mg/L.

The Subject underwent investigations including blood tests, revealing sodium at 113 mmol/L, potassium 4 mmol/L, creatinine 83 ug/L, creatinine clearance 82 ml/mn, urea 7.8 mmol/L, haemoglobin 9.9 g/dL, glycated haemoglobin 5.6%, white blood cells 12600/mm3, platelets 73000/mm3, C-reactive protein (CRP) 56.9 mg/L, haematocrit at 29.8%. International Normalised Ratio (INR) was 1.47 and prothrombin time (PT) 59%.

Physical examination revealed oedema of the lower limbs and venous stasis with right heart signs. Auscultation revealed irregular heart sounds, the presence of cardiac and vascular murmurs and signs of left and right ventricular insufficiency.

During the night of 01 July 2016, the Subject suffered a deterioration of his respiratory condition. The Subject was intubated and was treated with an increased dose of Lasix and oxygen.

An electrocardiogram (ECG) on 02 July 2016 revealed irregular sinus rhythm, normal QRS complex, 1st degree atrioventricular block (BAV1), left axis deviation, T waves in leads D3-AVF-V1-V3-V6.

On 02 July 2016, the Subject’s condition deteriorated. The Subjects experienced increased respiratory distress with signs of hypoxia. Lasix dosage was increased and high concentration oxygen was administered.

Desaturation at 85%, 3 litres of oxygen and hypotension 80/60. The support consisted of a bolus of furosemide.

The Subject was transferred to Respiratory resuscitation.

On 03 July 2016, echocardiography prior to transfer revealed a non-dilated left ventricle, with normal LV function. Severe pulmonary hypertension was present, with arterial pulmonary pressure at 60+15 mmHg and a dilated vena cava. Mitral and aortic valve abnormalities were identified and clarification is sought from the Investigator in respect of these findings.

On the same day, the Subject became bradycardic and was quickly intubated. An external heart massage was undertaken after administration of a bolus of adrenaline. Sinus rhythm was fluctuating. Despite resuscitation attempts for more than 45 minutes, an effective cardiac rhythm could not be recovered and the Subject died at 8.45pm.

The cause of death was reported to be unknown – pulmonary hypertension with congestive cardiac failure without impaired LVEF (left ventricular ejection fraction).

The Investigator assessed the relationship between the study drugs bortezomib, rituximab (i.v.), rituximab (s.c) and decompensated congestive heart failure as not related.

The Investigator assessed the relationship between the background therapies oral dexamethasone and oral cyclophosphamide and decompensated congestive heart failure as not related.

Further information received on 14 February 2018:

The outcome of the event was considered as fatal.

The Subject had previously experienced heart failure in 2012 and had a medical history of high blood pressure.

The date of death was confirmed as 02 July 2016.

Case correction was completed on 30 October 2019: During SAE reconciliation, the outcome was changed from death to fatal to be consistent with case conventions.

Pharmacovigilance comment:
Decompensated congestive heart failure is expected for bortezomib, rituximab (i.v.) and rituximab (s.c.) as per Investigators' Brochures for the IMPs. Decompensated congestive heart failure is also a known adverse

reaction associated with non-IMPs dexamethasone and cyclophosphamide.

There was a temporal relationship between subcutaneous rituximab, oral dexamethasone and oral cyclophosphamide and the onset of the decompensated congestive heart failure. The half-life of rituximab is approximately 22 days. The last administration of subcutaneous rituximab and oral dexamethasone prior to the onset was on 20 June 2016. The last administration of oral cyclophosphamide prior to the dysphagia onset was on 24 June 2016.

Confounding factors are the Subject's underlying cardiovascular conditions, including hypertension, aortic and mitral valve stenosis and severe pulmonary hypertension.

Investigator and Sponsor causality is assessed as not related for rituximab (i.v.), rituximab (s.c.) and bortezomib and decompensated congestive heart failure.

Investigator and Sponosr causality is assessed as not related for the background therapies dexamethasone and cyclophosphamide and decompensated congestive heart failure.

A 70-year-old male Subject **(Subject no. 120)** experienced a pleural effusion, right, whilst participating in the above study. Pleural effusion, right was considered serious due to requiring hospitalisation and being an important medical event.

The Subject's medical history included chronic obstructive pulmonary disease (COPD) COLD III, aortic valve stenosis, atrial fibrillation and hypertension.

Concomitant medication details were not reported.

On 03 May 2017, the Subject was administered dexamethasone 20 mg intravenously and cyclophosphamide 350 mg, orally, which are considered non-investigational medicinal products (IMPs) as defined by the study protocol.

On 27 May 2017, the Subject received one administration of rituximab 645 mg/m2 intravenously (i.v.).

The last administration of dexamethasone prior to the pleural effusion, right, was on 01 July 2017. The last administration of oral cyclophosphamide prior to the pleural effusion, right was on 05 July 2017.

On 06 June 2017, the Subject experienced dyspnoea.

On 06 June 2017, the Subject was admitted to hospital after experiencing dyspnoea due to pleural effusion, right. Pneumonia was also suspected; therefore, Subject was treated with Tazobactam.

On 08 of June 2017, a pleura puncture was performed.

Due to progression of pleural effusion the Subject was transferred for pleurodesis which has been performed on 16 June 2018 without complication, however Subject died to due the event of 06 July 2017.

The Subject developed respiratory failure due to pleural effusion and consequently died.

The Investigator assessed the relationship between the study drug rituximab (i.v.), and pleural effusion, right as not related.

The Investigator assessed the relationship between the background therapies dexamethasone and cyclophosphamide and the pleural effusion, right as not related.

Case correction was completed on 30 October 2019: During SAE reconciliation, the outcome was changed from death to fatal to be consistent with case conventions.

Additional information was received on 02 March 2020:

The Investigator confirmed the onset of the event pleural effusion as 08 June 2017.

On 15 June 2017, the outcome of the event was considered recovered.

Pharmacovigilance comment:
The expectedness of pleural effusion in relation to the IMP was not assessed as per the PVMP as the event was considered not related.

Confounding factors include the Subject's underlying COPD (COLD III) and the underlying disease under study, Waldenstrom's macroglobulinaemia. Both of these conditions would strongly predispose the Subject to pleural effusion. The Subject's concomitant atrial fibrillation would also be a risk factor for the development of pleural effusion.

Investigator causality is assessed as not related for rituximab (i.v) and pleural effusion.

The Sponsor causality is assessed as not related for rituximab (i.v) and pleural effusion.

A 81-year-old female Subject **(Subject no. 159)** experienced natural death (CTCAE grade 5), whilst participating in the above study. The adverse event of natural death was considered serious due to death of the Subject.

The Subject did not have any reported relevant medical history at the time of the event.

The Subject did not have any reported relevant concomitant medication at the time of the event.

On 07 December 2017, the Subject was administered rituximab 375 mg/m2, intravenously (i.v) as a single dose. On the same day, the Subject was adminsitered bortezomib, 1.6 mg/m2, ubcutaneously (s.c).

On 09 January 2018, subject was administered rituximab 1400 mg, subcutaneously (s.c). On 09 January 2018, the subject received last dose of subcutaneously rituximab prior to the event.

On 16 January 2018, the subject received the last dose of bortezomib prior to the event.

The Subject was also administered non-investigational medicinal products (NIMPs) as defined by the study protocol; dexamethasone, 20mg, oral from 07 December 2017 to 09 January 2018 and cyclophosphamide, 300mg, oral from 07 December 2017 to 14 January 2018.

On 21 January 2018, the Subject experienced natural death and died in his sleep.

The investigator assessed the relationship between bortezomib (s.c), rituximab (i.v) and rituximab (s.c) and natural death as not related.

The investigator assessed the relationship between the background therapy dexamethasone and cyclophosphamide and natural death as not related.

Case correction was completed on 25 October 2019: During SAE reconciliation, the outcome was changed from death to fatal to be consistent with case conventions.

Pharmacovigilance comment:
The expectedness of natural death in relation to the IMP was not assessed as per the PVMP.

Due to limited information there were no apparent confounding factors. However, patient's underlying disease of Waldenstrom's Macroglobulinemia may be a factor. Additionally, it is worth noting the risk of natural death increases with age and as patient is 81 years old this may be a factor in the death of the Subject.

The Investigator causality is assessed as not related for natural death with bortezomib (s.c), rituximab (i.v) and rituximab (s.c).

13.3.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events

The number of patients who died is higher in Arm B (Arm A: n = 9, Arm B: n = 17). The number of patients who died during the treatment phase is equal in both groups (Arm A: n = 3, Arm B: n = 3).

The number of patients with any AE of grade < 3 is lower in Arm A (Arm A: n=516, Arm B: n=598). Likewise, the number of patients with serious AEs and serious AE of grade ≥ 3 is lower in Arm A (Arm A: n=110, Arm B: n=146).

13.4 CLINICAL LABORATORY EVALUATION

13.4.1 Listings of individual laboratory measurements by patient and each abnormal laboratory value

A listing of individual laboratory measurements by patient will be provided with this report but can be made available on request.

13.4.2 Evaluation of each laboratory parameter

13.4.2.1 Laboratory values over time

Most important parameters are Hemoglobin and IgM at baseline and at the end of treatment. The results are presented in Table 21, Table 22, Table 23 and Table 24, respectively.

Table 21: Hemoglobin [g/dl] at C1D1

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
189	6	5.8	8.7	9.8	10,9	16.0	10	1.8
Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
93	3	6.4	8.7	9.7	10.9	15.4	9.9	1.7
Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
95	3	5.8	8.9	10	11.1	16	10.2	1.9

Table 22: Hemoglobin [g/dl] at the end of treatment

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
176	4	9.3	11.9	12.9	13.6	15.7	12.8	1.3
Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
88	1	9.3	11.9	12.9	13.6	15.7	12.9	1.4

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
88	3	9.5	12.1	12.8	13.8	15.7	12.7	1.3

Table 23: IgM [g/l] at C1D1

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
196	34	0.36	18.8	31.5	48.0	94.7	34.0	20.6

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
96	17	0.36	20.85	32.6	52.15	94.7	36.1	22.8

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
99	17	1.1	17.3	30.1	45.5	65.7	31.9	18.1

Table 24: IgM [g/l] at the end of treatment

Whole population								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
176	13	0.2	3.5	7.61	15.7	84.6	12.6	14.2

Treatment group: Arm A								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
89	6	0.36	4.4	9.43	15.7	84.6	14.7	16.4

Treatment group: Arm B								
N	N Miss	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	Mean	Std Dev
91	7	0.2	2.7	6.5	14.9	57.6	10.6	11.3

13.4.2.2 Individual patient changes

As expected an increase in Hb and a decrease in IgM was observed after treatment, reflecting the anti-lymphoma activity of the applied treatment.

14 DISCUSSION AND OVERALL CONCLUSIONS

This is the first and largest prospective randomized trial to evaluate bortezomib in combination with standard immunochemotherapy, demonstrating that B-DRC is a well-tolerated regimen which induces a high rate of major responses including deep remissions after 6 months of treatment with a median survival time for PFS in the ITT population of 50.1 months in the standard Arm A (DRC) (95% CI: 39.2; 69.4) versus 60.0 months in the experimental Arm B (Bortezomib-DRC) (95% CI: 46.0; n.a.). These data with a e median observation time of 68.8 months demonstrate that Bortezomib-DRC is well tolerated and highly effective in inducing rapidly deep responses in patients with WM in need of treatment. This analysis also showed that with longer follow-up there are only numerical non-significant differences in PFS in favour of Bortezomib-DRC and that OS is comparable between the two treatment arms. This illustrates that DRC on its own is highly effective in controlling WM as first line treatment and that it is still justified to consider DRC as one of the standard treatments in WM. Based on the numerically faster response induction and the substantially higher proportion of deep remissions , the data indicate that Bortezomib-DRC is a particularly appropriate treatment choice in symptomatic patients with a more dynamic disease and high tumor burden.

15 APPENDICES

15.1 LIST OF RESPONSIBLE IECS OR IRBS PER COUNTRY

Table 25: List of responsible Ethic Committees

Country	Body	Name
Czech Republic	Ethics Committee (Central)	Ethical committee of University Hospital Brno
France	Ethics Committee (Central)	Comité De Protection Des Personnes Nord Ouest IV
Germany	Ethics Committee (Central)	Ethikkommission der Universität Ulm
Greece	Ethics Committee (Central)	Hellenic Republic Ministry of Health, National Ethics Committee
Portugal	Ethics Committee (Central)	CEIC
Spain	Ethics Committee (Central)	Comité Etico de Investigacion Clinica, Hospital Universitario de Salamanca
Sweden	Ethics Committee (Central)	Regional Ethical Review board in Umea

15.2 LIST OF INVESTIGATORS

Table 26: List of Investigators per country

Germany:

First Name	Last Name	Institution	Department	Street	Post code	City
Peter	Staib	St. Antonius Hospital	Klinik f. Hämatologie u. Onkologie	Dechant-Deckers-Str. 8	52249	Eschweiler
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Ralf Ulrich	Trappe	DIAKO Ev. Diakonie-Krankenhaus gemeinnützige GmbH	Medizinische Klinik	Gröpelinger Heerstr. 406-408	28239	Bremen
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Thomas	Ernst	Universitätsklinikum Jena	Klinik für Innere Medizin II, Hämatologie und Internistische Onkologie	Erlanger Allee 101	07740	Jena
Ullrich	Graeven	Kliniken Maria Hilf GmbH (Krankenhaus St. Franziskus)	Medizinische Klinik I (Klinik f. Hämatologie, Onkologie, Gastroentereologie)	Viersener Str. 450	41063	Mönchengladbach
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Stephan	Fuhrmann	Helioskliniken Berlin-Buch	Klinik für Hämatologie, Onkologie und Tumorimmunologie	Schwanebecker Chaussee 50	13125	Berlin
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First Name	Last Name	Institution	Department	Street	Post code	City
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Gabriele	Käfer	Kliniken Landkreis Sigmaringen GmbH	Hämatologie u. Internistische Onkologie	Hohenzollernstr. 40	72488	Sigmaringen
Manfred	Glados	FÄ für Innere Medizin	Hämatologie / Onkologie	Münsterstr. 30	48653	Coesfeld
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France:

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Hacène	Zerazhi	CH Avignon	Médecine interne-onco-hematologie	305 rue Raoul Follereau	84902	AVIGNON
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Marie-Sarah	Dilhuydy	Hôpital Haut-Lévêque	Centre F Magendie Service d'Hématologie Clinique et Thérapie Cellulaire	Avenue de Magellan	33600	Pessac (Bordeaux)
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Olivier	Casasnovas	CHU de Dijon	Service d'hematologie clinique	2 bd Maréchal de Lattre de Tassigny	21000	Dijon
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Franck	Morschhauser	Hopital Huriez CHRU (CHRU de Lille)	Service des maladies du sang	2 avenue Oscar Lambret	59037	Lille
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First Name	Last Name	Institution	Department	Street	Post code	City
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Greece:

First Name	Last Name	Institution	Department	Street	Post code	City
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Sweden:

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Spain:

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Portugal:

First Name	Last Name	Institution	Department	Street	Post code	City
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Czech Republic:

First Name	Last Name	Institution	Department	Street	Post code	City
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15.3 RANDOMIZATION METHOD

Minimization Method of Pocock and Simon

$$MD = w_0 \mid n_A - n_B \mid + \sum_{i=1}^{K} w_i \sum_{j=1}^{K} \quad |n_{Aij} - n_{Bij}\mid$$

Arm A					Arm B				
PF	1 low	2 med	3 high	Total	PF	1 low	2 med	3 high	Total
Italy				Aj1	Italy				Bj1
France				Aj2	France				Bj2
Germany GLSG				Aj3	Germany GLSG				Bj3
Netherlands				Aj4	Netherlands				Bj4
Sweden				Aj5	Sweden				Bj5
Germany OSHO				Aj6	Germany OSHO				Bj6
Greece				Aj7	Greece				Bj7
Spain				Aj8	Spain				Bj8
UK				Aj9	UK				Bj9
Portugal				Aj10	Portugal				Bj10
Czech				Aj11	Czech				Bj11
Total	Ai1	Ai2	Ai3	nA	Total	Bi1	Bi2	Bi3	nB

MD= minimal discrepancy
$w_{0 =}$ Anzahl der Faktoren (Risk, Zentren)
nA= Summe Total im Arm A
nB= Summe Total im Arm B
Ai= Spaltensumme im Arm A
Bi=Spaltensumme im Arm B
Aj= Zeilensumme
Bj= Zeilensumme

MD = 2 | nA – nB| +1 (|Ai1 – Bi1 |+ |Ai2 – Bi2|+|Ai3-bi3|) +1 (|Aj1-Bj1| + |Aj2 – Bj2| + |Aj3 – Bj3| + … | Aj11 – Bj11|)

1. FIL (Italian Intergroup) (A. Tedeschi, Italy)
2. FCGCLLWM Group, (P. Morel, X. Leleu, V. LeBlond , France)
3. GLSG (C. Buske, M. Dreyling, W. Hiddemann/Germany)
4. HOVON (P. Sonneveld, M.-J. Kersten, Netherlands)
5. Nordic L. Group (E. Kimby, Sweden)
6. OSHO (M. Herold, Germany)
7. Greek Myeloma Study Group (M. Dimopoulos, Greece)
8. Spanish Study Group (R. Garcia Sanz, Spain)
9. BNLI (R. Owen, UK)

10. Portugese Lymphoma Study Group (M. Gomes da Silva, Portugal)
11. Czech Myeloma Group (Prof. Dr. Roman Hajek)

International Prognostic Index (ISSWM)

Risk group:	**Low**	**Intermediate**	**High**
Score	0-1 (except age)	Age or 2	≥ 3
5-years OS[1] (%)	87	68	36
Risk Factors	**Score**		
Age ≥ 65 years	1		
Other risk factors[2]			
Hb[3] ≤ 11,5 g / dl	1		
Thrombo[4] ≤ 100.000 x 10^9 / l	1		
β_2M[5] > 3 mg / l	1		
IgM[6] > 70 g / l	1		

12. [1]OS: overall survival [2]Each of the risk factors counts as one; [3] Hb - Hemoglobin; [4] Thrombo - Thrombocytes; [5] β_2M - beta$_2$ Microglobulin; [6] IgM – monoclonal protein concentration

15.4 DOCUMENTATION OF STATISTICAL METHODS

Continuous variables were summarized using the following standard descriptive summary statistics (if appropriate): number of observations, arithmetic mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Categorical data were described using absolute and relative frequencies, where appropriate. Time to event variables were investigated using Kaplan-Meier-plots. The median survival time was provided if appropriate. Efficacy analysis of the primary endpoint is based on the ITT principle. The primary endpoint was evaluated for the ITT population and the PP population. For the primary endpoint PFS and the secondary time to event outcomes, patients who dropped out were censored. Missing data in all other endpoints were not replaced. The logrank test was used to compare the time to event variables between both treatment arms. For estimating the treatment effect, the hazard ratio, incl. the two-sided 95% confidence interval was provided for the analysis of the primary endpoint PFS. Fisher's exact test was used to compare response rates between the two treatment groups. Occurrence of response (first response or best response) is a competing event with death before response. Therefore, a cumulative incidence of response (first or best) was

estimated using the Kalbfleish and Prentice method, provided by the cuminc function of the cmprsk package of R (CRAN). Comparison of the 2 incidences curve was done with the Fine and Gray test of the crr function of the same package. The type one error was set to alpha=0.05 (two-sided) for all statistical tests. An adjustment for multiple testing was not made.

15.5 PATIENTS WHO WERE EXCLUDED FROM THE PP POPULATION FOR PFS ANALYSIS

This listing shows those patients who were not included in the PFS evaluation.

Arm A

Pat ID	Reason for exclusion
143	Withdrawal of consent before the start of therapy
29, 109, 177	Screening Failure
84, 164, 169, 194	Withdrawal of consent during treatment
87, 187	Progression during treatment
3, 37	Deceased in cycle 1
38, 58, 116, 120	Early termination of treatment without staging (due to toxicity, intolerance, new therapy)
35, 188	Missing of relevant values
Total: 18	

Arm B

Pat ID	Reason for exclusion
11, 17	Withdrawal of consent before the start of therapy
50	Screening Failure
119, 182, 183	Withdrawal of consent during treatment / non-compliance by patient
59	Progression during treatment
62, 159	Deceased in cycle 2
6, 27	Early termination of treatment without staging (due to toxicity, intolerance, new therapy)
25, 93	additional malignancy during Follow Up
Total: 13	

15.6 AE/SAE/SAR

Table 27: List of Adverse Events (PT) with CTC AE Grade for Arm A and Arm B incl. number of SAEs

CTC AE Grade:	1	2	3	4	5	AE (total)	SAE (total)
Arm A: Induction standard arm	**247**	**264**	**87**	**22**	**2**	**622**	**34**
Blood and lymphatic system disorders	**28**	**65**	**56**	**18**		**167**	**4**
Anaemia	10	18	8			36	
Febrile neutropenia		1	1			2	2
Hyperviscosity syndrome	1					1	1
Leukocytosis				1		1	
Leukopenia	5	6	11			22	
Lymphopenia		1	2			3	
Neutropenia	5	30	30	15		80	1
Thrombocytopenia	7	9	4	2		22	
Cardiac disorders	**6**	**3**	**1**			**10**	**1**
Angina pectoris	1	1				2	
Aortic valve disease	1	1				2	
Arrhythmia			1			1	1
Atrial flutter		1				1	
Palpitations	2					2	
Sinus bradycardia	1					1	
Tachycardia	1					1	
Ear and labyrinth disorders	**4**	**2**	**1**			**7**	
External ear inflammation	1					1	
Middle ear inflammation		1				1	
Tinnitus	2	1	1			4	
Vertigo	1					1	
Endocrine disorders	**1**	**1**				**2**	
Hypothyroidism	1	1				2	
Eye disorders	**2**	**3**				**5**	**1**
Diplopia		1				1	1
Eyelid function disorder		1				1	
Ocular hypertension	1					1	
Periorbital oedema	1					1	
Vision blurred		1				1	
Gastrointestinal disorders	**60**	**58**	**1**			**119**	**5**
Abdominal pain	3	5	1			9	2
Abdominal pain upper	1					1	
Constipation	7	6				13	
Diarrhoea	5	3				8	
Diverticulum	1	1				2	
Dyspepsia		1				1	
Dysphagia	1	1				2	1

Gastritis		1				1	
Gastrointestinal toxicity	1					1	
Gastrooesophageal reflux disease	1					1	
Nausea	32	34				66	1
Rectal haemorrhage	1					1	
Vomiting	7	6				13	1
General disorders and administration site conditions	**43**	**32**	**3**	**1**	**1**	**80**	**6**
Chest pain		1				1	1
Chills	6	1				7	
Fatigue	19	9	1			29	
General physical health deterioration		1				1	
Influenza like illness		3				3	
Infusion site reaction				1		1	
Injection site reaction	2	2				4	
Localised oedema	3	3	1			7	
Multi-organ disorder	1					1	
Non-cardiac chest pain	1					1	
Oedema peripheral	3					3	
Pyrexia	8	12	1			21	4
Sudden death					1	1	1
Hepatobiliary disorders			**1**			**1**	**1**
Cholangitis			1			1	1
Immune system disorders	**1**	**7**	**1**			**9**	
Cytokine release syndrome		1				1	
Dermatitis allergic	1					1	
Hypersensitivity		6	1			7	
Infections and infestations	**10**	**17**	**2**	**2**		**31**	**2**
Bronchitis	1	3				4	
Conjunctivitis		1				1	
Folliculitis		1				1	
Herpes zoster		2				2	
Infection		1				1	
Kidney infection	1					1	
Mucosal infection	3	2	1			6	
Nail infection		1				1	
Oral herpes	1					1	
Pharyngitis	1					1	
Phlebitis infective		1				1	
Pneumonia		1	1			2	1
Rash pustular		1				1	
Sepsis				2		2	1
Sinusitis	2					2	
Upper respiratory tract infection		1				1	
Urinary tract infection	1	1				2	

Vaginal infection		1				1	
Injury, poisoning and procedural complications	**2**	**8**	**2**			**12**	**2**
Concussion		1				1	
Fracture		1				1	
Infusion related reaction	1	6				7	
Limb injury	1					1	
Shoulder fracture			1			1	1
Spinal fracture			1			1	1
Investigations	**2**	**2**				**4**	
Alanine aminotransferase increased		1				1	
Blood creatinine increased	1					1	
Weight decreased	1	1				2	
Metabolism and nutrition disorders	**9**	**5**	**3**	**1**		**18**	**1**
Decreased appetite	1	1	1			3	
Dehydration	2	1				3	
Food intolerance	1					1	
Hypercalcaemia	1	1	1			3	
Hyperglycaemia	1	1	1			3	
Hyperuricaemia	2					2	
Hypervolaemia	1					1	
Malnutrition		1				1	
Tumour lysis syndrome				1		1	1
Musculoskeletal and connective tissue disorders	**20**	**11**	**3**			**34**	**1**
Arthralgia	5	2	1			8	
Arthritis	1	2	1			4	1
Back pain	3	3				6	
Bone pain	7	2				9	
Intervertebral disc protrusion			1			1	
Joint range of motion decreased	1					1	
Myalgia	1					1	
Osteoarthritis		1				1	
Pain in extremity	1					1	
Sciatica	1	1				2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**3**	**4**			**7**	**3**
Basal cell carcinoma		2				2	1
Bladder cancer recurrent			1			1	
Myelodysplastic syndrome			1			1	1
Pancreatic carcinoma			1			1	
Seborrheic keratosis		1				1	
Second primary malignancy			1			1	1
Nervous system disorders	**18**	**11**	**1**		**1**	**31**	**1**
Brain hypoxia					1	1	1
Carpal tunnel syndrome		1				1	

Dizziness	1					1	
Headache	3	2	1			6	
Lumbar radiculopathy	1					1	
Neuralgia		1				1	
Neuropathy peripheral	2	2				4	
Paraesthesia	5					5	
Peripheral sensory neuropathy	6	4				10	
Trigeminal nerve disorder		1				1	
Psychiatric disorders	**8**	**6**				**14**	
Anxiety	1	2				3	
Depression	1	2				3	
Insomnia	5	2				7	
Restlessness	1					1	
Renal and urinary disorders	**1**	**2**				**3**	
Haematuria	1					1	
Renal failure		1				1	
Urinary tract pain		1				1	
Respiratory, thoracic and mediastinal disorders	**14**	**11**	**7**			**32**	**4**
Asthmatic crisis			1			1	1
Chylothorax			1			1	
Cough	3	3				6	
Dysphonia	1					1	
Dyspnoea	2	2	2			6	
Epistaxis	4	1				5	
Lung disorder		2				2	1
Oropharyngeal pain	1					1	
Pleural effusion	2		3			5	2
Pneumonitis		1				1	
Pulmonary oedema		1				1	
Rhinorrhoea		1				1	
Wheezing	1					1	
Skin and subcutaneous tissue disorders	**13**	**9**				**22**	**1**
Alopecia	1					1	
Erythema		2				2	1
Hyperhidrosis	5					5	
Petechiae	1	1				2	
Pruritus	3	1				4	
Rash	1	2				3	
Seborrheic dermatitis	1					1	
Skin exfoliation	1					1	
Skin induration		1				1	
Urticaria		2				2	
Surgical and medical procedures	**1**					**1**	
Skin neoplasm excision	1					1	

Vascular disorders	**4**	**8**	**1**			**13**	**1**
Haematoma		1				1	
Hot flush	2					2	
Hypertension	1	3				4	
Hypotension	1	1	1			3	1
Peripheral ischaemia		1				1	
Retinal vascular thrombosis		1				1	
Superficial vein thrombosis		1				1	
Arm B: Induction experimental arm	**307**	**288**	**111**	**39**	**2**	**747**	**33**
Blood and lymphatic system disorders	**39**	**62**	**67**	**36**		**204**	**1**
Anaemia	12	21	8			41	
Febrile neutropenia			1			1	
Leukocytosis		2	2			4	
Leukopenia	4	10	4	1		19	
Lymphopenia	1					1	
Neutropenia	10	13	46	29		98	
Pancytopenia				1		1	1
Thrombocytopenia	12	16	6	5		39	
Cardiac disorders	**3**	**3**	**2**		**1**	**9**	**3**
Angina pectoris	0					0	
Atrial fibrillation		1	1			2	
Atrial flutter		1				1	1
Cardiac failure					1	1	1
Coronary artery stenosis			1			1	1
Palpitations	1	1				2	
Sinus tachycardia	1					1	
Ventricular arrhythmia	1					1	
Ear and labyrinth disorders	**5**	**2**				**7**	
Ear pain		1				1	
Middle ear inflammation	1					1	
Otitis media acute		1				1	
Vertigo	4					4	
Endocrine disorders	**1**					**1**	
Hyperparathyroidism primary	1					1	
Eye disorders	**6**	**5**				**11**	
Cataract		1				1	
Conjunctival hyperaemia	1					1	
Eye pain	1					1	
Eyelid function disorder	2	2				4	
Lacrimation increased	1					1	
Papilloedema	1					1	
Retinal detachment		1				1	
Uveitis		1				1	
Gastrointestinal disorders	**91**	**75**	**10**			**176**	**1**
Abdominal distension	1					1	

Abdominal pain	5	2				7	
Constipation	13	11				24	
Diarrhea		1				1	
Diarrhoea	20	8	3			31	
Dyspepsia	5	1				6	
Gastritis	1					1	
Gastrointestinal haemorrhage			1			1	1
Intestinal obstruction	1					1	
Nausea	37	35	2			74	
Toothache		1				1	
Vomiting	8	16	4			28	
General disorders and administration site conditions	**49**	**27**	**1**		**1**	**78**	**5**
Chills	4	1				5	1
Death					1	1	1
Face oedema	1					1	
Fatigue	24	10				34	
General physical health deterioration		1	1			2	2
Hyperthermia		1				1	
Infusion site extravasation		1				1	
Injection site erythema	2					2	
Injection site reaction	5	1				6	
Malaise		1				1	
Oedema peripheral	2	1				3	
Pain	1	1				2	
Pyrexia	10	9				19	1
Immune system disorders	**1**	**2**	**1**			**4**	**1**
Cytokine release syndrome		1				1	
Hypersensitivity	1	1	1			3	1
Infections and infestations	**18**	**41**	**6**	**1**		**66**	**6**
Abdominal infection		1				1	
Bronchitis	1	7	1			9	1
Cervicitis		1				1	
Conjunctivitis	1	1				2	
COVID-19		1				1	
Device related infection		2				2	
Eye infection		1				1	
Gastroenteritis	1					1	
Gastrointestinal infection		1				1	
Hordeolum		2				2	
Infection		1				1	
Influenza		1	1			2	2
Mucosal infection	2					2	
Nasopharyngitis	1					1	
Paronychia		1				1	

Pharyngitis	2	1				3	
Pneumococcal sepsis			1			1	1
Pneumonia		1		1		2	1
Rash pustular	2	3				5	
Rhinitis	1	1				2	
Scrotal infection		1				1	
Sinusitis	2	2				4	
Tooth infection		1				1	
Upper respiratory tract infection	2	4	1			7	
Urinary tract infection	3	5	2			10	1
Wound infection		2				2	
Injury, poisoning and procedural complications		**6**	**1**			**7**	**1**
Ankle fracture		1				1	1
Fracture			1			1	
Infusion related reaction		5				5	
Investigations	**3**	**1**	**3**			**7**	
Alanine aminotransferase increased	1					1	
Aspartate aminotransferase increased			1			1	
Blood alkaline phosphatase increased			1			1	
Blood creatinine increased	1					1	
Gamma-glutamyltransferase increased			1			1	
Weight decreased		1				1	
Weight increased	1					1	
Metabolism and nutrition disorders	**4**	**7**	**3**	**1**		**15**	
Decreased appetite	2	3	1			6	
Hypercalcaemia		3				3	
Hyperglycaemia		1				1	
Hyperkalaemia	1		1			2	
Hyperuricaemia				1		1	
Hyponatraemia			1			1	
Malnutrition	1					1	
Musculoskeletal and connective tissue disorders	**11**	**9**				**20**	
Arthralgia	1					1	
Arthritis		1				1	
Back pain	1	3				4	
Bone pain	4	2				6	
Muscle spasms	1					1	
Muscular weakness		1				1	
Musculoskeletal chest pain		1				1	
Myalgia	2					2	
Pain in extremity	1					1	
Rheumatic disorder	1					1	
Sacroilliitis		1				1	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			**3**			**3**	**3**
Basal cell carcinoma			1			1	1
Pancreatic carcinoma			1			1	1
Squamous cell carcinoma			1			1	1
Nervous system disorders	**42**	**26**	**5**			**73**	**2**
Carpal tunnel syndrome	1	1				2	
Disturbance in attention	1					1	
Dizziness	4	3				7	
Dysaesthesia	1					1	
Dysgeusia		1				1	
Dyskinesia	1					1	
Headache	1	5				6	
Neuralgia	2					2	
Neuropathy peripheral	4	2				6	
Paraesthesia	4	1				5	
Peripheral motor neuropathy	2	1	2			5	
Peripheral sensory neuropathy	19	11	2			32	1
Polyneuropathy	1					1	
Seizure	1					1	
Syncope			1			1	1
Tension headache		1				1	
Psychiatric disorders	**3**	**2**				**5**	
Anxiety		1				1	
Depression	1	1				2	
Insomnia	1					1	
Mental disorder	1					1	
Renal and urinary disorders	**3**	**3**	**1**			**7**	
Glomerulonephritis membranoproliferative			1			1	
Nocturia	1					1	
Pollakiuria	1	2				3	
Urinary tract pain	1	1				2	
Reproductive system and breast disorders			**1**			**1**	**1**
Benign prostatic hyperplasia			1			1	1
Respiratory, thoracic and mediastinal disorders	**12**	**6**	**5**	**1**		**24**	**9**
Acute pulmonary oedema				1		1	1
Bronchial obstruction	1		1			2	
Bronchospasm			1			1	1
Chronic obstructive pulmonary disease		1				1	
Cough	2	3				5	2
Dyspnoea	4	2	1			7	3
Epistaxis	2					2	
Lung disorder			1			1	1

Nasal congestion	1					1	
Nasopharyngitis	1					1	
Pleural effusion	0					0	
Respiratory tract inflammation			1			1	1
Rhinitis	1					1	
Skin and subcutaneous tissue disorders	**10**	**8**	**1**			**19**	
Alopecia	2		1			3	
Dermatitis exfoliative generalised		1				1	
Eczema		1				1	
Erythema		1				1	
Hidradenitis		1				1	
Hyperhidrosis	2					2	
Pruritus	2	1				3	
Rash erythematous	1					1	
Rash maculo-papular	3					3	
Skin induration		1				1	
Skin lesion		2				2	
Vascular disorders	**6**	**3**	**1**			**10**	
Haematoma	2					2	
Hot flush	2					2	
Hypertension	1	1	1			3	
Phlebitis		1				1	
Raynaud's phenomenon		1				1	
Syncope	1					1	
Total	**554**	**552**	**198**	**61**	**4**	**1369**	**67**

Table 28: List of Adverse Events (PT) with causal relationship to Bortezomib

	Number of SARs related to Bortezomib	total
Arm A: Induction standard arm	**0**	**624**
Arm B: Induction experimental arm	**293**	**753**
Blood and lymphatic system disorders	**125**	**205**
Anaemia	14	41
Febrile neutropenia	1	1
Leukocytosis	4	4
Leukopenia	14	19
Lymphopenia	0	1
Neutropenia	61	99
Pancytopenia	1	1
Thrombocytopenia	30	39
Cardiac disorders	**3**	**10**
Angina pectoris	1	1
Atrial fibrillation	0	2

Atrial flutter	1	1
Cardiac failure	0	1
Coronary artery stenosis	0	1
Palpitations	0	2
Sinus tachycardia	0	1
Ventricular arrhythmia	1	1
Ear and labyrinth disorders	**0**	**7**
Ear pain	0	1
Middle ear inflammation	0	1
Otitis media acute	0	1
Vertigo	0	4
Endocrine disorders	**0**	**1**
Hyperparathyroidism primary	0	1
Eye disorders	**0**	**11**
Cataract	0	1
Conjunctival hyperaemia	0	1
Eye pain	0	1
Eyelid function disorder	0	4
Lacrimation increased	0	1
Papilloedema	0	1
Retinal detachment	0	1
Uveitis	0	1
Gastrointestinal disorders	**55**	**176**
Abdominal distension	0	1
Abdominal pain	1	7
Constipation	14	24
Diarrhea	0	1
Diarrhoea	11	31
Dyspepsia	0	6
Gastritis	0	1
Gastrointestinal haemorrhage	0	1
Intestinal obstruction	0	1
Nausea	20	74
Toothache	0	1
Vomiting	9	28
General disorders and administration site conditions	**29**	**80**
Chills	1	5
Death	0	1
Face oedema	0	1
Fatigue	12	34
General physical health deterioration	1	2
Hyperthermia	0	1
Infusion site extravasation	0	1
Injection site erythema	2	2

Injection site reaction	3	6
Malaise	0	1
Oedema peripheral	1	3
Pain	2	2
Pyrexia	7	21
Immune system disorders	**0**	**4**
Cytokine release syndrome	0	1
Hypersensitivity	0	3
Infections and infestations	**9**	**66**
Abdominal infection	0	1
Bronchitis	3	9
Cervicitis	0	1
Conjunctivitis	0	2
COVID-19	0	1
Device related infection	0	2
Eye infection	0	1
Gastroenteritis	0	1
Gastrointestinal infection	0	1
Hordeolum	0	2
Infection	0	1
Influenza	0	2
Mucosal infection	2	2
Nasopharyngitis	0	1
Paronychia	0	1
Pharyngitis	0	3
Pneumococcal sepsis	1	1
Pneumonia	0	2
Rash pustular	1	5
Rhinitis	1	2
Scrotal infection	0	1
Sinusitis	0	4
Tooth infection	0	1
Upper respiratory tract infection	1	7
Urinary tract infection	0	10
Wound infection	0	2
Injury, poisoning and procedural complications	**1**	**7**
Ankle fracture	0	1
Fracture	0	1
Infusion related reaction	1	5
Investigations	**3**	**7**
Alanine aminotransferase increased	0	1
Aspartate aminotransferase increased	1	1
Blood alkaline phosphatase increased	0	1
Blood creatinine increased	0	1
Gamma-glutamyltransferase increased	1	1

Weight decreased	1	1
Weight increased	0	1
Metabolism and nutrition disorders	**6**	**15**
Decreased appetite	5	6
Hypercalcaemia	0	3
Hyperglycaemia	0	1
Hyperkalaemia	1	2
Hyperuricaemia	0	1
Hyponatraemia	0	1
Malnutrition	0	1
Musculoskeletal and connective tissue disorders	**1**	**21**
Arthralgia	0	1
Arthritis	0	1
Back pain	0	4
Bone pain	0	7
Muscle spasms	1	1
Muscular weakness	0	1
Musculoskeletal chest pain	0	1
Myalgia	0	2
Pain in extremity	0	1
Rheumatic disorder	0	1
Sacroilliitis	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**3**
Basal cell carcinoma	0	1
Pancreatic carcinoma	0	1
Squamous cell carcinoma	1	1
Nervous system disorders	**50**	**73**
Carpal tunnel syndrome	2	2
Disturbance in attention	0	1
Dizziness	3	7
Dysaesthesia	1	1
Dysgeusia	1	1
Dyskinesia	0	1
Headache	1	6
Neuralgia	1	2
Neuropathy peripheral	3	6
Paraesthesia	4	5
Peripheral motor neuropathy	3	5
Peripheral sensory neuropathy	30	32
Polyneuropathy	1	1
Seizure	0	1
Syncope	0	1
Tension headache	0	1
Psychiatric disorders	**0**	**5**

Anxiety	0	1
Depression	0	2
Insomnia	0	1
Mental disorder	0	1
Renal and urinary disorders	**1**	**7**
Glomerulonephritis membranoproliferative	0	1
Nocturia	0	1
Pollakiuria	0	3
Urinary tract pain	1	2
Reproductive system and breast disorders	**0**	**1**
Benign prostatic hyperplasia	0	1
Respiratory, thoracic and mediastinal disorders	**5**	**25**
Acute pulmonary oedema	0	1
Bronchial obstruction	0	2
Bronchospasm	0	1
Chronic obstructive pulmonary disease	0	1
Cough	1	5
Dyspnoea	1	7
Epistaxis	0	2
Lung disorder	1	1
Nasal congestion	0	1
Nasopharyngitis	0	1
Pleural effusion	1	1
Respiratory tract inflammation	1	1
Rhinitis	0	1
Skin and subcutaneous tissue disorders	**3**	**19**
Alopecia	3	3
Dermatitis exfoliative generalised	0	1
Eczema	0	1
Erythema	0	1
Hidradenitis	0	1
Hyperhidrosis	0	2
Pruritus	0	3
Rash erythematous	0	1
Rash maculo-papular	0	3
Skin induration	0	1
Skin lesion	0	2
Vascular disorders	**1**	**10**
Haematoma	0	2
Hot flush	1	2
Hypertension	0	3
Phlebitis	0	1
Raynaud's phenomenon	0	1
Syncope	0	1
Total	**293**	**1377**

Table 29: List of Adverse Events (PT) with causal relationship to Rituximab (IV/SC) for Arm A and Arm B

	Number of SARs related to rituximab	Total
Arm A: Induction standard arm	**169**	**624**
Blood and lymphatic system disorders	**53**	**167**
Anaemia	4	36
Febrile neutropenia	2	2
Hyperviscosity syndrome	0	1
Leukocytosis	0	1
Leukopenia	9	22
Lymphopenia	3	3
Neutropenia	32	80
Thrombocytopenia	3	22
Cardiac disorders	**2**	**10**
Angina pectoris	0	2
Aortic valve disease	0	2
Arrhythmia	0	1
Atrial flutter	0	1
Palpitations	1	2
Sinus bradycardia	0	1
Tachycardia	1	1
Ear and labyrinth disorders	**2**	**7**
External ear inflammation	0	1
Middle ear inflammation	1	1
Tinnitus	1	4
Vertigo	0	1
Endocrine disorders	**0**	**2**
Hypothyroidism	0	2
Eye disorders	**1**	**5**
Diplopia	0	1
Eyelid function disorder	1	1
Ocular hypertension	0	1
Periorbital oedema	0	1
Vision blurred	0	1
Gastrointestinal disorders	**28**	**119**
Abdominal pain	0	9
Abdominal pain upper	1	1
Constipation	1	13
Diarrhoea	1	8
Diverticulum	0	2
Dyspepsia	0	1
Dysphagia	0	2

Gastritis	0	1
Gastrointestinal toxicity	0	1
Gastrooesophageal reflux disease	0	1
Nausea	20	66
Rectal haemorrhage	0	1
Vomiting	5	13
General disorders and administration site conditions	**31**	**80**
Chest pain	0	1
Chills	3	7
Fatigue	8	29
General physical health deterioration	0	1
Influenza like illness	0	3
Infusion site reaction	1	1
Injection site reaction	4	4
Localised oedema	3	7
Multi-organ disorder	0	1
Non-cardiac chest pain	0	1
Oedema peripheral	0	3
Pyrexia	12	21
Sudden death	0	1
Hepatobiliary disorders	**0**	**1**
Cholangitis	0	1
Immune system disorders	**8**	**9**
Cytokine release syndrome	1	1
Dermatitis allergic	0	1
Hypersensitivity	7	7
Infections and infestations	**5**	**32**
Bronchitis	0	4
Conjunctivitis	0	1
Folliculitis	0	1
Herpes zoster	0	2
Infection	0	1
Kidney infection	0	1
Mucosal infection	2	6
Nail infection	0	1
Oral herpes	0	1
Pharyngitis	0	2
Phlebitis infective	0	1
Pneumonia	2	2
Rash pustular	0	1
Sepsis	1	2
Sinusitis	0	2
Upper respiratory tract infection	0	1
Urinary tract infection	0	2

Vaginal infection	0	1
Injury, poisoning and procedural complications	**7**	**12**
Concussion	0	1
Fracture	0	1
Infusion related reaction	7	7
Limb injury	0	1
Shoulder fracture	0	1
Spinal fracture	0	1
Investigations	**0**	**4**
Alanine aminotransferase increased	0	1
Blood creatinine increased	0	1
Weight decreased	0	2
Metabolism and nutrition disorders	**2**	**18**
Decreased appetite	0	3
Dehydration	0	3
Food intolerance	0	1
Hypercalcaemia	0	3
Hyperglycaemia	0	3
Hyperuricaemia	0	2
Hypervolaemia	0	1
Malnutrition	1	1
Tumour lysis syndrome	1	1
Musculoskeletal and connective tissue disorders	**5**	**35**
Arthralgia	3	8
Arthritis	1	4
Back pain	0	7
Bone pain	1	9
Intervertebral disc protrusion	0	1
Joint range of motion decreased	0	1
Myalgia	0	1
Osteoarthritis	0	1
Pain in extremity	0	1
Sciatica	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**7**
Basal cell carcinoma	0	2
Bladder cancer recurrent	0	1
Myelodysplastic syndrome	0	1
Pancreatic carcinoma	0	1
Seborrheic keratosis	0	1
Second primary malignancy	1	1
Nervous system disorders	**4**	**31**
Brain hypoxia	0	1
Carpal tunnel syndrome	0	1
Dizziness	0	1

Headache	3	6
Lumbar radiculopathy	0	1
Neuralgia	0	1
Neuropathy peripheral	0	4
Paraesthesia	0	5
Peripheral sensory neuropathy	1	10
Trigeminal nerve disorder	0	1
Psychiatric disorders	**4**	**14**
Anxiety	1	3
Depression	0	3
Insomnia	3	7
Restlessness	0	1
Renal and urinary disorders	**1**	**3**
Haematuria	0	1
Renal failure	1	1
Urinary tract pain	0	1
Respiratory, thoracic and mediastinal disorders	**4**	**32**
Asthmatic crisis	0	1
Chylothorax	0	1
Cough	1	6
Dysphonia	0	1
Dyspnoea	1	6
Epistaxis	0	5
Lung disorder	1	2
Oropharyngeal pain	0	1
Pleural effusion	0	5
Pneumonitis	1	1
Pulmonary oedema	0	1
Rhinorrhoea	0	1
Wheezing	0	1
Skin and subcutaneous tissue disorders	**9**	**22**
Alopecia	0	1
Erythema	0	2
Hyperhidrosis	2	5
Petechiae	0	2
Pruritus	3	4
Rash	2	3
Seborrheic dermatitis	0	1
Skin exfoliation	0	1
Skin induration	1	1
Urticaria	1	2
Surgical and medical procedures	**0**	**1**
Skin neoplasm excision	0	1
Vascular disorders	**2**	**13**
Haematoma	0	1

Hot flush	0	2
Hypertension	0	4
Hypotension	2	3
Peripheral ischaemia	0	1
Retinal vascular thrombosis	0	1
Superficial vein thrombosis	0	1
Arm B: Induction experimental arm	**206**	**753**
Blood and lymphatic system disorders	**111**	**205**
Anaemia	11	41
Febrile neutropenia	1	1
Leukocytosis	4	4
Leukopenia	9	19
Lymphopenia	1	1
Neutropenia	59	99
Pancytopenia	1	1
Thrombocytopenia	25	39
Cardiac disorders	**3**	**10**
Angina pectoris	1	1
Atrial fibrillation	0	2
Atrial flutter	1	1
Cardiac failure	0	1
Coronary artery stenosis	0	1
Palpitations	0	2
Sinus tachycardia	0	1
Ventricular arrhythmia	1	1
Ear and labyrinth disorders	**0**	**7**
Ear pain	0	1
Middle ear inflammation	0	1
Otitis media acute	0	1
Vertigo	0	4
Endocrine disorders	**0**	**1**
Hyperparathyroidism primary	0	1
Eye disorders	**1**	**11**
Cataract	0	1
Conjunctival hyperaemia	0	1
Eye pain	0	1
Eyelid function disorder	1	4
Lacrimation increased	0	1
Papilloedema	0	1
Retinal detachment	0	1
Uveitis	0	1
Gastrointestinal disorders	**37**	**176**
Abdominal distension	0	1
Abdominal pain	0	7
Constipation	4	24

Diarrhea	0	1
Diarrhoea	6	31
Dyspepsia	0	6
Gastritis	0	1
Gastrointestinal haemorrhage	0	1
Intestinal obstruction	0	1
Nausea	19	74
Toothache	0	1
Vomiting	8	28
General disorders and administration site conditions	**15**	**80**
Chills	2	5
Death	0	1
Face oedema	0	1
Fatigue	6	34
General physical health deterioration	1	2
Hyperthermia	0	1
Infusion site extravasation	0	1
Injection site erythema	0	2
Injection site reaction	2	6
Malaise	0	1
Oedema peripheral	0	3
Pain	0	2
Pyrexia	4	21
Immune system disorders	**3**	**4**
Cytokine release syndrome	1	1
Hypersensitivity	2	3
Infections and infestations	**8**	**66**
Abdominal infection	0	1
Bronchitis	3	9
Cervicitis	0	1
Conjunctivitis	0	2
COVID-19	0	1
Device related infection	0	2
Eye infection	0	1
Gastroenteritis	0	1
Gastrointestinal infection	0	1
Hordeolum	0	2
Infection	0	1
Influenza	0	2
Mucosal infection	2	2
Nasopharyngitis	0	1
Paronychia	0	1
Pharyngitis	0	3
Pneumococcal sepsis	1	1

Pneumonia	0	2
Rash pustular	1	5
Rhinitis	0	2
Scrotal infection	0	1
Sinusitis	0	4
Tooth infection	0	1
Upper respiratory tract infection	1	7
Urinary tract infection	0	10
Wound infection	0	2
Injury, poisoning and procedural complications	**5**	**7**
Ankle fracture	0	1
Fracture	0	1
Infusion related reaction	5	5
Investigations	**1**	**7**
Alanine aminotransferase increased	0	1
Aspartate aminotransferase increased	0	1
Blood alkaline phosphatase increased	0	1
Blood creatinine increased	0	1
Gamma-glutamyltransferase increased	0	1
Weight decreased	1	1
Weight increased	0	1
Metabolism and nutrition disorders	**2**	**15**
Decreased appetite	1	6
Hypercalcaemia	0	3
Hyperglycaemia	0	1
Hyperkalaemia	1	2
Hyperuricaemia	0	1
Hyponatraemia	0	1
Malnutrition	0	1
Musculoskeletal and connective tissue disorders	**2**	**21**
Arthralgia	0	1
Arthritis	0	1
Back pain	0	4
Bone pain	1	7
Muscle spasms	0	1
Muscular weakness	0	1
Musculoskeletal chest pain	1	1
Myalgia	0	2
Pain in extremity	0	1
Rheumatic disorder	0	1
Sacroilliitis	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1**	**3**
Basal cell carcinoma	0	1
Pancreatic carcinoma	0	1

Squamous cell carcinoma	1	1
Nervous system disorders	**9**	**73**
Carpal tunnel syndrome	0	2
Disturbance in attention	0	1
Dizziness	1	7
Dysaesthesia	1	1
Dysgeusia	1	1
Dyskinesia	0	1
Headache	2	6
Neuralgia	0	2
Neuropathy peripheral	0	6
Paraesthesia	2	5
Peripheral motor neuropathy	0	5
Peripheral sensory neuropathy	2	32
Polyneuropathy	0	1
Seizure	0	1
Syncope	0	1
Tension headache	0	1
Psychiatric disorders	**0**	**5**
Anxiety	0	1
Depression	0	2
Insomnia	0	1
Mental disorder	0	1
Renal and urinary disorders	**0**	**7**
Glomerulonephritis membranoproliferative	0	1
Nocturia	0	1
Pollakiuria	0	3
Urinary tract pain	0	2
Reproductive system and breast disorders	**0**	**1**
Benign prostatic hyperplasia	0	1
Respiratory, thoracic and mediastinal disorders	**5**	**25**
Acute pulmonary oedema	0	1
Bronchial obstruction	0	2
Bronchospasm	1	1
Chronic obstructive pulmonary disease	0	1
Cough	1	5
Dyspnoea	1	7
Epistaxis	0	2
Lung disorder	1	1
Nasal congestion	0	1
Nasopharyngitis	0	1
Pleural effusion	1	1
Respiratory tract inflammation	0	1
Rhinitis	0	1
Skin and subcutaneous tissue disorders	**1**	**19**

Alopecia	0	3
Dermatitis exfoliative generalised	1	1
Eczema	0	1
Erythema	0	1
Hidradenitis	0	1
Hyperhidrosis	0	2
Pruritus	0	3
Rash erythematous	0	1
Rash maculo-papular	0	3
Skin induration	0	1
Skin lesion	0	2
Vascular disorders	**2**	**10**
Haematoma	0	2
Hot flush	2	2
Hypertension	0	3
Phlebitis	0	1
Raynaud's phenomenon	0	1
Syncope	0	1
Gesamtergebnis	**375**	**1377**

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