A randomized phase II trial comparing Bendamustine and Melphalan with Melphalan alone as conditioning regimen for autologous stem cell transplantation (ASCT) in myeloma patients (BEB-2 trial).

Clinical Study Protocol

Short title:	Bendamustine and melphalan in myeloma.
Study Type:	Clinical trial investigating the chemotherapeutic compound Bendamustine (Ribomustin®) in myeloma patients.
Study Categorisation:	Risk category according to LHR: category B
Study Registration:	SNCTP 000002150 Trials.gov #: NCT03187223
Study Identifier:	BEB-2 trial
Sponsor-Investigator:	This is an investigator initiated trial (IIT); Sponsor is the University Hospital/Inselspital; 3010 Bern. Sponsor/Principal Investigator is Prof. Dr. med. Thomas Pabst; Associate Professor; Department of Medical Oncology; University Hospital/Inselspital; 3010 Bern; Switzerland. Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: thomas.pabst@insel.ch;
Investigational Product:	Bendamustine hydrochloride (Ribomustin®)
Protocol Version and Date:	Version 2.2, 21.03.2018

Signature Page

Study number	EudraCT 2016-000231-40
Study Title	A randomized phase II trial comparing Bendamustine and Melphalan with Melphalan alone as conditioning regimen for autologous stem cell transplantation (ASCT) in myeloma patients (BEB-2 trial).

The Principle Investigator has approved the protocol version 2.1 (dated 21/03/2018), and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator: Prof. Dr. Thomas Pabst; Department of Medical Oncology; University Hospital/Inselspital; Freiburgstrasse 10; 3010 Berne.

Place/Date	Signature

The Local Principal Investigator at study site:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Site	.....
Local Principal investigator	.....

Place/Date	Signature

Table of Contents

Study synopsis

Sponsor / Sponsor-Investigator	This is an investigator initiated trial (IIT); Sponsor is the University Hospital/Inselspital; 3010 Berne. Sponsor/Principal Investigator is Prof. Dr. med. Thomas Pabst; Associate Professor; Department of Medical Oncology; University Hospital/Inselspital; 3010 Berne; Switzerland. Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: thomas.pabst@insel.ch.
Study Title:	A randomized phase II trial comparing Bendamustine and Melphalan with Melphalan alone as conditioning regimen for autologous stem cell transplantation (ASCT) in myeloma patients (BEB-2 trial).
Short Title / Study ID:	Bendamustine and melphalan in myeloma.
Protocol Version and Date:	Version 2.2; 21.03.2018
Trial registration:	SNCTP 000002150 Trials.gov #: NCT03187223
Study category and Rationale	Risk category according to LHR: category B. Bendamustine is licensed in Switzerland for the treatment of lymphoma patients; in this study, it is used as a part of a conditioning regimen together with melphalan before autologous transplantation in myeloma patients. Melphalan is licensed in Switzerland for the treatment of myeloma patients. Monotherapy with high-dose melphalan is standard of care as a conditioning treatment before ASCT.
Clinical Phase:	Randomized prospective non-blinded clinical phase II trial investigating the drugs bendamustine hydrochloride and melphalan.

Background and Rationale:	Consolidation of the first-line treatment in myeloma patients with high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) is standard of care since more than 20 years, and Melphalan at a total dose of 200mg/m^{2}is the standard HDCT conditioning regimen before ASCT in the last two decades. Despite remarkable progress using novel agents both for induction before ASCT as well for maintenance after ASCT, definite cure in myeloma patients remains exceptional due to residual disease escaping intensive treatment. Current treatment efforts aim at achieving high-quality complete remssions. Thus, improving effectiveness of myeloma treatment remains an unmet clinical need. Alternative conditioning regimens have been reported including combinations of melphalan with other compounds such as with bortezomib (MelVel), with etoposide, cytarabine and BCNU (BEAM), and with busulfan (BuMel). However, no randomized trial has ever prospectively compared high-dose melphalan alone with a melphalan combination (or with another regimen) before ASCT in myeloma patients. Consequently, high-dose melphalan alone has remained the standard conditioning regimen in HDCT in myeloma patients. Two phase 1 and 2 studies have reported combinations of melphalan with bendamustine as first-line conditioning regimen before ASCT in myeloma patients. A phase 1 trial added escalating doses of bendamustine to standard melphalan, with melphalan given at a dose of 100 mg/m^2/day at days -2 and -1. 25 patients were enrolled into 6 cohorts; a maximum tolerated dose of bendamustine was not encountered; the highest dose level cohort of bendamustine comprising 125 mg/m2/day on day -2 and 100 mg/m2/day on day -1 together with melphalan 100 mg/m^2/day at days -2 and -1 was expanded to further evaluate safety. At day +100, overall response rate was 79%, with 38% of stringent CR, 4% of CR, 33% of VGPR and 4% of PR. Ten patients progressed after a median of 473 days after ASCT, and six patients died. Median PFS was 791 days, and the median OS was not reached, but the 2-year OS rate was 70%. Martino et al. recently reported data on the feasibility and efficacy of the combination of bendamustine and melphalan (BenMel) as a conditioning regimen to second ASCT in patients with myeloma. All 32 patients enrolled have received melphalan 100 mg/m^2/day at days -2 and -1 as conditioning regimen before the first ASCT. The conditioning regimen before second ASCT was bendamustine (100 mg/m^2/day at days -4 and -3) and melphalan (140 mg/m^2/day at day -2). No added toxicity was observed between the first and second ASCT. The 2y-OS and 2y-PFS were 97% and 79%, respectively. In addition, extensive experience is available on the use of bendamustine (200mg/m^2/day given on days -7 and -6) together with melphalan (140mg/m^2/day day -1) and two additional drugs, cytarabine and etoposide (each on days -5 to -2) in the BeEAM conditioning regimen which is increasingly used as the standard conditioning regimen in lymphoma patients, also in our clinic, with an acceptable tolerability and safety profile. In summary, these data suggest that combinations of melphalan and bendamustine are usually well tolerated and that the maximum tolerated dose of bendamustine is not reached with the doses of 200mg/m^2/day given on two days added to melphalan, etoposide and cytarabine (BeEAM regimen). We therefore suggest in this study to directly compare bendamustine 200 mg/m^2/day (on days -4 and -3) plus melphalan 100mg/m^2/day (on days -2 and -1) with melphalan 100mg/m^2/day (days -2 and -1) in a randomized trial.

Objective(s):	Primary objective: • To show a clinically meaningful improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan. • Secondary objectives:To assess acute and late toxicities/adverse events (CTCAE 4.0) during the study period in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone. • To assess the hematologic engraftment in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone. • To particularly assess early renal toxicity in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone. • To assess differences in overall survival and progression free survival in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone after one year. • To assess the quality of life prior to ASCT and at day 60 assessment thereafter.
Outcome(s):	To assess the rate of complete remission (CR1) 60 days after ASCT in myeloma patients treated with the combination of bendamustine and melphalan as compared to melphalan alone by routine laboratory myeloma parameters (serum M-gradient and light chain ratio) and bone marrow assessments in patients with CR1.
Study design:	Randomized two-arm open-label prospective phase II trial.

Inclusion / Exclusion Criteria:	Key inclusion criteria: Eligible are myeloma patients after standard first-line induction treatment. A second induction regimen in refractory myeloma patients is allowed. Patients must be considered being fit for subsequent consolidation with high-dose chemotherapy with melphalan with autologous stem cell support. Patients must be aged 18-75 years. Patients must have an ECOG < 3. Patients must have a creatinine clearance ≥ 40 ml/min. Patients must have a LVEF ≥ 40% within three months prior to start of study medication (Echo can be postponed to study treatment visit if clinically indicated). Female patients of child-bearing potential;. No known pregnancy (a pregnancy test in female patients of child-bearing potential is not mandatory since patients are already under induction chemotherapy or mobilization chemotherapy, and pregnancy was excluded before starting chemotherapy…) Patients must have given voluntary written informed consent. Key exclusion criteria: Patients with uncontrolled acute infection. Patients with a transplantation comorbidity index (HCTCI) > 6 points. Patients with concurrent malignant disease with the exception of basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then. Patients with major coagulopathy or bleeding disorder. Patients with other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery. Lack of patient cooperation to allow study treatment as outlined in this protocol. Pregnancy or lactating female patients. The use of any anti-cancer investigational agents within 14 days prior to the expected start of trial treatment. Contraindications and hypersensitivity to any of the active chemotherapy compounds.
Measurements	The primary endpoint is improvement of the complete remission (CR1) rate 60 days after ASCT in myeloma patients treated with the combination of bendamustine and melphalan as compared to melphalan alone. This assessment will be performed by routine laboratory myeloma parameters (serum M-gradient and light chain ratio). A bone marrow assessment will be done in patients with CR1 according to serum myeloma parameters to assess the quality of CR1. Quality of life Forms (EORTC Q30) will be collected at screening and at the day 60 assessment; for details see Appendix 6.

Study Product and Interventions:	Two HDCT regimens (melphalan alone versus the combination of melphalan and bendamustine) used for conditioning treatment before ASCT will be compared in a 1:1 randomization. The experimental arm is the bendamustine and melphalan (BenMel) combined regimen. The melphalan alone (Mel) regimen is the control (standard) treatment. BenMel regimen (experimental arm): Patients will receive bendamustine at a total dose of 400mg/m^2, divided in two doses of 200mg/m^2/day on days -4 and -3. Melphalan is given at a total dose of 200mg/m^2, divided in two doses of 100mg/m^2/day, each on days -2 and -1, with the ASCT at day 0. In patients with a reduced renal function with a creatinine clearance of ≥ 40 ml/min and <50 ml/min, the bendamustine dose will be reduced to a total dose of 200mg/m^2, divided in two doses of 100mg/m^2/day on days -4 and -3; the melphalan dose will be reduced to a total dose of 140mg/m^2, divided in two doses of 70mg/m^2day on days -2 and -1, with the ASCT at day 0.
Control Intervention:	Mel regimen (standard arm): Patients will receive melphalan at a total dose of 200mg/m^2, divided in two doses of 100mg/m^2/day on days -2 and -1, with the ASCT at day 0. In patients with a reduced renal function with a creatinine clearance of ≥ 40 ml/min and <50 ml/min, the melphalan dose will be reduced to a total dose of 140mg/m^2, divided in two doses of 70mg/m^2/day on days -2 and -1, with the ASCT at day 0.
Number of Participants with Rationale:	Applying a statistical power of 80% and a one-sided significance level of 20%, 60 evaluablepatients will be needed in each group to show a clinically meaningful improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients, from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan. Thus, a total of 120 evaluable patients will be needed.
Study Duration:	The total study duration is 36 months. The University Hospital/Inselspital in Bern/Switzerland is currently treating 60-70 first-line myeloma patients per year. Thus, a total of 36 months is considered to be sufficient to recruit the 120 patients needed.
Study Schedule:	Submission to EC authorities/Swissmedic: March 2016 Trial activation: March 2017 First-Participant-In: April 2017 Last-Participant-In: April 2020 Last-Patient-evaluable: October 2020 First-Analysis-available: December 2020 Final-Analysis-available: March 2021
Investigator(s) / Study Center(s):	Prof. Dr. Thomas Pabst; Department for Medical Oncology; University Hospital/Inselspital; 3010 Berne; Phone +41 31 632 84 30; Fax +41 31 632 34 10; Email: thomas.pabst@insel.ch. Single center: Berne / Switzerland.
Stratification Parameters:	Two stratification parameters will be applied: (1) Remission status at registration: CR/VGPR versus PR/SD/PD (2) Renal function: creatinine-clearance ≥50 ml/min versus <50 ml/min

Statistical Considerations:	This study involves two treatment arms and applies a 1:1 randomization, additionally considering the stratification for remission status and renal function. No interim analysis is planned, and all calculations will be performed on anintention-to-treat basis. The primary endpoint is to show animprovement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan. Arm A is the standard arm (Mel: melphalan alone chemotherapy), and arm B is the experimental arm (BenMel: bendamustine and melphalan chemotherapy). The null hypothesis is that the rate of complete remissions (CR1) determined 60 days after ASCT is equal in both arms ($CR1_A$ = $CR1_B$). The aim of the study is to ultimately show an improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan, with $CR1_A < CR1_B$. Based on a previous cohort of 122 myeloma patients at our center (2010-2013), we anticipate a CR1 rate in the standard (Mel) arm of 50% ($CR1_A$). Our hypothesis is that the experimental (BenMel) arm will show a CR1 rate of ≥ 65% ($CR1_B$), thus a difference of at least 15 percentage points. The superiority margin in the proposed prospective randomized study is 0.15, i.e. the improvement of the CR1 rate in the experimental arm (BenMel) is considered a success compared to the standard (Mel) arm if its CR1 rate at least 15 percentage points better. With $CR1_A$ and $CR1_B$ being the (true) success rates in the Mel arm and in the BenMel arm, respectively, the hypotheses are: H0: CR1 BenMel chemotherapy is < 0.65 when CR1 Mel is 0.50. H1: CR1 BenMel chemotherapy is ≥ 0.65 when CR1 Mel is 0.50. Applying a one-sided significance level of 20%, 60 evaluable patients will be needed in each group to have 80% power to reject the null hypothesis of no difference between the CR1 rates of the treatment arms using a t-test. Thus, a total of 120 evaluable patients will be needed. The significance level actually achieved by this design is 0.2057. All statistical analysis for sample size calculations were performed using the software package PASS 11. For statistical analysis of this study, continuous endpoints will be summarized using descriptive statistics including mean, median, standard deviation, first and third quartiles, minimum and maximum values, and where appropriate by graphical techniques (e.g. histogram, box plot). For categorical endpoints, the number and percentage of patients in each category will be summarized. Where appropriate, a two-sided 95% confidence interval for the proportion will be reported. The primary endpoint in the two groups will be tested using a t-test.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

Study summary in local language

Die Hochdosis-Chemotherapie (HDCT) mit Melphalan gefolgt von einer autologen Stammzell-Transplantation (ASCT) ist Teil der Standard Erstlinien-Therapie bei Patienten mit Therapie-bedürftigem Multiplem Myelom. Dabei ist die HDCT seit mehr als zwei Dekaden unverändert Melphalan in einer totalen Dosis von 200mg/m^2. Verschiedene Modifikationen dieses Schema wurden in Phase 1 und 2 Studien untersucht, so die Zugabe von Bortezomib (VelMel), von BCNU, Cytarabin und Etoposid (BEAM), oder von Busulfan (BuMel). Keines dieser Schemas wurde allerdings je randomisiert prospektiv geprüft gegen Melphalan allein, und so bleibt Melphalan Monotherapie bis heute die Standard Konditionierungs-Chemotherapie vor ASCT für Myelom Patienten.

Bendamustin ist zugelassen in der Schweiz für die Behandlung von Lymphom Patienten. Es wird in der Schweiz neben der Lymphom-Therapie durchaus ab der dritten Linie auch bei Myelom-Patienten eingesetzt, ist hierzu aber in der Schweiz nicht zugelassen. In der EU ist Bendamustin beim multiplen Myelom zugelassen, falls eine Hochdosistherapie mit ASCT, oder falls eine Thalidomid oder Bortezomib enthaltende Behandlung nicht geeignet ist. Bisher haben zwei Studien die Kombination von Melphalan und Bendamustin als Konditionierung vor ASCT untersucht. Eine Phase 1 Studie fügte in 6 Kohorten eine Dosissteigerung von Bendamustin einer Standard Melphalan Therapie von total Dosis von 200 mg/m^2 zu (100mg/m^2 pro Tag an den Tagen -2 and -1). Eine maximal tolerierte Dosis von Bendamustin wurde dabei nicht identifiziert, mit einer höchsten Bendamustin Totaldosis von 225 mg/m^2 gegeben an den gleichen Tagen wie Melphalan (Bendamustin 125 mg/m^2 pro Tag am Tag -2 und 100 mg/m^2 pro Tag am Tag -1). 100 Tage nach ASCT war die Gesamtansprechrate 79%, mit 38% stringent CR1, 4% CR1, 33% VGPR und 4% PR. Das mediane progressions-freie Überleben (PFS) betrug 791 Tage, und das mediane Überleben (OS) wurde bisher nicht erreicht. Das 2y-OS betrug 70%.

In einer Phase 2 Studie wurden Bendamustin und Melphalan kombiniert eingesetzt bei Myelom Patienten als Konditionierung vor einer zweiten ASCT. Die Patienten erhielten dabei Melphalan 100 mg/m^2 pro Tag an den Tagen -2 and -1 als Konditionierung vor der ersten ASCT. Das Konditionierungs-Regime vor der zweiten ASCT war Bendamustine (100 mg/m^2 pro Tag, Tage -4 and -3) und Melphalan (140 mg/m^2 pro Tag, Tag -2). Dabei wurde keine zusätzliche Toxizität beobachtet zwischen der ersten und zweiten ASCT. Das 2y-OS war 97% und das 2y-PFS war 79%.

In der vorliegenden prospektiven zwei-armigen monozentrischen Studie wird nun in einer 1:1 Randomisierung die Standard-HDCT mit Melphalan (totale Dosis von 200 mg/m^2) verglichen mit der experimentellen HDCT mit der Kombination von Bendamustin und Melphalan. Melphalan wird in beiden Armen gesplittet verabreicht, in einer Dosis von jeweils 100 mg/m^2 pro Tag an den Tagen -2 und -1, vor der ASCT am Tag 0. Im experimentellen Arm wird Bendamustin verabreicht in einer Dosis von jeweils 200 mg/m^2 pro Tag an den Tagen -4 und -3. Mit dieser Studie möchten wir eine Verbesserung der CR1 Rate 60 Tage nach ASCT um 15% erreichen. Wir gehen auf Grund einer früheren Kohorte von 122 Myelom Patienten mit ASCT am Inselspital (2010-2013) von einer CR1 Rate von 50% aus mit Melphalan alleine, und wir erhoffen uns von der Bendamustin/Melphalan Kombination eine Verbesserung der CR1 Rate auf über 65%. Dazu sind total 120 Patienten nötig, und wir planen dazu eine Studiendauer von 36 Monaten.

Abbreviations

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
BCNU	1,3-Bis(2-chloroethyl)-1-nitrosourea, Carmustine
BEAM	BCNU-Etoposide-Cytarabin-Melphalan
BeEAM	Bendamustine-Etoposide-Cytarabine-Melphalan
BenMel	Bendamustine-Melphalan
BM	Bone Marrow
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CR	Complete Remission
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DFS	Disease Free Survival
DSUR	Development safety update report
DSMC	Data safety monitoring committee
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
HC	Hematopoietic cell
HCTCI	hematopoietic cell transplantation comorbidity index
HDCT	High-dose chemotherapy
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research)
HMG	Heilmittelgesetz
HRA	Federal Act on Research involving Human Beings
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
LC	

Mel	Light Chain
LVEF	Melphalan
MGUS	Left ventricular ejection fraction
MM	Monoclonal Gammopathy of Unknown Significance
	Multiple Myeloma
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
OS	Overall Survival
PI	Principal Investigator
PLT	Platelets
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Remission
RBC	Red blood cell
SAE	Serious Adverse Event
SD	Stable Disease
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TRM	Treatment related mortality
VGPR	Very Good Partial Remission
QoL	Quality of life

Study schedule

Study Periods	Screening	Treatment	Day 60 assessment	Follow-up
Visits	1	2	3	4 [10]
Time (days)	-35 to -5	-4 until end of hospitalization	+30 to +75	___
Patient informed consent	x			
Height/weight/body surface	x			
In- / exclusion criteria	x			
HCTCI score	x			
ECOG score,	x		x	
Echocardiogaphy (TTE)[1]	x			
Hematology	x	x [2]	x	
Serum biochemistry [3]	x	x [4]	x	
Pregnancy Test[5]	x			
Randomization	x			
Response (serum free light chain ratio and M-gradient; [6]	x		x	x
QoL (EORTC Q30)	x		x	
Administer study medication		x		
Number of CD34+ cells for ASCT [7]		x		
Engraftment, lymphocyte, neutrophil and platelet recovery		x		
RBC & platelet transfusions		x		
Days of T>38.0°; number of febrile episodes		x	x	
Bone marrow			x [8]	
CD4/CD8 determination (bone marrow)			x [9]	
CD4/CD8 determination (blood)			x [9]	
Adverse Events		x	x	

[1] Echo results can be accepted within three months prior to HDCTX ,the echo can be omitted or postponed untill treatment visit if clinically indicated

[2] Hematology (hemoglobin, leukocytes, platelets) will be assessed on a a daily basis as soon as leukocytes drop < 0.5 G/L until and including the day of neutrophils raising again > 0.5 G/l, lymphocytes raising > 0.5 G/l and platelets raising > 20 G/l.

[3] Biochemistry includes creatinine, urea, and uric acid; creatinine clearance is assessed once during screening and at the day 60 assessment.

[4] Starting with the first day of HDCT treatment, creatinine, urea, and uric acid will be assessed on a daily basis until including day 3 after ASCT. In case of clinically significant renal toxicity, creatinine, urea, and uric acid will be assessed as long as clinically indicated.

[5] pregnancy test will be requested at screening visit or before study treatment, if indicated

[6]Assessment includes free light chain kappa and lambda and the ratio, serum electrophoresis with immunofixation, and urine electrophoresis with immunofixation if indicated.

[7]Apheresis of hematopoietic cell could be possible also before day -35, representing a part of the standard of care for myeloma patients.

[8]optional: Bone marrow is performed only in patients fulfilling the criteria for CR1. The bone marrow can alternatively be performed at the end of the ASCT hospitalization, thus before the day 60 assessment. Bone marrow should include flowcytometric assessment of minimal residual disease (MRD) for clonal plasma cells. Bone marrow assessment can be done between recovery from neutropenia until day +75.

[9]CD4 and CD8 determination is performed at the day of bone marrow (+/- 14 days, in bone marrow and in blood) and could be repeated in blood between day (+30- +75)

[10] Follow-up is according to the treating physician. It should include assessment of myeloma serum parameters (without urine analysis and without bone marrow). If relapse is suspected, assessment of myeloma serum parameters (including urine analysis) should be performed. Patients withdrawn from the protocol are documented until the day 60 assessment.

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor

University Hospital/Inselspital
Freiburgstrasse 10; 3010 Bern

1.2 Principal Investigator

Prof. Thomas Pabst; M.D.
Department for Medical Oncology; University Hospital/Inselspital
Freiburgstrasse 10; 3010 Bern
Tel: +41 31 632 84 30; Fax: +41 31 632 34 10; E-Mail: thomas.pabst@insel.ch

1.3 Statistician ("Biostatistician")

Dr. Martin Bigler
SAKK Coordinating Center
Effingerstrasse 40; 3008 Bern
Tel: +41 31 389 93 54; Fax: +41 31 389 92 00; E-Mail: martin.bigler@sakk.ch

1.4 Laboratory

Not applicable; no central specific laboratory analyses are planned in this trial.

1.5 Monitoring institution

Monitoring will be performed by the Clinical Trial Unit (CTU) of the University of Berne, Switzerland.

1.6 Data Safety Monitoring Committee (DSMC)

Not applicable; no DSMC is useful for this single-center trial.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the patient information and the consent form as well as other study-specific documents will be submitted to the Competent Ethics Committee (CEC) in Berne and to the competent authorities (Swissmedic) for formal approval. Any amendment to the protocol will as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic competent authority concerning the conduct of the study will be made in writing to the Principle Investigator before commencement of the study. The clinical study can only begin once written approval from the required authoritiy has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

This study is registered in the WHO International Clinical Trials Registry Platform (ICTRP, ***http://www.who.int/ictrp/en/***): (http://clinicaltrials.gov). In addition, it is registered in the Swiss Federal Complementary Database (Portal) http://www.kofam.ch/gesuch-verfahren/klinischen-versuch-registrieren-via-snctp.html.

2.2 Categorisation of study

This clinical trial falls into Category B since the investigational compound bendamustine (Ribomustin®) is approved in Switzerland for the treatment of Non-Hodgkin lymphoma (NHL) patients. However, it is formally not registered for the treatment of myeloma patients representing a specific subtype of NHL. In this trial, Bendamustine is used for the treatment of myeloma patients as a part of a high-dose chemotherapy regimen, thus definitely outside of its approved indication.

2.3 Competent Ethics Committee (CEC)

The principle investigator ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study. All changes in the research activity and all unanticipated problems involving risks to humans will be reported including in case of planned or premature study end and the final report. No changes will be made to the protocol without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

The Sponsor will obtain approval from the competent authority (Swissmedic) before the start of the clinical trial. All changes in the research activity and all unanticipated problems involving risks to humans will be reported including in case of planned or premature study end and the final report. No changes will be made to the protocol without prior approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

2.5 Ethical Conduct of the Study

This trial will be conducted in compliance with the protocol, ICH guidelines (International Conference on Harmonisation) and the applicable local regulatory requirement(s) and directives. The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki as well as the guidelines of Good Clinical Practice (GCP) issued by ICH. The competent Ethics Committees (CECs) and local regulatory authorities will receive annual Development Safety Update Report (DSUR) and be informed about study stop/end in agreement with local requirements and institutional SOP. Any changes or amendments to the study protocol will be documented by the Principle Investigator in writing and sent to the local CEC, and regulatory authorities.

2.6 Declaration of interest

No conflicts of interest are reported.

2.7 Patient Information and Informed Consent

Participants will be comprehensively informed about the study and consent is sought from each participant; no compensation for study participation is made in this trial. The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participants to make an informed decision about their participation in the study. Enough time needs to be given to the participant to ask questions and decide whether to participate or not. The patient information sheet and the consent form will be submitted to the CEC to be approved. The consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant will read and consider the statement before signing and dating the informed consent form, and will be given a copy of the signed document. The original consent form will also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances for example:

- Ethical concerns;
- Insufficient participant recruitment;
- When the safety of the participants is doubtful or at risk, respectively;
- Alterations in accepted clinical practice that make the continuation of a clinical trial unwise;
- Early evidence of benefit or harm of the experimental intervention.

2.10 Protocol amendments

The Principle Investigator is allowed to amend the protocol or to provide suggestions for a protocol amendment. Substantial amendments are only implemented after approval of the CEC and CA, respectively. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible. All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

High-dose chemotherapy with melphalan and autologous stem cell transplantation (ASCT) remains an integral component of the myeloma treatment algorithm for patients considered eligible for the procedure, nowadays performed in myeloma patients up to the age of 75 years. The traditional approach to patients with newly diagnosed myeloma, considered to be candidates for ASCT, has been to provide initial therapy with 4 to 6 cycles of a non–alkylator-containing regimen followed by collection of stem cells and high-dose therapy. The initial therapy for the disease allows time to obtain necessary insurance approvals as well as control disease-related symptoms, simultaneously controlling toxicity by limiting the number of cycles. In addition, adequate disease control provides an opportunity to reverse disease-related complications wherever feasible, and generally improve the functional status of the patient, allowing for a safer transplantation.

The majority of the randomized clinical trials have demonstrated a superior progression-free survival among patients undergoing ASCT compared with those treated with only conventional therapies, and ASCT was associated with superior overall survival in the majority of those studies (1-7). Subsequent randomized trials have further defined the role of ASCT by demonstrating equivalent overall survival for delayed transplantation compared with upfront ASCT, albeit with some compromise in the quality-of-life parameters (8). Introduction of novel agents such as thalidomide, lenalidomide, and bortezomib have resulted in a paradigm change in the therapy of myeloma (9-14). The high response rates with these agents, hitherto seen only in the context of high-dose therapy, have once again raised questions regarding the utility of ASCT in the setting of myeloma. Given the lack of long-term follow-up of patients treated with these new agents, the durability of these responses as well as their potential long-term adverse effects remain to be demonstrated. Noteworthy, recently published studies suggest that the novel induction regimens together with consolidating high-dose treatment act in an additive manner allowing increasing rates of complete remission ranging between 50 up to 70% after autologous transplantation. Thus, ASCT continues to be an important part of myeloma therapy, nowadays more than ever. At the University Hospital in Bern, the number of ASCT is increasing each year, with myeloma representing the most common entity, comprising roughly 50% of all ASCT.

These facts add to the observation that there is a continuous increase in the number of ASCTs reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Currently, the novel agents appear best suited to be used as first-line therapy, enhancing the quality of responses prior to proceeding to ASCT or as adjuncts to transplant conditioning regimens or as maintenance therapy in patients undergoing ASCT (15-23). Furthermore, in a randomized trial evaluating single versus double ASCT a survival advantage with tandem ASCT was demonstrated in an unplanned subset analysis for those patients not obtaining at least a very good partial response after the first ASCT. This observation has increased the number of ASCTs being performed for patients not achieving very good partial response after the first ASCT (24). In addition, ASCT can also be used as part of second-line therapy after relapse, especially among patients who achieved a durable response after the first ASCT (6;23).

3.2 Investigational Product

The bendamustine molecule is composed of three structural elements: a bis (2-chloroetylo) amine group (nitrogen mustard), a purine-like benzimidazolering and a butyric acid side chain (24). The bis (2-chloroetylo) amine group confers the alkylator properties and the benzimidazole ring that replaces the benzene ring present in chlorambucil, the antimetabolite properties. While, the butyric acid side chain makes this drug water soluble (25). The antineoplastic effect of bendamustine is due to production of both single- and doublestrand breaks (26–29). The DNA breaks, observed after bendamustine exposure, are more extensive and significantly more durable than those induced by other alkylators. This extensive DNA damage leads to inefficient DNA repair mechanisms, resulting in mitotic checkpoint inhibition (26).

In addition, bendamustine can also lead to phosphorylation of Ser-15 and increases protein expression of Bax, inducing a traditional apoptosis via the activation of P53-dependent pathways (26, 27). Bendamustine is administered intravenously (i.v.) over 30–60 min; peak plasma concentration (Cmax) occurs at the end of the infusion. The majority of the drug (95%) is bound to serum plasma proteins, particularly to albumin; however, only unbound bendamustine is pharmacologically active (30–34). Some preclinical and clinical studies demonstrated that bendamustine undergoes extensive first-pass hepatic metabolism, primarily by hydrolysis, via the cytochrome P450 1A2 (CYP1A2) isoenzyme (31; 32; 35).

The major metabolite is β-hydroxybendamustine, which does not significantly contribute to bendamustine's activity (36). Phase II conjugation with glutathione also plays a role in the metabolism of bendamustine (35). The drug is eliminated mainly via the faeces (90%) and to a lesser extent in the urine (37). Following a single dose of bendamustine, concentrations declined in a triphasic manner, with rapid distribution, intermediate and slow terminal phases (34). Estimates of $t_{1/2a}$, $t_{1/2b}$ and $t_{1/2c}$ for bendamustine were 0.29 h, 0.7 h and 110 h, respectively. The AUC for the terminal phase accounted for <1% of the total AUC; thus, the $t_{1/2}$ of the b-phase (40 min) is considered to be reflective of half-life of bendamustine (25). Age, as well as mild or moderate renal impairment or hepatic dysfunction did not alter bendamustine pharmacokinetics. Nevertheless, it is recommended to use this drug with caution in patients with mild to moderate hepatic impairment, and it should be avoided in those with severe hepatic dysfunction (26). Furthermore, some drugs such as omeprazole or tobacco, strong inducers of CYP1A2, seem to decrease bendamustine concentration in plasma and reduce its efficacy (38).

3.3 Evidence of clinical activity of Bendamustine from previous studies

Knop et al. (39) published 2005 the results of a phase I study of bendamustine in 31 patients up to age 70 yr with myeloma progressing after high-dose therapy + autologous stem cell transplantation (HDT + ASCT). The initial dose was 30 mg/m^2/day on days 1 and 2 of each 28-days cycle, and it was escalated up to 50 mg/m^2/day. The total dose of 100 mg/m^2 was found to be the maximum dose tolerated (MDT). The overall response rate (ORR) was 55%, with a median progression free survival (PFS) of 26 week. A retrospective analysis investigated the use of bendamustine in 39 relapsed myeloma patients (40). Patients have received a median of 3 (1–10) cycles of bendamustine at the dosage of 80–150 mg/m^2/day on days 1 and 2 every 28 days. In 39% of cases, bendamustine was administered alone, while in the remaining 61%, in combination with steroids. The ORR was 36% [no complete response (CR) was observed]; the median event-free survival (EFS) and overall survival (OS) were 7 and 17 months, respectively. No difference in terms of response rate was observed between elderly and younger patients (40). Finally, Damaj et al. reported data of a French compassionate use programme that had enrolled 110 relapsed/refractory myeloma patients who received bendamustine at dosage of 60–150 mg/m^2/day on days -3 and -2 in combination with variable dose of steroids for a median of 4 (range 1–13) cycles every 28 days. The ORR was 30%, including 2% of CR; the median PFS and OS were 9.3 and 12.4 months (41). These results highlight the role of bendamustine as an effective salvage therapy option for relapsed/refractory myeloma patients. Further, bendamustin is approved in the EU for the treatment of multiple myeloma patients not eligible to receive a HDT with ASCT or a thalidomide or bortezomib-containing regimen (Ref Fachinformation bendamustin).

3.4 Evidence for selecting Bendamustine as a component of a high-dose chemotherapy regimen

High dose melphalan is the standard of care conditioning regimen before ASCT (42), given at a total dose of 200 mg/m^2, for myeloma patients (43, 44). As bendamustine showed a good efficacy and safety profile, a phase I trial was conducted with the aim of evaluating whether the addition of bendamustine to melphalan in the ASCT conditioning could improve the response without adding toxicity (45). Escalating doses of bendamustine (from 30 mg/m^2/day at day -1 up to 125 mg/m^2/day at day -2 plus 100 mg/m^2/day at day -1 added to melphalan 100 mg/m^2/day at the same days (days -2 and -1) were administered to 25 patients with active myeloma as conditioning regimen. The MTD was not encountered at the highest dose level. At day +100, ORR was 79%, with 38% of stringent CR, 4% of CR, 33% of VGPR and 4% of PR. Ten patients progressed after a median of 473 d after ASCT and six patients died. Median PFS was 791 d, and the median OS was not reached, but the 2-yr OS rate was 70% (45).
Martino et al. recently reported phase II data regarding feasibility and efficacy of the association between bendamustine and melphalan (BM) as a conditioning regimen to second ASCT in patients with myeloma (46). All 32 patients enrolled have received a bortezomib-containing regimen as first-line induction therapy and received melphalan 100 mg/m^2/day on days -2 and -1 as conditioning regimen before the first ASCT. The conditioning regimen before second ASCT was bendamustine (100 mg/m^2/day on days -4 and -3) and melphalan (140 mg/m^2/day on day -2). No added toxicity was observed between the first and second ASCT. The 2y-OS and 2y-PFS were, respectively 97% and 79% (46). Finally, Breitkreutz et al. recently reported data of 28 consecutive myeloma patients treated with a dose-intensified bendamustine (180 mg/m^2/day, days -3 and -2) followed by autologous blood stem-cell support (ASCS) (47). All patients relapsed from the last treatment (median of 3 prior lines of therapy) with very limited bone marrow function and were therefore ineligible for conventional chemotherapy, novel agents or trial enrolment. This schedule allowed of improving hematopoiesis as reflected by a significant increase of platelet counts and white blood cell counts at day +100. Furthermore, 36% of patients achieved at least

a minimal response. Nevertheless, the median PFS was limited to 2.14 months. Most importantly, patients, by improving the hematopoiesis, were once again eligible for alternative treatments including enrolment into clinical trials (47).

Justification and definition of primary endpoint: The achievement of stringent CR1 is generally considered a prerequisite for potential long-time cure in myeloma patients. This highlights the importance of not only achieving normalization of light chain ratio and absence of a paraprotein in the serum, but also of complete elimination of clonal plasma cells in the bone marrow assessed by sensitive flowcytoemtric analysis. These facts form the basis of our attempt of an intensified conditioning HDCT regimen aiming to increase the proportion of patients with CR1 after ASCT, thus representing the primary endpoint of this study.

3.5 Dose Rationale for Bendamustine in conditioning regimens

As outlined above (section 3.4), two phase 1 and 2 studies have reported combinations of melphalan with bendamustine as first-line conditioning regimen before ASCT in myeloma patients. The phase 1 trial added escalating doses of bendamustine (days -2 and -1) to standard melphalan. Bendamustine was administered at the same days of melphalan and maximum tolerated dose was not encountered; the highest dose level cohort of bendamustine total dose of 225 mg/m^2 and melphalan total dose of 200 mg/m^2 was expanded to further evaluate safety (45).
Recently, Martino et al. reported their data regarding feasibility and efficacy of the combination of bendamustine and melphalan (BM) as a conditioning regimen to second ASCT in patients with Myeloma (46). In this phase II study multiple myeloma patients underwent tandem autologous stem cell transplants as part of their treatment. All patients (n= 32) received melphalan 100 mg/m^2/day on days -2 and -1 as conditioning regimen before the first ASCT. Bendamustine 200 mg/m^2/day on days -4 and -3 plus melphalan 140 mg/m^2/day on day -2 was the conditioning regimen before the second ASCT. 2y-OS was 79% and 2y-OS was 97%. No added toxicities were observed between the first and the second ASCT: differences in toxicities were not statistically significant, except for mucositis and nausea that were higher after the first conditioning regimen with only melphalan (!). The majority of the toxicities were grade 1 or 2. No treatment related mortality was reported (46).
In addition, extensive experience is available on the use of bendamustine (200mg/m^2/day given on days -7 and -6) together with melphalan (140mg/m^2/day day -1) and cytarabine/etoposide (each on days -5 to -2) in the BeEAM conditioning regimen which is increasingly used as the standard conditioning regimen in lymphoma patients, as is also the case in our clinic, in which we observe acceptable toxicity justifying the use of high dose bendamustine HDCT conditioning (48-50).
In summary, these data suggest that combinations of melphalan and bendamustine are usually well tolerated and that the maximum tolerated dose of bendamustine is not reached with the dose of 200mg/m^2/daygiven on two days added to melphalan, etoposide cytarabine (BeEAM regimen). We therefore suggest in this study to directly compare bendamustine 200 mg/m^2/day given on days -4 and -3 plus melphalan at standard dose of 100mg/m^2/day on days -2 and -1 versus with standard melphalan alone (100mg/m^2/day on days -2 and -1), in a randomized trial in order to compare effectiveness and tolerability of the combination treatment. To limit toxicity, the schedule for the administration of the study medication is planned as follows: bendamustine given on days -4 and -3 and melphalan on days -2 and -1, thereby avoiding to administer both drugs at the same days (-2 and -1).

3.6 Explanation for choice of comparator

Improving the efficacy of HDCT with Melphalan together with ASCT is an unmet clinical need in myeloma patients. Currently, this approach is not curative and adds significant transient burden in terms of impaired quality of life. The combination of bendamustine and melphalan appears promising and reasonable, based upon the results summarized above. We therefore consider a direct randomized comparison justified between melphalan versus the combination of melphalan with bendamustine.

3.7 Risks / Benefits

Routinely performed high-dose chemotherapy with ASCT is associated with significant side effects requiring detailed information of the patient. Usually, it is associated with a hospitalization of at least 3 weeks. Bendamustine treatment is usually associated with a good safety profile. In fact, when this drug is administered alone or in combination with steroids, toxicity is usually moderate. The most frequently reported adverse events (AEs) are reversible myelosuppression, fever, allergic reactions,

gastrointestinal symptoms (nausea and vomiting) and infections (51). When administered alone or in combination with steroids in relapsed/ refractory myeloma patients, the majority of AEs were mild and consisted mainly of hematological AEs (39–41). As first-line therapy, myeloma patients who received bendamustine and prednisone showed a higher rate of severe nausea and vomiting compared with those who received melphalan plus prednisone (52). Although no significant differences in the incidence of various hematological adverse events were observed, the percentage of patients receiving bendamustine and prednisone who required dose reduction for leukopenia (8.6 vs. 4.1%) and thrombocytopenia (1.8 vs. 0.9%) was higher than that of patients receiving melphalan and prednisone (52). The combination of bendamustine with bortezomib and steroids was well tolerated in relapsed/refractory patients (53). Also in this setting, the most frequent severe AEs were hematological, while severe non-hematological AEs were uncommon and consisted in gastrointestinal disturbances, fatigue and infections (53). When administered as first-line treatment, safety profile of this combination was manageable and most AEs were of grade 1–2. The most common toxicities were as follows: peripheral neuropathy, neutropenia, asthenia and infection (54,55). The combinations of bendamustine with thalidomide plus dexamethasone/prednisone (56) and with lenalidomide plus dexamethasone/prednisone (57) showed acceptable tolerability profiles in relapsed/refractory patients. Again, the most frequent severe AEs were hematological.
Although in the absence of anticoagulant prophylaxis, no thromboembolic events were observed. Finally, the addition of bendamustine to high-dose melphalan in ASCT conditioning does not seem to enhance toxicities. No transplant-related mortality events correlated to bendamustine administration were reported (45, 46). Patients should be observed for dehydration which is another common AE.

3.8 Justification of choice of study population

This study does not involve vulnerable participants (e.g. minors, adolescents, participants incapable of judgement or participants under tutelage, emergency treatment of unconscious patients or others). The age limits are between 18 and 75 years. However, high-dose bendamustine and melphalan require adequate renal function. This requires that myeloma patients with significantly reduced renal function (defined as a creatinine clearance < 40 ml/min) are not eligible for this study.

4. STUDY OBJECTIVES

4.1 Overall Objective

This study aims to demonstrate that adding bendamustine to standard high-dose melphalan conditioning chemotherapy before ASCT is improving response rates in myeloma patients.

4.2 Primary Objective

- This study aims to show a clinically meaningful improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan.

4.3 Secondary Objectives

This study intends

- to assess acute and late toxicities/adverse events (CTCAE 4.0) during the study period in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone;
- to assess the hematologic engraftment in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone;
- to particularly assess early renal toxicity in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone;
- to assess differences in overall survival and progression free survival in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone after one year;

- to assess the quality of life prior to ASCT and 60 days thereafter.

4.4 Safety Objectives

As one of the secondary objectives outlined above, this study aims to assess toxicities of bendamustine combined with high-dose melphalan as compared to melphalan alone in myeloma patients undergoing high-dose chemotherapy with autologous stem cell transplantation. Particular attention will be given to detect and monitor eventual renal toxicity. Any other adverse event will be also recorded.

5. STUDY OUTCOMES

5.1 Primary Outcome

A clinically meaningful increase of the efficacy of a novel high-dose conditioning chemotherapy is defined in this study as an increase of the rate of complete remissions (CR1) 60 days after ASCT from 50% with melphalan alone to ≥ 65% with the combination melphalan and bendamustine (see appendix 3 for definition of CR).

5.2 Secondary Outcomes

Toxicities/adverse events are assessed according to the CTCAE 4.0 during the study period.

Hematologic engraftment after high-dose chemotherapy induced myelosuppression is defined as the first day of neutrophils rising again above 0.5 G/l, and of platelets rising again above 20 G/L in the absence of platelet transfusions in the previous 3 days.

Overall survival is defined as the time from ASCT until death of any cause or date of last follow-up.

Progression free survival is defined as the time from ASCT until first recurrence of myeloma or date of last follow-up whatever occurs first.

5.3 Other Outcomes of Interest

Not applicable.

5.4 Safety Outcomes

This study aims to assess toxicities of bendamustine combined with high-dose melphalan as compared to melphalan alone in myeloma patients undergoing high-dose chemotherapy with autologous stem cell transplantation. Particular attention will be given to detect and monitor eventual renal toxicity. Any other adverse event will also be recorded.

6. STUDY DESIGN

6.1 General study design

This is a 1.1 randomized parallel open-label prospective phase II trial investigating myeloma patients considered clinically fit to undergo high-dose chemotherapy with autologous stem cell transplantation.

Two high-dose chemotherapy regimens (Mel versus BenMel) used for conditioning treatment before autologous stem cell transplantation will be compared in a 1:1 randomization (see trial diagram below). The experimental arm is the BenMel regimen; the Mel regimen is the control treatment. Both regimens use melphalan at identical doses and at identical days (100mg/m^2/day each on days -2 and -1). However, myeloma patients in the experimental arm receive two additional doses of bendamustine 200 mg/m^2/day given on days -4 and -3. Response will be assessed by serum light chain ratio and M-gradient before study treatment and 60 days after ASCT.

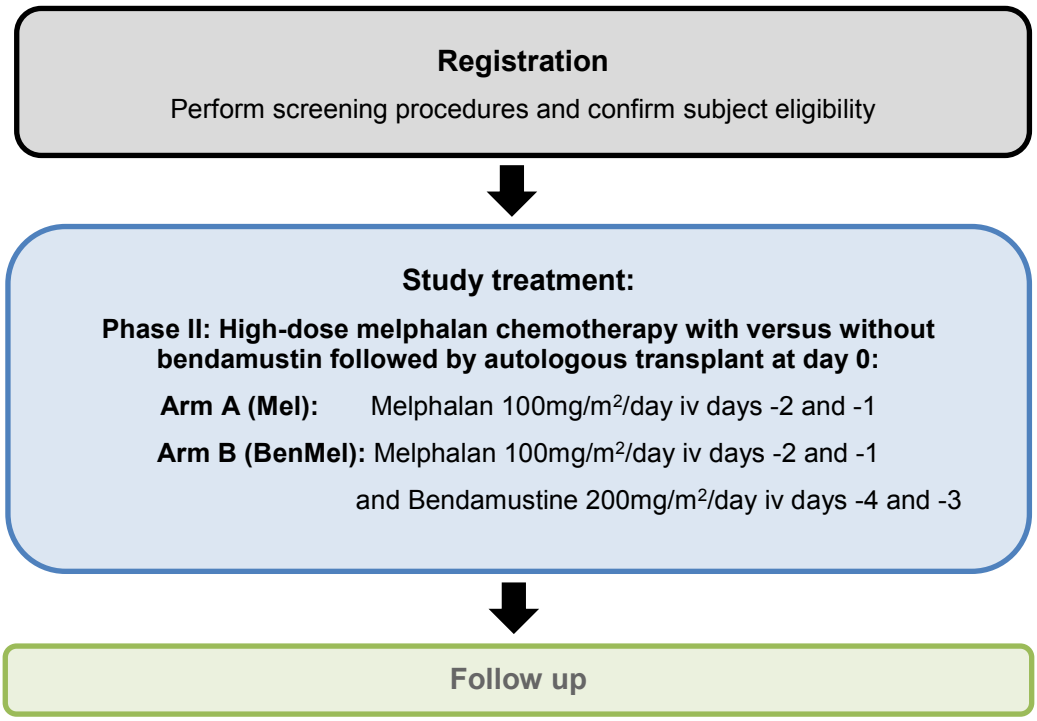
There will be 60 patients in each group to show a clinically meaningful improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients, from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan. The anticipated total study duration will be 36 months

Methods of minimising bias: this is a 1:1 randomized parallel open-label prospective phase II trial. Patients will be stratified for remission status (CR/VGPR versus PR/SD/PD), and for presence/absence of reduced renal function defined as a creatinine clearance ≥ 50 ml/min versus <50 ml/min but ≥ 40 ml/min.

Randomization is performed by the coordinating study nurse, the specifically designed study nurse or his/her replacent of the Klinische Forschungseinheit Onkologie, University Hospital/Inselspital, 3010 Bern. Randomisation will be performed using REDCap software. Two stratification parameters (response and renal function) will be applied. Patients can be registered 24 h / 7 days.

Blinding procedures: not applicable; this is an open-label trial.

Unblinding Procedures (Code break): not applicable; this is an open-label trial.



7. STUDY POPULATION

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Eligible are myeloma patients after standard first-line induction treatment. A second induction regimen in refractory myeloma patients is allowed.
- Patients must be considered being fit for subsequent consolidation with high-dose chemotherapy with melphalan with autologous stem cell support.
- Patients must be aged 18-75 years.
- Patients must have an ECOG < 3.
- Patients must have a creatinine clearance ≥ 40 ml/min.
- Patients must have a LVEF ≥ 40% within three months prior to start of study medication (Echo can be postponed to study treatment visit in asymptomatic patients).
- Female patients of child-bearing potential;. . No known pregnancy (a pregnancy test in female patients of child-bearing potential is not mandatory since patients are already under induction chemotherapy or mobilization chemotherapy, and pregnancy was excluded before starting chemotherapy. Patient must implement adequate measures (hormonal treatment p.o. or i.m.,

intra uterine surgical devices, or latex condoms) to avoid pregnancy during study treatment and for additional 12 months. No pregnant or lactating patients are allowed. Thus Pregnancy test could be omitted from the screening visit and could be postponed to the study treatment if indicated.

- Patients must have given voluntary written informed consent.

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Patients with uncontrolled acute infection.
- Patients with a transplantation comorbidity index (HCTCI) > 6 points.(HCTCI may be postponed to the treatment visit)
- Patients with concurrent malignant disease with the exception of basalioma/spinalioma of the skin or early-stage cervix carcinoma, or early-stage prostate cancer. Previous treatment for other malignancies (not listed above) must have been terminated at least 24 months before registration and no evidence of active disease shall be documented since then.
- Patients with major coagulopathy or bleeding disorder.
- Patients with other serious medical condition that could potentially interfere with the completion of treatment according to this protocol or that would impair tolerance to therapy or prolong hematological recovery.
- Patients with lack of cooperation to allow study treatment as outlined in this protocol.
- Pregnancy or lactating female patients.
- The use of any anti-cancer investigational agents within 14 days prior to the expected start of trial treatment
- Patients with contraindications and hypersensitivity to any of the active chemotherapy compounds.

7.2 Recruitment and screening

Participants are recruited to this study by screening myeloma patients routinely referred to our centre for autologous stem cell transplantations. No specific advertisement for this study is performed. The screening procedure is outlined in section 9.3.1. No payment or compensation is given to study participants.

7.3 Assignment to study groups

Randomization is performed by the coordinating study nurse, the specifically designed study nurse or his/her replacent of the Klinische Forschungseinheit Onkologie, University Hospital/Inselspital, 3010 Bern. Randomisation will be performed using REDCap software. Two stratification parameters (response and renal function) will be applied. Patients can be registered 24 h / 7 days.

Patients will be stratified for remission status (CR/VGPR versus PR/SD/PD), and for presence/absence of reduced renal function defined as a creatinine clearance ≥ 50 ml/min versus <50 ml/min but ≥ 40 ml/min. If an already registered patient is later found not to completely fulfill the inclusion/exclusion criterias, he/she will be documented on the enrollment-log at the centre. The exclusion of this patient will be reported to the coordinating investigator. The patient will not be included in the final analysis, and his/her patient number will not be replaced by another patient.

7.4 Criteria for withdrawal / discontinuation of participants

- Withdrawal of informed consent by the participant;
- lack of compliance of the participant to follow the study procedures;
- relevant protocol violation;
- lost to follow up;
- Unacceptable toxicity or death.

Any participant has the right to withdraw the consent to participation in this trial at any time. Details of the date and the circumstances of the withdrawal have to be recorded in the patient charts and in the eCRFs. The treating physician can withdraw the patient from the study if considered necessary. Again, the date and the circumstances of the withdrawal have to be recorded in the patient charts and in the eCRFs. Patients withdrawn from this protocol are documented up to 60 days after ASCT. All patients terminating study treatment before 60 days after ASCT will be analyzed until the last documented follow-up. Patients withdrawn from the protocol won't be replaced.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment)

This is a 1.1 randomized parallel open-label prospective phase II trial investigating myeloma patients in first remission considered clinically fit to undergo high-dose chemotherapy with autologous stem cell transplantation.

Two high-dose chemotherapy regimens (Mel versus BenMel) used for conditioning treatment before autologous stem cell transplantation will be compared in a 1:1 randomization. The experimental arm is the BenMel regimen; the Mel regimen is the control treatment. Both regimens use melphalan at identical doses and at identical days (100mg/m^2/day each on days -2 and -1). However, myeloma patients in the experimental arm receive two additional doses of bendamustine 200 mg/m^2/day given on days -4 and -3. ASCT is performed in both arms on day 0. Response will be assessed by serum light chain ratio and M-gradient before study treatment and 60 days after ASCT (day 60 assessment is possible from day +35 to day +75).

- Experimental Intervention (treatment) BenMel regimen

Bendamustine	120min iv	200mg/m^2/day	days -4 and -3
Melphalan	60min iv	100mg/m^2/day	days -2 and -1

- Control Intervention (standard treatment) Mel regimen

Melphalan	60min iv	100mg/m^2/day	days -2 and -1

8.2 Packaging, Labelling and Supply (re-supply)

Bendamustine (Ribomustin®) will be provided in single brown glass vials containing 100 mg of bendamustine hydrochloride (HCl) powder. Labeling of bendamustine is performed by the manufacturer in accordance to GMP and the local regulatory requirements. Each vial will be affixed with a label describing the protocol number, patient number, content of each vial, dosage form, and route of administration, lot number, expiration date, storage conditions, and the Sponsor's name. The label will contain also the sentences "for clinical use only". Packaging and shipping will be according to the manufacturer's standards and local regulations. Upon receipt of bendamustine by the study site, pharmacy personnel should check for damage and verify proper quantity, identity, and integrity. Any complaints and deviations from the delivery notes have to be reported to Mundipharma Medical Company upon discovery. Starting from April 2018 the commercial product (Ribomustine®) will be used after adding the study label.

Mundipharma Medical Company will receive orderings for bendamustine study medication via a specific fax ordering form. Distribution of bendamustine will be performed by Alloga Switzerland to the pharmacy of the study site in Berne/Switzerland. A stock of study medication will be provided in advance which has to be replenished by fax-order sent to Mundipharma Medical Company. Appropriate fax ordering forms and fax numbers are provided in the Investigator Study File.

Drug supply has to be ordered by study staff by fax to the local hospital pharmacy for each patient prior to treatment start. Appropriate fax ordering forms and fax numbers are provided in the Investigator Study File.

Storage of Investigational Product: the investigational product bendamustine will be stored at < 25°C and protected from light in a secure location accessible only by authorized personnel. All drug supplies

are to be used only for this protocol and not for any other purpose.

Commercial products will be used for Melphalan (Alkeran ®).

8.3 Administration of experimental and control interventions

8.3.1 Experimental Intervention – high-dose chemotherapy BenMel (Bendamustine and Melphalan)

Bendamustine: before administration, bendamustine powder must be dissolved in sterile water for injection and then immediately diluted in 500 ml of 0.9% sodium chloride. Once reconstituted, bendamustine is chemically and physically stable in conventional polyethylene i.v. bags and infusion sets for 3.5 hours at room temperature (25°C/60% relative humidity) or for maximally two days under refrigerated conditions (2º-8ºC) and is photostable. From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user. Because compatibility studies have not been performed, bendamustine should not be combined with other agents or solutions (e.g. glucose).

Bendamustine will be given at a dose of 200mg/m^2/day at days -4 and -3, and the dose will be calculated according to the BSA (body surface area). No dose capping (e.g. for under-weight or over-weight patients) will be performed. The BSA has to be determined only once at screening. Bendamustine is administered by i.v. infusion over 120 minutes with sufficient hydration before and after administration of bendamustine (volume of at least 4000 ml of NaCL 0.9% solution administered i.v as in the following schedule: 2000ml before bendamustine, plus furosemide 20 mg i.v., and 2000 ml NaCl 0.9% thereafter). An in-line filter is not required for administration. For patients with decreased renal function defined as a creatinine clearance <50 ml/min and ≥ 40 ml/min, bendamustine will be reduced to 100 mg/m^2/day at days -4 and -3.

As bendamustine is a mildly to moderately emetogenic drug, premedication with antiemetic drugs is advised (e.g. a 5-HT3 receptor antagonist). Bendamustine is not considered to be a vesicant when diluted and administered as recommended. However, if bendamustine extravasates during infusion, it might cause some irritation to affected tissues (follow instructions of SmPC in case of extravasation).

Vials are for single use only. Vials used for one subject may not be used for any other subject. Partly unused or expired medication can be destroyed by the pharmacy at the study site according to local guidelines, but only after monitor's approval. The destruction shall be either documented by completing the drug return or the drug destruction log.

Melphalan at a dose of 100mg/m^2/day will be administered as single i.v. infusion over 60 minutes at days -2 and -1 before ASCT (day 0). No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, extensive hydration, control of renal function and supportive care are according to local hospital guidelines. For patients with decreased renal function defined as a creatinine clearance <50 ml/min and ≥ 40 ml/min, melphalan will be reduced to 70 mg/m^2/day at days -2 and -1.

8.3.2 Control Intervention – high-dose chemotherapy Mel (with Melphalan only)

Melphalan at a dose of 100mg/m^2/day will be administered as single i.v. infusion over 60 minutes at days -2 and -1 before ASCT (day 0). No dose capping (e.g. for under-weight or over-weight patients) will be performed. Antiemetics, extensive hydration, control of renal function and supportive care are according to local hospital guidelines. For patients with decreased renal function defined as a creatinine clearance <50 ml/min and ≥ 40 ml/min, melphalan will be reduced to 70 mg/m^2/day at days -2 and -1.

8.4 Dose modifications

No discontinuation of (one or several) study compounds or dose modification of the allocated interventions is allowed by this protocol for a given trial participant. However, for patients with decreased renal function defined as a creatinine clearance <50 ml/min and ≥ 40 ml/min, melphalan will be reduced to 70 mg/m^2/day at days -2 and -1, and bendamustine will be reduced to 100 mg/m^2/day at days -4 and -3.

8.5 Compliance with study intervention

All study data come from procedures and treatments performed in the University Hospital of Bern, Switzerland, by staff authorized for this study. The adherence to the study protocol implies for subjects in the experimental arm two extra days caused by drug administration (and hospitalization): days -4 and

-3 for bendamustine 200 mg/m^2/day. Other screening procedures, measument, assessment or treatments of the study protocol are identical in both arms. The control group will receive the standard procedure for screening, treatment and follow-up. The administration of the entire study treatment (including investigational products) and the assessment data will be recorded in the appropriate sections of the electronic case report forms. According to the intention-to-treat principle, non-compliant patients will not be excluded from the analysis. Non-compliant patients will be documented for a total of 60 days after ASCT. All patients terminating study treatment before 12 months will be analyzed until the last documented follow-up.

8.6 Data Collection and Follow-up for withdrawn participants

Any participant has the right to withdraw the consent to participation in this trial at any time. Details of the date and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. The treating physician can withdraw the patient from the study treatment if considered necessary. Again, the date and the circumstances of the withdrawal have to be registered in the patient charts and in the CRFs. Patients withdrawn from this protocol are documented for up to 60 days after ASCT. All patients terminating study treatment before 60 days after ASCT will be analyzed until the last documented follow-up. If patients withdraw their consent to this study, their study data will be anonymized after completion of the study analysis.

8.7 Trial specific preventive measures

Not included in this trial will be female participants of childbearing potential, which are not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases. Female participants who are surgically sterilized, hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential. Men should not father a chilld during and up to 12 months after the trial intervention.

8.8 Concomitant Interventions (treatments)

No specific recommendations are made excluding specific medication not allowed during study treatment.

8.9 Supportive treatment during neutropenia after ASCT

- All patients receive G-CSF (filgrastim) 5 µg/kg b.w. starting at day +6 for a total of seven days after ASCT (or longer if clinically indicated).
- Platelet infusions are given if levels < 10.000/µl; or in case of fever or coagulopathy if platelets are <20.000 µl or if clinically indicated.
- Red cell transfusions if Hb < 8 /dL. Packed RBCs and platelet transfusions should be given to maintain a hemoglobin level > 8 g/dL and a platelet count > 10x10^9/L, or if clinically indicated.
- Fungal prophylaxis with 400mg of fluconazole p.o. ought to be given starting at day +1 once per week until recovery from myelosuppression.
- Cotrimoxazole prophylaxis three times a week for 3 weeks after ASCT, and Acyclovir prophylaxis twice daily 500mg p.o. for three months will be administered to the patients or according to the hospital policy, until recovery from myelosuppression.
- Daily clinical assessment and documentation of toxicities exceeding grade 2 during neutropenia.

8.10 Study Drug Accountability

The investigational product is Bendamustine (Ribomustin®). Accordingly, Bendamustine is provided free of charge for all patients in this study by the company Mundipharma, and all Bendamustine sent to the sites must be accounted for. All other components of the chemotherapy conditioning before ASCT are considered standard of care, and are reimbursed by the insurance company of the patients. The investigator is responsible for the control of application and handling of the drugs as requested per

protocol.

Adequate records of receipt, administration, storage, destruction or return of the study drugs have to be maintained. All logs have to be completed by the study site staff in a timely manner, and thus should be kept current. All records, logs and study drugs (used and un-used) at the site have to be available for the inspection at any time. Upon termination of the study, all logs have to be completed and returned to the monitor to be passed to the Sponsor. Copies thereof, have to be maintained by the study site.

8.11 Return or Destruction of Study Drug

All Bendamustine sent to the site must be accounted for. In addition, the amount (in mg) of Bendamustine dispensed for each patient must be recorded on an Investigational Product Accountability Log and the amount (in mg) administered documented on the case report form (CRF). An accurate record of the date and amount of Bendamustine dispensed to each patient must be available for inspection at any time. Partially used vials may be destroyed per institutional guidelines and documented. All unopened and unused vials of Bendamustine will be destroyed upon completion of the study or if drug expires unless otherwise directed by the Principle Investigator. The study site will document all receipt, complete destruction, and return (if applicable) of Bendamustine.

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments. Study schedule

.

Study schedule

Study Periods	Screening	Treatment	Day 60 assessment	Follow-up
Visits	1	2	3	4 [10]
Time (days)	-35 to -5	-4 until end of hospitalization	+30 to +75	___
Patient informed consent	x			
Height/weight/body surface	x			
In- / exclusion criteria	x			
HCTCI score	x			
ECOG score,	x		x	
Echocardiogaphy (TTE)[1]	x			
Hematology	x	x [2]	x	
Serum biochemistry [3]	x	x [4]	x	
Pregnancy Test[5]	x			
Randomization	x			
Response (serum free light chain ratio and M-gradient; [6]	x		x	x
QoL (EORTC Q30)	x		x	
Administer study medication		x		
Number of CD34+ cells for ASCT [7]		x		
Engraftment, lymphocyte, neutrophil and platelet recovery		x		
RBC & platelet transfusions		x		
Days of T>38.0°; number of febrile episodes		x	x	
Bone marrow			x [8]	
CD4/CD8 determination (bone marrow)			x [9]	
CD4/CD8 determination (blood)			x [9]	
Adverse Events		x	x	

[1] Echo results can be accepted within three months prior to HDCTX ,the echo can be omitted or postponed untill treatment visit if clinically indicated

[2] Hematology (hemoglobin, leukocytes, platelets) will be assessed on a a daily basis as soon as leukocytes drop < 0.5 G/L until and including the day of neutrophils raising again > 0.5 G/l, lymphocytes raising > 0.5 G/l and platelets raising > 20 G/l.

[3] Biochemistry includes creatinine, urea, and uric acid; creatinine clearance is assessed once during screening and at the day 60 assessment.

[4] Starting with the first day of HDCT treatment, creatinine, urea, and uric acid will be assessed on a daily basis until including day 3 after ASCT. In case of clinically significant renal toxicity, creatinine, urea, and uric acid will be assessed as long as clinically indicated.

[5] pregnancy test will be requested at screening visit or before study treatment if indicated

[46]Assessment includes free light chain kappa and lambda and the ratio, serum electrophoresis with immunofixation, and urine electrophoresis with immunofixation if indicated.

[57]Apheresis of hematopoietic cell could be possible also before day -35, representing a part of the standard of care for myeloma patients.

[68]optional: Bone marrow is performed only in patients fulfilling the criteria for CR1. The bone marrow can alternatively be performed at the end of the ASCT hospitalization, thus before the day 60 assessment. Bone marrow should include flowcytometric assessment of minimal residual disease (MRD) for clonal plasma cells. Bone marrow assessment can be done between recovery from neutropenia until day +75.

[9]CD4 and CD8 determination is performed at the day of bone marrow (+/- 14 days, in bone marrow and in blood) and could be repeated in blood between day (+30- +75)

[10] Follow-up is according to the treating physician. It should include assessment of myeloma serum parameters (without urine analysis and without bone marrow). If relapse is suspected, assessment of myeloma serum parameters (including urine analysis) should be performed. Patients withdrawn from the protocol are documented until the day 60 assessment.

Assessments of outcomes

9.1.1 Assessment of primary outcome

The primary outcome – thus, to show a clinically meaningful increase of the CR1 rate - will be assessed by determining the serum M-gradient and light chain ratio and the. A bone marrow at the day 60 assessment, including the myeloma immunophenotype, is recommended in patients with complete remission according to the serum. Since this is an open-label trial, assessment of the primary endpoint cannot occur in a blinded manner.

9.1.2 Assessment of secondary outcomes

- to assess acute and late toxicity/adverse events using the CTCAE 4.0 classification during the study period in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone;
- to assess the hematologic engraftment on a a daily basis starting on the day of ASCT until and including the day of neutrophils raising again > 0.5 G/l, lymphocytes raising > 0.5 G/l and platelets raising > 20 G/l;
- to particularly assess early renal toxicity in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone; Starting with the first day of HDCT treatment, creatinine, urea, and uric acid will be assessed on a daily basis until including day 3 after ASCT. In case of clinically significant renal toxicity, creatinine, urea, and uric acid will be assessed as long as clinically indicated;
- to assess differences in overall survival and progression free survival in patients treated with the combination of bendamustine and melphalan as compared to melphalan alone. Follow-up is according to the treating physician. It should include assessment of myeloma serum parameters (without urine analysis and without bone marrow). If relapse is suspected, assessment of myeloma serum parameters should be performed;
- to assess the quality of life prior to ASCT and 60 days thereafter. The EORTC Q30 questionnaire will be given to patients at screening and at the day 60 assessment.

9.1.3 Assessment of safety outcomes

Adverse events

For AE definition and procedures, see section 10.

9.1.4 Assessments in participants who prematurely stop the study

According to the intention-to-treat principle, non-compliant patients will not be excluded from the analysis. Non-compliant patients will be documented until to the day 60 assessment. All patients terminating study treatment before the day 60 assessment will be analyzed until the last documented follow-up.

Any participant has the right to withdraw the consent to participation in this trial at any time. Details of the date and the circumstances of the withdrawal have to be registered in the patient charts and in the eCRFs. The treating physician can withdraw the patient from the study treatment if considered necessary. Again, the date and the circumstances of the withdrawal have to be registered in the patient charts and in the eCRFs. Patients withdrawn from this protocol are documented until to the day 60 assessment. All patients terminating study treatment before the day 60 assessment will be analyzed until the last documented follow-up. If patients withdraw their consent to this study, their study data will be anonymized after completion of the study analysis.

9.2 Procedures at each visit

9.2.1 Screening visit (Day -35 to -5)

- Written informed consent
- Height, weight and body surface
- Pregnancy test pregnancy test will be requested at screening visit or before study treatment, if indicated
- Hematopoietic stem cell transplantation comorbidity score (HCTCI) 39 (see Appendix 4)
- ECOG Score (see Appendix 2)
- Echocardiography (Echo results can be accepted within three months prior to HDCTX ,the echo can be omitted or postponed untill treatment visit if clinically indicated)
- Hematology
- Biochemistry
- Myeloma assessment
- QoL (EORTC Q30) : for details see Appendix 6

9.2.2 Assessments during ASCT (Day -4 until day of hospital discharge)

- Date of ASCT and date of engraftment
- Number of CD34+ cells transplanted and lymphocyte count in the autograft
- Number of infused red blood cell (RBC) units and platelet transfusion units
- Hematology to assess the time to platelet recovery > 20 x 10^9/L and > 50 x 10^9/L, the time of lymphocyte recovery >1x10^9/L, and the time to recovery of ANC > 0,5x10^9/L
- Biochemistry to assess renal function
- Number of days of temperature > 38.0° and number of febrile episodes
- Assessment of CTCAE 4.0 highest toxicity score observed during ASCT until dismission from hospital for toxicities with at least grade 3

9.2.3 Assessments after ASCT (Day +30 to +75 after ASCT)

- ECOG Score
- Hematology
- Biochemistry (according to the centres policy)
- Myeloma assessment
- Acute and late toxicity/adverse events (CTCAE 4.0)
- QoL (EORTC Q30): for details see Appendix 6
- Bone marrow in case of CR1. If a bone marrow assessment is performed, determination of CD4 and CD8 at the day of bone marrow (in bone marrow and blood) and between day +30 and day +75 (in blood) will be collected.

Any relapse or death will be reported as soon as known. The remission status will be assessed using serum myeloma parameters, and intervals of follow-ups are at the discretion of the treating physician. A three months control interval is recommended. If relapse is suspected, assessments of myeloma parameters are recommended.

9.2.4 Response criteria

- See Appendix 3 attached

10. SAFETY

10.1 Study type

This is a Category B trial. During the study, all serious adverse events (SAEs) until day 60 after ASCT are collected, fully investigated and documented in source documents and electronic case report forms (eCRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including the day 60 assessments.

Adverse Events have to be reported in the source documents and in the electronic case report forms from the time the participant is randomised until 30 days after ASCT. Serious Adverse Events have to be reported in case report forms from the time the participant signs the informed consent until 60 days after ASCT.

Adverse Events have to be reported, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases eCRF.
- AEs of CTCAE grade ≤2 (including AEs leading to a postponement of HDCT)
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents.
- Progression of the disease under study; complications as a result of disease progression remain reportable Adverse Events.
-
- Nausea/vomiting/loss of appetite.
- Hematological toxicities.
- Diarrhoea.
- Febrile neutropenia: The number of episodes are captured in the eCRF; thus, episodes do not need to be additionally reported as AEs
- Other expected AEs during HDCT.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An Adverse Event (AE) is any untoward medical occurrence in a patient after administration of a pharmaceutical product which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires in-patient hospitalization more than 24 hours or prolongation of existing hospitalization.
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/ birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalization more than 24 hours, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

The involved Investigator makes a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description

Definite	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probable	Temporal relationship Improvement after dechallenge No other cause evident
Possible	Temporal relationship Other cause possible
Unlikely/remote	Any assessable reaction that does not fulfil the above conditions
Unrelated	Causal relationship can be ruled out
Cannot be classified	Reaction that cannot be judged because information is insufficient or contradictory and data that cannot be supplemented or verified
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

To document the severity grades, the “Common Terminology Criteria for Adverse Events CTCAE Version 4.0” terminology will be used.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

All SAEs and other relevant safety related events until day 60 after ASCT have to be reported by the local investigator immediately to the Prinicipal Investigator within 24h of knowledge. The appropriate fax-numbers and email addresses are provided on the SAE-reporting form.

SAEs of all patients, who received study medication in this trial, have to be reported to the Prinicipal Investigator until day 60 assessment visit

Excluded from the reporting are as follows:

- All planned surgeries or hospitalizations known at the time of study initiation,
- All routinely required hospitalizations for chemotherapy and/or ASCT,
- Progression or death due to the underlying malignancy.
- Hematological toxicities.
- Expected SAEs during HDCT

10.1.3 Reporting to the manufacturer of bendamustine hydrochloride

The Sponsor-Investigator will supply Mundipharma (i.e.Mundipharma Research GmbH & Co.KG, Germany, and Mundipharma Medical Company, Switzerland) with

- A copy of all SAEs until 60 days after ASCT within 24 hours of being aware of the event regardless of whether or not the event is listed in the reference document (Product Information).
- A copy of all pregnancy reports within 24 hours of being aware of the event.
- A copy of all SUSARs within one business day at the time of the submission to the regulatory authorities, the ECs and investigators
- A copy of the DSUR at the time of the submission to the regulatory authorities and the ECs.

The appropriate and actual fax-numbers and email addresses are provided in the separate Safety Data Exchage Agreement (SDEA) agreement with Mundipharma.

10.1.4 Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator and Principal Investigator of the study by using the SAE reporting form. The Sponsor-Investigator and Principal Investigator will re-evaluate the SAE and return the form to the site.

10.1.5 Reporting of Deaths

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days. The other in the trial involved Ethics Committees receive SAEs resulting in death via the Principle Investigator within 7 days.

10.1.6 Reporting of SUSARs

A SUSAR needs to be reported to the local Ethics Committee (local event via local Investigator) and to Swissmedic for category B and C studies (via Principle Investigator for Swiss centers) within 7 days, if the event is fatal, or within 15 days (all other events).

This is not a multi-centre trial: The Principle Investigator (Sponsor) must inform all investigators participating in the clinical study of the occurrence of a SUSAR. The involved Ethics Committee will be informed about SUSARs in Switzerland via the Principle Investigator according to the local reporting requirements, directives and timelines.

10.1.7 Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Principal Investigator (Sponsor) within 24 hours. The Principal Investigator must report the safety signals within 7 days to the local Ethics Committee (local event via local investigator) and to Swissmedic.

This is not a multi-centre trial: the Principle Investigator must immediately inform all participating investigators about all safety signals. The involved Ethics Committee will be informed about safety signals in Switzerland via the Principle Investigator.

10.1.8 Reporting and Handling of Pregnancies

Pregnant participants must immediately be withdrawn from the clinical study. Any pregnancy during the treatment phase of the study and within 6 months after discontinuation of study medication will be reported to the Principle Investigator within 24 hours. The course and outcome of the pregnancy should be followed up carefully until birth of the child, and any abnormal outcome regarding the mother or the child should be documented and reported according to local reporting requirements, directives and timelines.

10.1.9 DSUR

The DSUR is submitted once a year to the local Ethics Committee and to Swissmedic via the Principle Investigator (Sponsor). The Principle Investigator is responsible for the data collection and preparation of the DSUR, and submits it to the local EC.

10.1.10 Follow up of (Serious) Adverse Events

The follow up of participants terminating the study (either regularly or prematurely) with reported ongoing

SAE, or any ongoing AEs of laboratory values or of vital signs being beyond the alert will be documented until resolution or death of the patient. All adverse events (AE) (until 30 days after ASCT) and all serious adverse events (SAE) (until day 60 assment visit) are collected, fully investigated and documented in the source document and appropriate case report form (CRF).

11. STATISTICAL METHODS

11.1 Hypothesis

This study involves two treatment arms and applies a 1:1 randomization, additionally considering the stratification for remission status and renal function. No interim analysis is planned, and all calculations will be performed on a strict intention-to-treat basis. The primary objective is to show a clinically meaningful improvement by 15% of the primary endpoint, the rate of complete remission (CR1) 60 days after ASCT in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan.

11.2 Determination of Sample Size

Arm A is the control arm (Mel: Melphalan alone chemotherapy), and arm B is the experimental arm (BenMel: bendamustine and melphalan chemotherapy). The null hypothesis is that the rate of complete remissions (CR1) determined 60 days after ASCT is equal in both arms ($CR1_A = CR1_B$). The aim of the study is to ultimately show an improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT
in myeloma patients from 50% with melphalan alone to 65% with the combination of bendamustine and melphalan, with $CR1_A < CR1_B$.
Based on a cohort of 122 myeloma patients at our cohort (2010-2013), we anticipate a CR1 rate in the standard (Mel) arm of 50% ($CR1_A$). Our hypothesis is that the experimental (BenMel) arm will show a CR1 rate of ≥ 65% ($CR1_B$), thus a difference of at least 15 percentage points.

With $CR1_A$ and $CR1_B$ being the (true) success rates in the Mel arm and in the BenMel arm, respectively, the hypotheses are:

H0: CR1 BenMel chemotherapy = CR1 Mel.

H1: CR1 BenMel chemotherapy ≥ CR1 Mel is 0.50.

Applying a one-sided significance level of 20%, 60 patients will be needed in each group to have 80% power to reject the null hypothesis of no difference between the CR1 rates of the treatment arms using a t-test. Thus, a total of 120 evaluable patients are needed. The significance level actually achieved by this design is 0.2057. All statistical analysis for sample size calculations were performed using the software package PASS 11.

For statistical analysis of this study, continuous endpoints will be summarized using descriptive statistics including mean, median, standard deviation, first and third quartiles, minimum and maximum values, and where appropriate by graphical techniques (e.g. histogram, box plot). For categorical endpoints, the number and percentage of patients in each category will be summarized. Where appropriate, a two-sided 95% confidence interval for the proportion will be reported. The primary endpoint in the two groups will be tested using a t-test. Progression free survival and overall survival will be assessed using Kaplan-Meier plots and log-rank test.

11.3 Randomization

Randomization is performed by the coordinating study nurse, the specifically designed study nurse or his/her replacent of the Klinische Forschungseinheit Onkologie, University Hospital/Inselspital, 3010 Bern. Randomisation will be performed using REDCap software. Two stratification parameters (response and renal function) will be applied. Patients can be registered 24h/7days.

11.4 Populations for Analysis

All patients randomised to treatment who have taken at least one dose of study medication will be considered evaluable and will be included in the evaluation of safety. The entire analysis will be on an intention-to-treat basis (ITT). The ITT set includes all randomized patients in the groups to which they

were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. The evaluation of efficacy will be based on the intention to treat (ITT) population.

11.5 Planned Analyses / Analytical Methods

All analyses will be on an intention-to-treat basis (ITT). All other statistical testing will be two-tailed at the 5% level of significance. The final analysis of the study will be initiated 12 months after inclusion of the last study patient. No subgroup analysis is planned. No interim analysis is planned. Safety analysis will be performed at the end of the study. No data safety monitoring board is planned in this study.

11.6 Analysis of demographics and baseline characteristics

Continuous measurements (e.g. age) will be summarized using n, mean, standard deviation (SD), median, minimum and maximum while discrete measurements (e.g. sex) will be summarised using frequency counts and percentages. No formal statistical testing will be performed on these data.

11.7 Analysis of primary efficacy parameter

This is a superiority trial (see also section 11.2). The study aims to show an improvement by 15% of the rate of complete remission (CR1) 60 days after ASCT in myeloma patients. Day 60 CR1 for the control arm (Mel) is assumed as 50% and for experimental arm (BenMel) as 65%. The hypotesis for the primary endpoint will be tested using one-sided t-test. The trial will be considered statistically positive, if the p-value for the comparison of the CR1 rates 60 days after ASCT between the arms is <0.20.

11.8 Analysis of secondary efficacy parameters

For the description of quantitative variables, median and mean values will be used as well as standard deviations, minimum and maximum values. For qualitative variables such as hematologic recovery and engraftment after three months, percentages and absolute frequency will be indicated. Early and late toxicities, particularly renal toxicity, will be compared using Fishers Exact Test tests. Survival rates (OS; PFS) will be assessed after 12 months.

11.9 Analysis of safety

Acute and late toxicities will be graded and described using the highest grade observed.

11.10 Statistical criteria of termination of trial

Given the existing (own and by others) data on the promising tolerance and efficacy of the experimental treatment (BenMel chemotherapy), no stopping rules or discontinuation criteria are planned in this trial for individual participants, for parts of the trial and for the entire trial.

11.11 Deviation(s) from the original statistical plan

No major deviation(s) from the original statistical plan are to be expected.

11.12 Handling of missing data and drop-outs

The design of the trial does not consider a relevant drop-out rate, thus a toal of 60 patients are supposed to be included in each of the two treatment arms.

12 QUALITY ASSURANCE AND CONTROL

The following procedures guarantee quality of trial conduct:

- Reviews of protocol and forms according to standard operating procedures.
- No paper CRFs will be used. Data will be entered into a database using the REDCap system.

Computerized consistency checks will be performed.

- Data review by the primary local investigator or a delegated person.
- Safety monitoring.
- Validation of database and statistical analysis.
- Accountability of study drugs.
- Requirements for potential sub-investigators for participation: signed and dated CV.

12.1 Data handling and record keeping / archiving

Source data are kept available for auditing and monitoring by the competent authorities.

The randomization list is concealed from any personnel involved in patient recruitment.

12.1.1 Case Report Forms

No paper CRFs will be used. Data will be entered into a database using the REDCap system. Computerized consistency checks will be performed. eCRFs will be kept current to reflect subject status at each phase during the course of study. Participants will not be identified in the eCRF by name or initials and birth date. Appropriate coded identification, e.g. participant number will be used (e.g. combination of initials and year of birth). A defined study nurse will be identified to be authorized to perform eCRF entries, and it will be assured that any authorized person can be identified.

12.1.2 Specification of source documents

Source data will be available at the site to document the existence of the study participants. Source data will include the original documents relating to the study, as well as the medical treatment and medical history of the participant. The path where to find all the source documents/data will be summarized in a form called “Source Data Location List”. Only authorized study staff can access to this document and manage it.

12.1.3 Record keeping / archiving

All study data will be archived in the center for a minimum of 10 years after study termination or premature termination of the clinical trial. The investigator will retain copies of the patient trial records (patient informed consent statement, laboratory printouts, drug transportation and destruction forms, and all other information collected during the trial) and documentation until at least 10 years after the termination of the trial. In the event that the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer will be given in written to the EC.

12.1.4 Data Management System

No paper CRFs will be used. Data will be entered into a database using the REDCap system. Computerized consistency checks will be performed. eCRFs will be kept current to reflect subject status at each phase during the course of study. Participants will not be identified in the CRF by name or initials and birth date. Appropriate coded identification, e.g. participant number will be used (e.g. combination of initials and year of birth). A defined study nurse will be identified to be authorized to perform eCRF entries, and it will be assured that any authorized person can be identified.

12.1.5 Data security, access and back-up

The database used will be based on the REDCap software. Access to database information will be restricted to the Principle investigator, to the data management team and to the responsible statistician. Changes to database entries as well as user information will be documented using audit trial function. Data entries will only be made by authorized personnel of the data management team. Patient data are entered anonymously using unique patient identification number and not using full name or complete date of birth. Key (patient identification log) to get information about patient identity is only available at treatment site of patient. The key will not be available to sponsor (with exception of patient data from site of sponsor-investigator) and third parties.

12.1.6 Analysis and archiving

All study data will be archived in the center for a minimum of 10 years after study termination or premature termination of the clinical trial. The investigator will retain copies of the patient trial records (eCRFs, patient informed consent statement, laboratory printouts, drug transportation and destruction forms, and all other information collected during the trial) and other relevant documentation (protocol, contracts etc.) until at least 10 years after the termination of the trial. In the event that the investigator retires or changes employment, custody of the records may be transferred to another suitable person who will accept responsibility for those records. Notice of such transfer will be given in written to the Sponsor and CEC.

12.1.7 Electronic and central data validation

Computerized and manual consistency checks will be performed.

12.2 Monitoring

The clinical trial unit (CTU) in Berne will perform monitoring of this trial. The monitors will be allowed to inspect the various records of the trial in accordance with local requirements. The monitor will maintain patient confidentiality. Source data verification of the Informed Consent will be performed for every patient and of the following data in 20% of the patients

- Inclusion/exclusion criteria.
- Serious Adverse Events (SAE).
- Primary endpoint.
- Accountability of study drugs.

12.3 Audits and Inspections

Regulatory authorities and delegates of the local Ethic Committees have the right to perform inspections and to verify original data. The investigators are obliged to actively participate during an audit or inspection. They have to ensure that all required source data and collected patient data are made available during an audit or inspection and that adequate facilities are provided for the audit or inspection. Access to source data verification has to be provided within a reasonable peiod of time, In case of an announcement of an inspection, the investigator has to inform the Sponsor promptly.

12.4 Confidentiality, Data Protection

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. All patients will be informed as to the strict confidentiality of their patient data, which will not be handed over to non-authorized third parties. However, they will also be informed and have given written informed consent that their medical records (anonymised data) may be reviewed for trial, scientific or monitoring purposes by authorized individuals other than their treating physicians.

12.5 Storage of biological material and related health data

No samples are stored in this study, and no biobank will be involved in this study.

13 PUBLICATION AND DISSEMINATION POLICY

The Principal Investigator will be responsible to publish the data of the trial in a peer-reviewed journal within 12 months after study completion. All study data collected will be kept confidential by all investigators prior to publication. Release of any abstract, manuscript or presentation will be shared and discussed between the Principal Investigator and Co-investigators. The company supplying the study medication has the right to review manuscripts and abstracts prior to submission for publication.

The Principle Investigator agrees to inform the company supplying the study medication about any impending publication and release of any abstract, relating to the outcome of the trial. Without prejudice to the Principle Investigator’s autonomy in respect to the publication of the results of the trial, the Principle Investigator agrees to provide to the companies the proposed manuscript in advance at least

thirty and abstracts at least fourteen days before. The Supplier may propose changes to the text up to twenty-eight days from receipt of the manuscript and up to twelve days from receipt of the abstract. The Principle Investigator shall respond in good faith to any reasonable and justified requested revisions of the manuscript, always provided that the Principle Investigator shall have the final say in deciding on the contents and wording of the text. The Principle Investigator shall give appropriate acknowledgement to the Supplier's or its Associates employees, if applicable, in the publication.

14 FUNDING AND SUPPORT

14.1 Funding

This study is supported in Switzerland by a grant from the company Mundipharma Medical Company. Bendamustine hydrochloride is provided free of charge by the company Munidpharma Medical Company in Switzerland.

14.2 Other Support

No other support is available for this study.

15 INSURANCE

The Inselspital Berne is sponsor of this study. The insurance for patients in Switzerland will be provided by the Sponsor. A copy of the certificate is filed in each investigator site file and the trial master file.

16 APPENDICES

16.1 Appendix 1: Translated excerpt from CTC adverse events version v4.0

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Adverse event/ Toxizitäts-Grad	1 gering – Leicht	2 mäßig – deutlich	3 stark – ausgeprägt	4 lebensbedrohlich
Neutropenie	< LLN – 1500/mm³	< 1500 – 1000/mm³	< 1000 – 500/mm³	< 500/mm³
Thrombopenie	< LLN – 75.000/mm³	< 75.000 – 50.000/mm³	< 50.000 – 25.000/mm³	< 25.000/mm³
Anämie	Hb < LLN – 10.0 g/dl	Hb 10.0 – 8.0 g/dl	Hb 8.0 – 6.5 g/dl	Hb < 6.5 g/dl
Nausea	Appetitsverlust ohne Veränderung der normalen Essgewohnheiten	Nahrungsaufnahme etwas vermindert- , Kein Gewichtsverlust	Unzureichende orale Kalorien bzw. Flüssigkeitszufuhr; i.v. Flüssigkeits- zufuhr, parenterale Ernährung > 24h	Lebensbedrohliche Konsequenzen
Erbrechen	1 Episode in 24 h	2 – 5 Episoden in 24 h; i.v. Flüssigkeitszufuhr < 24 h	6 oder mehr Episoden in 24 h; i.v. Flüssigkeits- zufuhr bzw. parenterale Ernährung > 24 h	Lebensbedrohliche Konsequenzen
Diarrhoe	Anstieg auf < 4 Stühle pro Tag über baseline	Anstieg auf 4-6 Stühle pro Tag über baseline; i.v. Flüssigkeitszufuhr < 24 h; beeinträchtigt Alltagsaktivitäten nicht	Anstieg über 7 Stühle pro Tag über baseline; i.v. Flüssigkeitszufuhr > 24 h; stationäre Aufnahme; beeinträchtigt Alltagsaktivitäten	Lebensbedrohliche Konsequenzen d. Diarrhoe
Fatigue	Leichte Fatigue; stärker als bei baseline	Mäßige Fatigue; beeinflusst Ausübung einiger Aktivitäten	Schwere Fatigue; Alltagsaktivitäten beeinträchtigt	Inaktivierend
Mukositis klin. Untersuchung	Erythem der Schleimhaut	Nicht konfluierende Ulzerationen od. Pseudomembranen	Konfluierende Ulzerationen od. Pseudomembranen; Blutung bei Minimaltrauma	Gewebsnekrose; signifikante spontane Blutung; lebensbedrohliche Konsequenzen
Neuropathie Sensorisch	Abgeschwächte Sehnenreflexe oder Parästhesien; keine Funktions-Einschränkung	Veränderung der Sensorik od. Parästhesien; Funktions-Einschränkung, jedoch Alltagsaktivität nicht beeinträchtigt	Veränderung der Sensorik od. Parästhesie; Alltagsaktivität beeinträchtigt	Inaktivität
Infektion – Febrile Neutropenie	---	---	Bestehende febrile Neutropenie	Lebensbedrohliche Konsequenzen (z.B. septischer Schock, Hypotension, Acidose, Nekrose)
Allergien	Transienter Rush Fieber< 38°	Rush, Urtikaria, Dyspnoe Fieber>38°	Symptomatische Bronchospasmen die intravenöse Medikation erfordern, Hypotension	Anaphylaxie

Schmerzen	Leicht, keine Funktionseinschränkung	Mittel mit Funktionseinschränkung	Schwer mit massiver Funktionseinschränkung	
Dysphagia	Symptomatisch, kann normale Ernährung zu sich nehmen	Symptomatisch, mit veränderten Ess- und Schluckgewohnheiten; i.v. Flüssigkeitszufuhr < 24 h	Symptomatisch mit stark veränderten Ess- und Schluckgewohnheiten; i.v. Flüssigkeitszufuhr, parenterale Ernährung >24 h	Lebensbedrohliche Konsequenzen (z.B. Obstruktion, Perforation)
Gewichtsverlust	5 – < 10 % von Baseline	10 – < 20 % von Baseline; Zusatzernährung indiziert	> 20 % von Baseline; PEG-Sonde oder parenterale Ernährung indiziert	___
Soor	___	Lokalisiert; lokale Therapie nötig	i.v. Intervention nötig; Radiologischer oder operativer Eingriff nötig	Lebensbedrohliche Konsequenzen (z.B. septischer Schock, Hypotonus, Acidose, Nekrose)

16.2 Appendix 2: Performance status scale (ECOG)

0	normale Aktivität möglich ohne Einschränkung
1	Einschränkung bei körperlich anstrengender Tätigkeit aber leichte Tätigkeiten möglich und keine Bettlägerigkeit
2	nicht arbeitsfähig, selbständig, tagsüber weniger als 50% Ruhe bzw. Hinlegen erforderlich
3	Selbstversorgung sehr eingeschränkt möglich, tagsüber mehr als 50% Ruhe bzw. Hinlegen erforderlich, Pflege bzw. Hilfe erforderlich
4	bettlägerig und völlig pflegebedürftig
5	tot

16.3 Appendix 3: Response criteria

The response criteria used in this study are modified. As a basis, the Bladé Response Criteria for patients diagnosed with Multiple Myeloma [58] are used for definition of response, relapse and progression in patients with multiple myeloma treated by high dose therapy and stem cell transplantation.

Complete Response (CR):

Requires all of the following

- Absence of the original monoclonal paraprotein (M-gradient) in the serum by immunofixation. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- Normalized light chain ratio in the serum.
- < 5% plasma cells in a bone marrow aspirate and bone biopsy if biopsy / aspirate are performed. A bone marrow examination is not needed for assessing CR.
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
- Disappearance of soft tissue plasmocytomas.

Stringent Complete Response (sCR):

Requires all of the following

- All criteria above defining complete response (CR)
- Bone marrow: minimal residual disease (MRD) is assessed by flow cytometry from bone marrow samples, and MRD negativity is required for sCR. sCR is defined as less than 50 aberrant plasma cell events, and at least 200'000 cell events need to have been analysed.

Very Good Partial response (VGPR):

Requires all of the following

- ≥ 90% reduction in the level of the serum monoclonal paraprotein (M-gradient and light chain).
- For patients with non secretory myeloma only, ≥ 50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed,
- No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Partial response (PR):

Requires all of the following

- ≥ 50% reduction in the level of the serum monoclonal paraprotein (M-gradient and light chain).
- For patients with non secretory myeloma only, ≥ 50% in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed,
- ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Minimal response (MR):

Requires all of the following

- 25-49% reduction in the level of the serum monoclonal paraprotein (M-gradient and light chain).
- For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed.
- No increase in the size or number of lytic bone lesions (development of a compression fracture does not exclude response).

No change (NC):

- Not meeting the criteria for either minimal response or progressive disease

Relapse from CR:

Requires at least one of the following

- Reappearance of serum paraprotein (M-gradient or light chain) on immunofixation or routine electrophoresis confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
- ≥ 5% plasma cells in a bone marrow aspirate or on trephine bone biopsy.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypocalcaemia (corrected serum calcium > 2.8 mmol/l) not attributable to any other cause.

Progressive disease (for patients not in CR):

Requires one of more of the following

- > 25% increase in the level of the serum monoclonal paraprotein (M-gradient or light chain) which must also be an absolute increase of at least 5g/l (M-gradient) and confirmed by at least one repeated investigation.
- > 25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy which must be also an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypocalcaemia (corrected serum calcium > 2.8 mmol/l) not attributable to any other cause.

16.4 Appendix 4: HCTCI score

Comorbidity	Explanation	HCT-CI score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiac	Coronary artery disease, congestive heart failure, myocardial infarction or EF < 50%	1
IBD	Crohn's disease or ulcerative colitis	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics	1
CVD	Transient ischemic attack or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild[1]	Chronic hepatitis: bilirubin >ULN to 2.0 × ULN and AST/or ALT >ULN to 3.0 × ULN lasting for at least 2 months	1
Obesity	Patients with a body mass index >35 kg/m^2	1
Infection	Requiring treatment after day 0	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/severe renal	Serum creatinine > 180 µmol/lor dialysis, or prior renal transplantation	2
Moderate pulmonary	DLCO and FEV1 66–80% or dyspnea on slight activity	2
Prior solid tumor	Treated at any time point in the patient's history, excluding non-melanoma skin cancer	3
Heart valve disease	Except mitral valve prolapse	3
Severe pulmonary	DLCO and FEV1 ≤65% or dyspnea at rest or requiring oxygen	3
Moderate/severe hepatic	Liver cirrhosis, bilirubin >ULN to 2.0 × ULN and AST or ALT >ULN to 3.0 × ULN lasting for at least 2 months	3

Abbreviations: AST/ALT=aspartate aminotransferase/alanine aminotransferase; CTD=connective tissue disease; CVA=cerebrovascular disease; DLCO=diffusion capacity of carbon monoxide; EF=ejection fraction; FEV1, forced expiratory volume in 1 second; HCT-CI=hematopoietic cell transplantation-specific comorbidity index; IBD=inflammatory bowel disease; RA=rheumatoid arthritis; SLE=systemic lupus erythematosis; ULN=upper limit of normal. [1]AST or ALT has to be measured.

16.5 Appendix 5: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce

or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial

provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community l eaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for

involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

16.6 Appendix 6: Fragebogen zur Lebensqualität EORTC QLQ-C30

UPN: ……... ☐ vor ASCT ☐ 3 Monate nach ASCT

Hier möchten wir Sie bitten, die Kästchen der Fragen so genau wie es Ihnen möglich ist, anzukreuzen. Herzlichen Dank!

---

1) Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z. B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

2) Bereitet es Ihnen Schwierigkeiten einen längeren Spaziergang zu machen?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

3) Bereitet es Ihnen Schwierigkeiten eine kurze Strecke außer Haus zu gehen?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

4) Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

5) Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

6) Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

7) Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

8) Waren Sie kurzatmig?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

9) Hatten Sie Schmerzen?
   ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

10) Mussten Sie sich ausruhen?
    ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

11) Hatten Sie Schlafstörungen?
    ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

12) Fühlten Sie sich wach?
    ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

13) Hatten Sie Appetitmangel?
    ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

14) War Ihnen übel?
    ☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

15) Haben Sie erbrochen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

16) Hatten Sie Verstopfung?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

17) Hatten Sie Durchfall?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

18) Waren Sie müde?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

19) Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

20) Hatten Sie Schwierigkeiten sich auf etwas zu konzentrieren, z. B. auf das Lesen oder das Fernsehen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

21) Fühlten Sie sich angespannt?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

22) Haben Sie sich Sorgen gemacht?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

23) Waren Sie reizbar?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

24) Fühlten Sie sich niedergeschlagen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

25) Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

26) Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

27) Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

28) Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

29) Hatten Sie Knochenschmerzen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

30) Hatten Sie Rückenschmerzen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

31) Hatten Sie Schmerzen in der Hüfte?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

32) Hatten Sie Schmerzen in den Armen oder Schultern?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

33) Hatten Sie Brustschmerzen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

34) Wenn Sie Schmerzen hatten, verstärkten sie sich bei körperlicher Tätigkeit?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

35) Fühlten Sie sich schläfrig?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

36) Waren Sie durstig?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

37) Fühlten Sie sich krank?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

38) Hatten Sie einen trockenen Mund?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

39) Hatten Sie Haarausfall?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

40) Nur bei Haarausfall ausfüllen:
Hat Sie der Haarausfall belastet?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

41) Verspürten Sie ein Kribbeln in Händen oder Füssen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

42) Fühlten Sie sich unruhig oder aufgeregt?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

43) Hatten Sie saures Aufstossen oder Sodbrennen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

44) Hatten Sie brennende oder entzündete Augen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

45) Fühlten Sie sich wegen Ihrer Erkrankung oder Behandlung körperlich weniger anziehend?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

46) Haben Sie sich Gedanken über Ihre Krankheit gemacht?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

47) Befürchteten Sie, sterben zu müssen?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

48) Haben Sie sich Sorgen über Ihre künftige Gesundheit gemacht?

☐ überhaupt nicht ☐ wenig ☐ mässig ☐ sehr

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 (= miserabel) und 7 (= optimal) an, die am besten auf Sie zutrifft

49) Wie würden Sie insgesamt Ihren Gesundheitszustand einschätzen?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

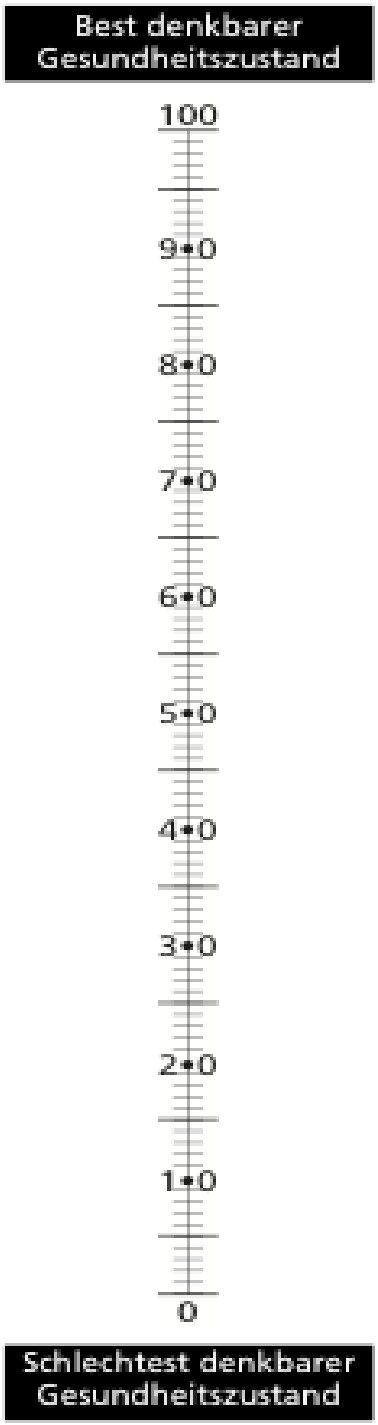
50) Wie würden Sie insgesamt Ihre Lebensqualität einschätzen?

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbare Gesundheitszustand ist mit einer „100“ gekennzeichnet, der schlechteste mit „0“.

Wir möchten Sie nun bitten, auf dieser Skala zu kennzeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand ist, indem Sie einen horizontalen Strich auf der Skala setzen.

Ihr aktueller Zustand



17 REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma: Intergroupe Francais du Myelome. N Engl J Med. 1996;335:91–97.
2. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol. 2006;24:929–936.
3. Bladé J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005;106:3755–3759.
4. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348:1875–1883.
5. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol. 2005;23:9227–9233.
6. Fermand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? results of a multicenter sequential randomized clinical trial. Blood. 1998;92:3131–3136.
7. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. Blood. 2004;104:3052–3057.
8. Fermand JP, Ravaud P, Chevret S, et al. Early versus late high dose therapy (HDT) and autologous peripheral blood stem cell transplantation in multiple myeloma (MM): results of a prospective randomized trial [abstract]. Blood. 1996;88(suppl 1):685a.
9. Rajkumar SV, Blood E, Vesole DH, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24:431–436.
10. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol. 2002;20:4319–4323.
11. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood. 2005;106:4050–4053.
12. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group [abstract]. J Clin Oncol. 2007;25(18S):LBA8025 *(ASCo Annual Meeting Abstracts)*.
13. Richardson P, Chanan-Khan A, Schlossman R, et al. A multicenter phase II trial of bortezomib in patients with previously untreated multiple myeloma: efficacy with manageable toxicity in patients with unexpectedly high rates of baseline peripheral neuropathy [abstract]. Blood. 2005;106:2548 *(ASH Annual Meeting Abstracts)*.
14. Richardson P, Jagannath S, Raje N, et al. Lenalidomide, Bortezomib, and dexamethasone (Rev/Vel/Dex) as front-line therapy for patients with multiple myeloma (MM): preliminary results of a phase 1/2 study [abstract]. Blood. 2007;110:187 *(ASH Annual Meeting Abstracts)*.
15. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24:431–436.
16. Rajkumar SV, Jacobus S, Callander N, et al. Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: analysis of

response, survival, and outcome with primary therapy and with stem cell transplantation [abstract]. J Clin Oncol. 2008;26:8504 *(Meeting Abstracts)*.

17. Harousseau JL, Mathiot C, Attal M, et al. Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantion (ASCT) in previously untreated multiple myeloma (MM): updated data from IFM 2005/01 trial [abstract]. J Clin Oncol. 2008;26:8505 *(Meeting Abstracts)*.
18. Cavo M, Zamagni E, Tosi P, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicindexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood. 2005;106:35–39.
19. Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232 [abstract]. Blood. 2007;110:77 *(ASH Annual Meeting Abstracts)*.
20. Sonneveld P, van der Holt B, Schmidt-Wolf IGH, et al. First analysis of HOVON-65/GMMG-HD4 randomized phase iii trial comparing bortezomib, adriamycine, dexamethasone (PAD) vs VAD as induction treatment prior to high dose melphalan (HDM) in patients with newly diagnosed multiple myeloma (MM) [abstract]. Blood. 2008;112:653 *(ASH Annual Meeting Abstracts)*.
21. Jagannath S, Durie BG, Wolf J, et al. Bortezomib therapy alone and in combination with dexamethasone for previously untreated symptomatic multiple myeloma. Br J Haematol. 2005;129:776–783.
22. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108:3289–3294.
23. Abdelkefi A, Ladeb S, Torjman L, et al. Single autologous stem-cell transplantation followed by maintenance therapy with thalidomide is superior to double autologous transplantation in multiple myeloma: results of a multicenter randomized clinical trial. Blood. 2008;111:1805–1810.
24. Ozegowski W, Krebs D. IMET3393 ([1methyl-5-bis-(b-chloroethyl)-aminobenz-imidazolyl-(2)]-butyric acid hydrochloride, a new cytotoxic agent from among the series of benzimidazole mustard compounds [in German]. Zbl Pharm 1971;110:1013–1019.
25. Ogura M, Uchida M, Taniwaki M, et al. Phase I and pharmacokinetic study of bendamustine in relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. Cancer Sci 2010;101:2054–2058.
26. Leoni LM, Bailey B, Reifert J, Bendall HH, Zeller RW, Corbeil J, Elliott G, Niemeyer CC. Bendamustine (Treanda) displays a distinct pattern of cytotoxicity and unique mechanism features compared with other alkylating agent. Clin Cancer Res 2008;14:309–317.
27. Roue G, L_opez-Guerra M, Milpied P, P_erez-Gal_an P, Villamor N, Montserrat E, Campo E, Colomer D. Bendamustine is effective in p53-deficient B-cell neoplasms and requires oxidative stress and caspase-independent signaling. Clin Cancer Res 2008;14:6907–6915.
28. Tageja N, Nagi J. Bendamustine: something old, something new. Cancer Chemother Pharmacol 2010;66:413–423.
29. Hartmann M, Zimmer C. Investigationof cross-link formation in DNA by thealkylating, cytostatic IMET 3106,3393 and 3943. Biochim Biophys Acta 1972;287:386–389
30. Haase D, Preiss R, Sohr R. Untersuchungen zur Plasmaeiweissbindung von Bendamustine (Cytostasan) und Ambazon. Z Klein Med 1990;45:1267–1272.
31. Preiss R, Sohr R, Matthias M, Brockmann B, Huller H. The pharmacokinetics of bendamustine (Cytostasan) in humans. Pharmazie 1985;40:782–784.
32. Chovan JP, Li F, Yu E, Ring SC. Metabolic profile of [(14)C] bendamustine in rat urine and bile:preliminary structural identification of metabolites. Drug Metab Dispos 2007;35:1744–1755.
33. Gandhi V. Metabolism and mechanism of action of bendamustine: rationales for combination therapy. Semin Oncol 2002;29(Suppl 13):4–11.

34. Owen JS, Melhem M, Passarell JA, D'Andrea D, Darwish M, Kahl B. Bendamustine pharmacokinetic profile and exposure response relationship in patients with indolent non-Hodgkin's lymphoma. Cancer Chemother Pharmacol 2010;66:1039–1049.
35. Teichert J, Sohr R, Hennig L, Baumann F, Schoppmeyer K, Nacetyl- L-cysteine S-conjugates of bendamustine and its sulfoxides in human bile after administration of bendamustine hydrochloride. Drug Metab Dispos 2009;37:292–301.
36. Bremer K. High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin's lymphomas. J Cancer Res Clin Oncol 2002;128:603–609.
37. Cephalon, Inc. Treanda_ [prescribing information] Bendamustine hydrochloride for injection for intravenous infusion. Cephalon, Inc: Frazer (PA), 2009 April. http://www.treanda.com/300-nhl-home.aspx.
38. Elefante A, Czuczman MS. Bendamustine for the treatment of indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Am J Health Syst Pharm 2010;67:713–723.
39. Knop S, Straka C, Haen M, Schwedes R, Hebart H, Einsele H. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica 2005;90:1287–1288.
40. Michael M, Bruns I, Bölke E, Zohren F, Czibere A, Safaian NN, Neumann F, Haas R, Kobbe G, Fenk R. Bendamustine in patients with relapsed or refractory multiple myeloma. Eur J Med Res 2010;15:13–19.
41. Damaj G, Malard F, Hulin C, et al. Efficacy of bendamustine in relapsed/refractory myeloma patients: results from the French compassionate use program. Leuk Lymphoma 2012;53:632–634
42. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma .Intergroupe Francais du Myelome. N Engl J Med 1996;335:91–97.
43. Moreau P., Facon T, Attal M, Hulin C, et al, Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial, Blood 2002; 99:731-735.
44. Shah N, Callander N, Ganguly S, Gul Z, Hamadani M, Costa L et al, Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation, Biol Blood Marrow Transplant 2015;21:1155-1166.
45. Mark TM, Reid W, Niesvizky R, Gergis U, Pearse R, Mayer S, Greenberg J, Coleman M, Van Besien K, Shore T. A phase 1 study of bendamustine and melphalan conditioning for autologous stem cell transplantation in multiple myeloma. Biol Blood Marrow Transplant 2013;19:831–837.
46. M Martino M, Tripepi G, Messina G, Vincelli I D, Console G, A G Recchia A G, M Gentile M, Molica S and Morabito F, A phase II, single-arm, prospective study of bendamustine plus melphalan conditioning for second autologous stem cell transplantation in de novo multiple myeloma patients through a tandem transplant strategy. Bone Marrow Transplantation 2016;51: 1197–1203 .
47. Breitkreutz I, Becker N, Benner A, Kosely F, Heining C, Hillengass J, Egerer G, Ho AD, Goldschmidt H, Raab MS. Dose-intensified bendamustine followed by autologous peripheral blood stem cell support in relapsed and refractory multiple myeloma with impaired bone marrow function. Hematol Oncol 2016;34(4):200-207
48. Visani G, Malerba L, Stefani PM, et al. BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. Blood 2011;118(12):3419–25.
49. Visani G, Stefani PM, Capria S, et al. Bendamustine, etoposide, cytarabine, melphalan, and autologous stem cell rescue produce a 72% 3-year PFS in resistant lymphoma. Blood 2014;124(19):3029–31.

50. Gilli S, Novak U., Mansouri Taleghani B., Baerlocher GM Leibundgut K, Banz Y, Zander T, Betticher D, Egger T, Rauch D, Pabst T. BeEAM conditioning with bendamustine replacing BCNU before autologous transplantation is safe and effective in lymphoma patients. Ann Hematol 2016; Dec 24. doi: 10.1007/s00277-016-2900-y [Epub ahead of print].
51. Napp Pharmaceuticals Limited. Levact 2.5 mg/ml powder for concentrate for solution for infusion. Summary of product characteristics [online]. www.medicines.org.uk/emc/medicine/23469.
52. Ponisch W, Mitrou PS, Merkle K, et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone – a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol 2006;132:205–212.
53. Ludwig H, Kasparu H, Leitgeb C, et al. Bendamustine, bortezomib- dexamethasone is an active and well tolerated regimen in patients with relapsed or refractory multiple myeloma. Blood 2014;123:985–991.
54. Mateos MV, Oriol A, Rosi~nol L, et al. Bendamustine, bortezomib and prednisone for the treatment of newly diagnosed multiple myeloma patients: results of a prospective phase 2 Spanish/Pethema trial. Haematologica 2015;100:1096-1102.
55. Ponisch W, Holzvogt B, Pl€otze M, et al. Bendamustine and prednisone in combination with bortezomib (BPV) in the treatment of patients with newly diagnosed/untreated multiple myeloma. J Cancer Res Clin Oncol 2014;140:1947–1956.
56. Grey-Davies E, Bosworth JL, Boyd KD, Ebdon C, Saso R, Chitnavis D, Mercieca JE, Morgan GJ, Davies FE. Bendamustine, thalidomide and dexamethasone is an effective salvage regimen for advanced stage multiple myeloma. Br J Haematol 2012;156:552–555.
57. Pozzi S, Badiali S, Corso A, et al. Bendamustine, low-dose dexamethasone, and lenalidomide (BdL) for the treatment of patients with relapsed multiple myeloma confirms very promising results in a phase I/II study. Blood 2013;122:3212
58. Bladé J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005;106:3755–3759.