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clinical trial protocol

– INDIGO –

prospective phase II trial to assess feasibility of individualized, model-guided optimization of proton beam treatment planning in patients with low grade glioma

multicentric, prospective interventional, randomized, observer blind two arm (active control), parallel group investigator-initiated phase II trial

Version 1.1 / 21.10.2022

Reg.-Nr.: TBA

principal investigator

Dr. Semi Harrabi
University Hospital Heidelberg
Im Neuenheimer Feld 400
69120 Heidelberg

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Abbreviations

AE	Adverse Event
CEBL	contrast enhancing brain lesion
CNS	central nervous system
CR	complete response
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	ethics committee
eCRF	electronic Case Report Form
FAS	full analysis set
FSI	First subject in
FU	follow up
GCP	good clinical practice
Gy	Gray
HIT	Heidelberg Ion-Beam Therapy Center
IMPT	Intensity Modulated Proton Therapy
ISF	Investigator Site File
ITT	intention to treat
LGG	low-grade glioma
LSI	Last subject in
LSO	Last subject out
MoCA	Montreal neurocognitive assessment
MRI	magnetic resonance imaging
NCI	national cancer institute
NCT	national center for tumor diseases
NTCP	normal tissue complication probability
OS	overall survival
PD	progressive disease
PFS	progression free survival
PP	per protocol
PR	partial response
PRO-	patient reported outcome
PRT	Proton Beam Therapy
PTV	Planning Target Volume
QoL	quality of life
RBE	relative biological effectiveness
RT	Radiotherapy
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMF	Trial Master File
WHO	world health organization

Responsibilities

Coordinating center:	**University Hospital Heidelberg** **Prof. Dr. Dr. Jürgen Debus** **-Head of the Department-** Dept. of Radiation Oncology Heidelberg Ion Beam Therapy Center (HIT) Im Neuenheimer Feld 400 69120 Heidelberg
Principal investigator:	**Dr. Semi Harrabi** Dept. of Radiation Oncology University Hospital Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg
Co-investigator:	**Prof. Dr. Mechthild Krause** **-head of the department-** Oncoray University Hospital Dresden Fetscherstraße 47 01307 Dresden
Participating centers:	**University Hospital Dresden** Oncoray Fetscherstraße 47 01307 Dresden
Clinical Trial Office:	**Dr. Adriane Hommertgen** Dept. of Radiation Oncology University Hospital Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg
Study nurse & documentation:	**Study Nurse Team** Dept. of Radiation Oncology University Hospital Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg
IT:	**Andreas Kudak** Dept. of Radiation Oncology University Hospital Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg
Trial Statistician:	**M.Sc. Christopher Büsch** Institute of Medical Biometry University Hospital Heidelberg Im Neuenheimer Feld 130.3

	69120 Heidelberg
Responsible Statistician:	**Dr. Johannes Krisam** Institute of Medical Biometry University Hospital Heidelberg Im Neuenheimer Feld 130.3 69120 Heidelberg
Data-Safety-Monitoring-Board:	**Dr. David Krug** Dept. of Radiation Oncology University Hospital Schleswig-Holstein Arnold-Heller-Straße 3 24105 Kiel **Prof. Dr. Marc Münter** Dept. of Radiation Oncology Katharinenhospital Kriegsbergstraße 60 70174 Stuttgart **Dr. Claudia Schmoor** Head of Biometry and Data Management Clinicical Trials Unit University Hospital Freiburg Stefan-Meier-Straße 26 79104 Freiburg

Summary

Title	INDIGO - prospective phase II trial to assess feasibility of model-guided optimization of proton beam treatment planning in patients with low grade glioma
Summary	Radiotherapy can be considered as standard treatment option for patients with **low grade glioma**. Typically, a dose of 45-54 Gy in conventional fractionation of 1.8-2 Gy is applied. Age of the patient, size and localization of the tumor as well as neurologic status can affect the choice of the appropriate irradiation modality. Irradiation with photons is still the predominantly used modality. Considering that the prognosis is typically favorable the prevention of late sequelae is of particular importance. **Proton beam therapy** (PRT) and its advantageous physical properties has the potential to further reduce the burden of treatment related side effects. However, in about 20 % of all patients, **late contrast-enhancing brain lesions** (CEBL) appear on follow-up MR images 6 – 24 months after treatment. At HIT in Heidelberg and at OncoRay in Dresden, CEBLs have been observed to occur at very distinct locations in the brain and treatment field. Retrospective analysis has elucidated potential key factors that lead to CEBL occurrence. However, avoidance of CEBLs is hardly feasible using conventional treatment planning strategies. **Model-aided risk avoidance** denotes the use of model-based CEBL risk calculations as an auxiliary tool for clinical treatment planning: Model-based risk calculations and risk reduction via software-based optimization help the clinician to minimize risk of CEBL occurrence during treatment planning. In a **randomized-controlled trial**, patients with low-grade glioma will be treated based on treatment plans that rely on either conventional planning strategies (control arm), or planning with model-aided risk avoidance (interventional arm). Through regular follow-up examinations during a period of at least 24 months post treatment, occurrence of CEBLs will be examined by MR imaging in all patients. The hypothesis will be tested that model-aided risk avoidance reduces the overall incidence of CEBLs.
Principal investigator / Trial Coordinator	Dr. Semi Harrabi
Clinical Trial Office	Dr. Adriane Hommertgen

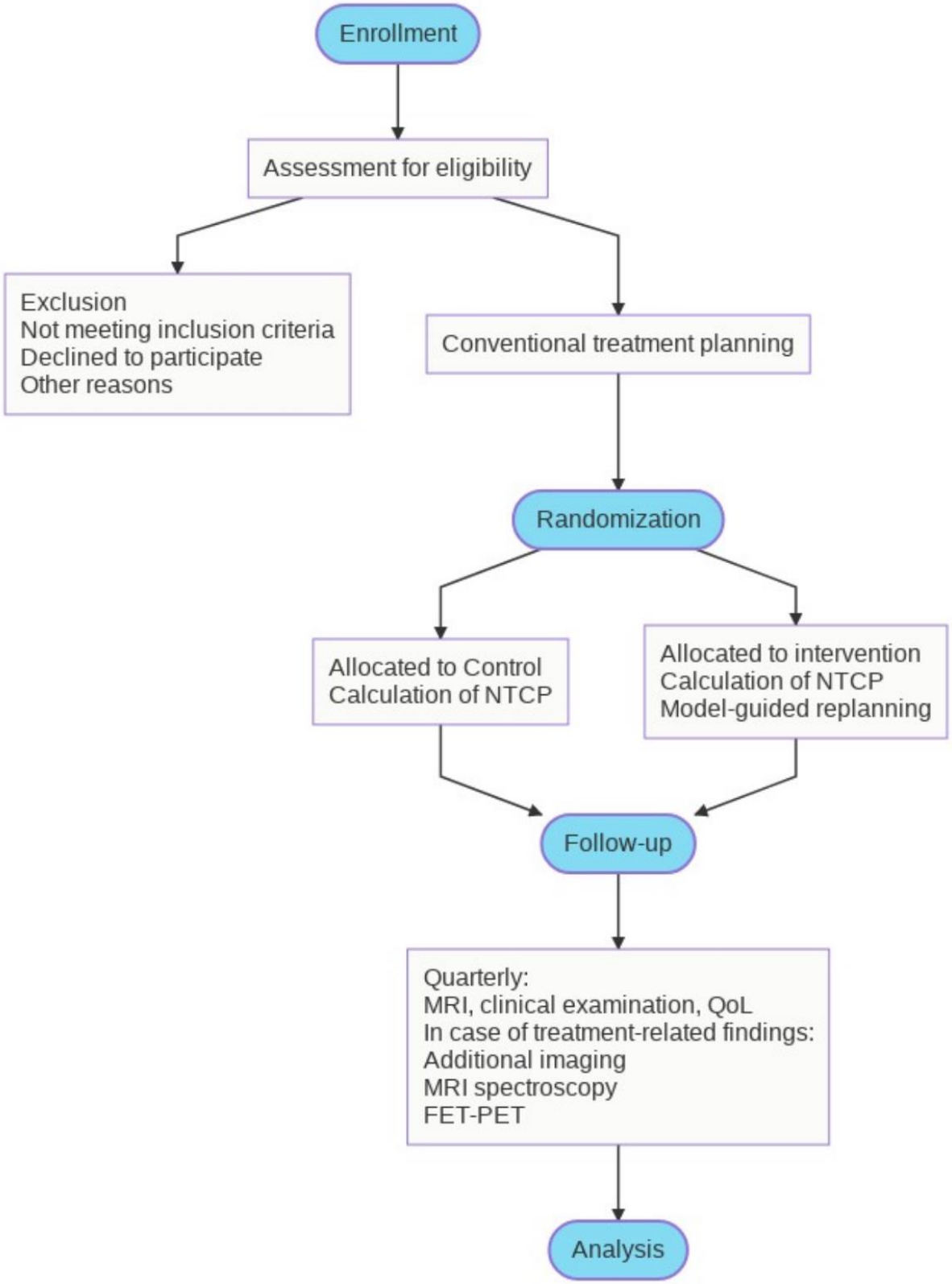
Trial population	**inclusion criteria**: - Age › 18 years - histologically proven low-grade glioma - indication for definitive or adjuvant radiotherapy - ability to understand character and personal consequences of the clinical trial - written informed consent **exclusion criteria**: - previous cerebral irradiation - contraindication for contrast-enhanced MRI - neurofibromatosis - participation in another clinical trial with competing objectives
Trial design	Multicentric prospective interventional, randomized, observer blind two arm (active control), parallel group investigator-initiated phase II trial with interim analysis to assess feasibility of model-aided optimization of proton beam treatment planning
Sample size	To be assessed for eligibility: n = 150 To be allocated to trial: n = 120 To be analyzed: n = 100
Trial treatment	Patients will be randomized to either conventional or model-aided treatment planning arm stratified by center. Both arms receive standard radiotherapy for patients with low grade glioma up to 54 Gy RBE.
Treatment technique	Protons, active raster-scanning, SBO/IMPT, model-guided re-planning
Trial hypotheses	Model-guided risk avoidance reduces the risk of contrast-enhancing brain lesions in low-grade glioma patients treated with proton-beam therapy. To formalize the statistical approach, the following notation will be used: p_{conv}/p_{aided}: cumulative incidence CEBL negative binomial rate within 24 months in the conventional / model-aided experimental group. The following test problem is defined: $H_0: p_{\text{aided}} \geq p_{conv}$ vs. $H_1: p_{\text{aided}} < p_{conv}$, which will be assessed at a one-sided significance level of 2.5 %.
Outcome(s)	**Primary endpoint**: cumulative incidence of contrast-enhancing brain lesions within 2 years. Contrast-enhancing brain lesions are defined as focal spots diagnosed by contrast-enhanced MRI within or adjacent to the irradiated high dose volume, but outside the initial tumor volume (independently diagnosed by two radiologists). **Key secondary endpoint(s)**: Incidence of radiation-induced brain injuries › CTC°II, progression-free survival, overall survival, safety.

	Assessment of safety: Safety will be assessed by the type, incidence, severity (graded by the NCT CTCAE Version 5.0) and relatedness of AEs to treatment.
Sample size calculation	Sample size calculation is based on the primary endpoint "cumulative incidence of contrast enhancing brain lesions (CEBL) observed within 24 months after PRT". Analyses based on own retrospective data showed that the primary endpoint is negative binomial distributed and that an 86% cumulative incidence CBL rate (of greater or equal than one), $p$conv , as well as dispersion parameter of Φ=0.2597 can be assumed in the conventional group. On the bases of additional experiments, a 60% reduction of $p$conv in the model-aided experimental group is assumed, hence $paided$=0.6∗$p$conv, when assuming the same dispersion parameter in both groups. For a fixed sample size design, the sample size required to achieve a power of $1-\beta$ of 80% for the one-sided negative binomial regression at a significance level of α=0.025 assuming the same dispersion-parameter in conventional and experimental group and a randomization allocation ratio of 1:1 as well as the above-mentioned assumptions, amounts to 2∗46=92 . It can be expected that including covariates of prognostic importance in the negative binomial regression model as defined for the confirmatory analysis (see Section 9) will increase the power as compared to no included covariates. A group-sequential design with interim analysis allowing to prematurely stop the trial for efficacy or futility (using O'Brien-Fleming- type alpha and beta spending functions) is performed. This will allow to prematurely declare the treatment as effective in case of a substantially large treatment effect, as well as to stop the trial in case the treatment does not prove to be effective. The interim analysis is conducted after half of the patients did reach the primary endpoint. Additionally, the study can be stopped in the interim analysis due to futility. These assumptions would lead to a sample size of 98 (49 per group) without consideration of drop-outs or premature death within 12 months after randomization. With an assumed 18% drop-out rate, 120 patients (60 per group) are needed to achieve a power of 80%. Calculations were performed with R packages gscounts (Mütze et al. 2018) for sample size calculations and MASS (Venables & Ripley 2002) for estimation of the dispersion parameter. R version 4.1.2 was used.
Statistical analysis	**Primary Endpoint**

	The primary endpoint of this clinical trial is the cumulative incidence of CEBLs within 24 months after PRT measured by quarterly contrast enhanced MRI of the brain. The null hypothesis is tested with a two-level negative binomial regression model including the covariates treatment, prescribed dose, and the random factor center at an overall one-sided significance level of $\alpha = 0.025$ is applied. Confirmatory analysis of the primary endpoint will be primarily based on the Full Analysis Set. An evaluation of the per protocol and safety set is performed additionally. Also, multiple sensitivity analyses of the primary endpoint will be performed. A group-sequential design with interim analysis according to O'Brien-Fleming type alpha and beta spending decision boundaries is performed. The interim analysis is conducted after n = 49 patients did reach the primary endpoint within 24 months, which is half of the planned total sample size not considering dropouts or premature deaths. No sample size recalculation is performed at the interim analysis. This design allows early stopping of the trial under control of the overall type I error rate, or, alternatively, a stop for futility. Results of the interim analysis will be presented to the Data Safety and Monitoring Board (DSMB) who will advise the Steering Committee of the trial to either terminate or to continue the trial. **Secondary endpoints** The secondary endpoints overall survival and progression-free survival will be analyzed using Kaplan-Meier-Curves. The 1-year and 2-year survival rates as well as the median survival rate will be provided alongside two-sided 95%- confidence intervals. Furthermore, progression-free-survival and overall survival will be descriptively assessed at the interim analysis using Kaplan-Meier curves. A Cox regression frailty model will be conducted to compare the two treatment groups. The other secondary endpoints and the patients' characteristics will be displayed by descriptive measures grouped by treatment group. Continuous variables will be described using number non-missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum. For binary or categorical variables absolute and relative frequencies will be provided. **Safety analysis** For safety analysis, laboratory parameters, all AEs and all SAEs will be analyzed via descriptive statistical methods in the safety population. The

	safety analysis includes calculation of frequencies and rates of complications and serious adverse events together with corresponding 95%-confidence intervals. In addition, tolerability and dosing will be described by numbers of patients in whom treatment was given as planned, delayed or permanently stopped. Detailed procedures of the interim and final analysis will be specified in separate Statistical Analyses Plans (SAP), which will be finalized before interim/final database lock.
Trial duration	Overall duration: 60 months Minimal Follow-up: 24 months FSI (first subject in): 01/2023 50% accrual: 09/2024 LSI (last subject in): 01/2026 LSO (last subject out): 01/2028
Participating sites	University Hospital Heidelberg - HIT University Hospital Dresden - OncoRay

Flowchart


Enrollment
Assessment for eligibility
Exclusion
Not meeting inclusion criteria
Declined to participate
Other reasons
Conventional treatment planning
Randomization
Allocated to Control
Calculation of NTCP
Allocated to intervention
Calculation of NTCP
Model-guided replanning
Follow-up
Quarterly:
MRI, clinical examination, QoL
In case of treatment-related findings:
Additional imaging
MRI spectroscopy
FET-PET
Analysis

Treatment schedule	baseline visit	weekly during RT	end of RT	FU 1 6 weeks post RT	FU 2 3 months post RT	FU 3 6 months post RT	FU 4 9 months post RT	FU 5 12 months post RT	FU 6 15 months post RT	FU 7 18 months post RT	FU 8 21 months post RT	FU 9 24 months post RT
Informed consent	√											
Inclusion/ exclusion criteria	√											
Demographic information	√											
Anamnesis/ clinical examination	√			√	√	√	√	√	√	√	√	√
randomization	√											
AEs und SAEs	√	√	√	√	√	√	√	√	√	√	√	√
Symptoms/toxicity	√	√	√	√	√	√	√	√	√	√	√	√
MRI	√			√	√	√	√	√	√	√	√	√
QLQ-C30 & QLQ-BN20	√		√			√		√				√
PRO-CTCAE	√	√	√	√	√	√	√	√	√	√	√	√
(Cognitive assessment)	√		√			√		√				√

1 Introduction

1.1 Scientific background

Low-grade glioma (LGG) represent typically slowly growing primary brain tumors with world health organization (WHO) grade I or II who affect young adults around their fourth decade. Radiological feature on MRI is a predominantly T2 hyperintense signal, LGG show typically no contrast uptake. Radiotherapy plays an important role in the treatment of LGG. However, not least because of the good prognosis with long term survivorship the timing of radiotherapy has been discussed controversially. In order to avoid long term sequelae such as neurocognitive impairment, malignant transformation or secondary neoplasms initiation of irradiation was often postponed as long as possible [1].

The use of proton beam therapy (PRT) has constantly increased over the last decade. On account of the low entrance dose and effectively no dose distally, PRT most commonly utilizes just one to three radiation beams. Since this allows highly conformal treatment fields with very low integral dose absorbed by the surrounding healthy brain tissue, PRT seems to be a very promising technique to improve the clinical outcome of patients with LGG even further [2]. Corresponding dosimetric data have illustrated significantly decreased doses to various normal tissues for a variety of central nervous system (CNS) tumors independent of their localization within the brain [3].

However, there is lack of data in the literature regarding the risk of radiation induced contrast enhancement following PRT. Proton beam therapy is still considered as sparsely ionizing irradiation with a similar biological effect as photons. Currently, in clinical practice the physical dose of protons is multiplied with a fixed relative biological effectiveness (RBE) factor of 1.1 to obtain the biological effective dose in units of Gray RBE [4]. There is an intensifying controversial discussion whether this fixed RBE of 1.1 should further be used for protons or not.

1.2 Trial rationale

Since patients with low grade glioma are expected to become long-term survivors, the prevention of long-term sequelae is particularly important. In addition to disease progression, also treatment related side effects such as decline of neurocognitive function, endocrine impairment or sensorineural deficits can have a negative impact on patient's quality of life.

Owing to the biophysical properties of protons with an inverse depth dose profile compared to photons and a steep dose fall of to the normal tissue, there is a strong rationale for the use of PRT in the treatment of patients with low-grade glioma. Although data from large randomized trials are still missing there is increasing evidence from smaller prospective trials and retrospective analyses that the expected advantages indeed transform into clinical advantages [5,6].

However, in about 20 % of all patients, late contrast-enhancing brain lesions (CEBL) appear on follow-up MR images 6 – 24 months after treatment [7]. At HIT in Heidelberg and at OncoRay in Dresden, CEBLs have been observed to occur at very distinct locations in the brain and relative to the treatment field. Retrospective analysis has elucidated potential key factors that lead to CEBL occurrence. However, avoidance of CEBLs is hardly feasible using conventional treatment planning strategies. Model-aided risk avoidance denotes the use of model-based CEBL risk calculations as an auxiliary tool for clinical treatment planning: Model-based risk calculations and risk reduction via software-based optimization help the clinician to minimize risk of CEBL occurrence during treatment planning.

1.3 Benefit / risk assessment

Patients will be treated according to international accepted standard protocols. Target volume definition and dose prescription will be the same in both treatment arms. It is recommended that patients should receive a dose of 45 – 54 Gy in 1.8 – 2 Gy fractions [8-10]. Proton beam therapy is an established treatment option for patients with low grade glioma. The possible side effects of the treatment in this study correspond to those of conventional photon radiotherapy. However, the frequency of asymptomatic treatment related changes seen on MRI follow-up is higher compared to conventional radiotherapy. The avoidance of CEBL occurrence has large potential benefit for the patients. In severe cases, they may develop into brain necrosis and lead to significant reduction in QoL and neurocognitive performance. The potential harm is ameliorated by the fact that CEBLs can often not be clearly distinguished from tumor progression. False classification may lead to either untreated tumor recurrence or to unnecessary treatment with radiation or chemotherapy of an already impaired brain tissue, causing further deterioration.

1.4 Risk/Benefit Consideration with reagard to SARS-CoV-2 pandemic

The specified measures and guidelines within the Covid-19 pandemic of the respective study centers are strictly adhered to in the INDIGO trial. Participation in the study does not lead to an increased risk with regard to SARS-CoV-2, since the number of fractions and thus the number of days on which the patient is irradiated on site is not increased.

Therefore, despite the current overall situation, study initiation is reasonable considering the following aspects. The study education and the study inclusion take place under observance of the hygiene measures. Also, in the further course of the study, no additional, purely study-specific appointments are planned beyond the standard procedures required for patients with brain metastases. If a study patient becomes infected with SARS-CoV-2 during the study participation or if there is a justified suspicion, the health department and the principal investigator and study coordinator and the clinic director and local study director of the respective study center must be informed immediately. In this case, the regulations of the respective clinic for the handling of patients with evidence or reasonable suspicion of a Covid-19 infection apply. If infection occurs during radiotherapy, early discontinuation of therapy is usually required until complete and proven recovery of the patient. If infection occurs during the follow-up interval, the follow-up appointment can be postponed until proven recovery of the patient. If there are changes in the study schedule due to the pandemic, the study participants will be informed by the principal investigator or his representative.

2 Trial objectives

2.1 Primary objectives

The primary endpoint of this clinical trial is the cumulative incidence of contrast enhancing brain lesions observed within 24 months after PRT measured by quarterly contrast enhanced MRI of the brain. In case patients are not followed up for 24 months, e.g. due to death, loss to follow-up or withdrawal of informed consent, but are observed for at least 12 months after randomization, their primary endpoint will be set to the number of lesions observed until last date of follow-up. Otherwise, e.g. if the follow-up of a patient is less than 12 months, the primary endpoint will be set to missing.

2.2 Secondary objectives

- incidence of radiation-induced brain injuries › CTC°II
- progression-free survival
- overall survival
- safety
- patient reported outcome (PRO-CTCAE)
- quality of life (QLQ-C30 and QLQ-BN20)

3 Trial design and schedule

3.1 Trial design

Multicentric, prospective interventional, randomized, observer blind two arm (active control), parallel group, investigator-initiated phase II trial with interim analysis to assess feasibility of model-guided optimization of proton beam treatment planning.

3.2 Trial duration and schedule

Overall duration	60 months
Minimal Follow-up:	24 months
FSI (first subject in):	01/2023
50% accrual:	06/2024
LSI (last subject in):	01/2026
LSO (last subject out):	01/2028
Recruitment period	01/2023 – 01/2026

3.3 Participating centers

coordinating center:

Prof. Dr. Dr. Jürgen Debus

University Hospital Heidelberg

Heidelberg Ion Beam Therapy Center (HIT)

Im Neuenheimer Feld 400

69120 Heidelberg

Principal investigator and responsible coordinator for this trial is Dr. Semi Harrabi, department radiation oncology at Heidelberg University Hospital. Administrative trial coordinator is Dr. Adriane Hommertgen, Head of the Clinical Trial Office, department radiation oncology at Heidelberg University Hospital. Trial documentation is performed by the department's Study Nurse Team, clinical trial office department radiation oncology at Heidelberg University Hospital. Biometrical planning and statistical analysis are conducted by Christopher Büsch M.Sc., institute for medical biometry and informatics, Heidelberg University Hospital. Responsible statistician is Dr. Johannes Krisam, institute for medical biometry and informatics, Heidelberg University Hospital.

Further participating centers are:

University Hospital Dresden
Oncoray
Fetscherstraße 47
01307 Dresden

3.3.1 Requirements for participating centers

Participating centers are required to successfully perform a dummy run for model-aided optimized re-planning before initiation of the trial.

4 Trial population

The predictive model used in this study is based on retrospective data from low-grade glioma patients. Predictions from the model were used in the design of the trial to calculate e.g. sample size. Therefore, a restriction to the same, homogeneous population seems necessary. Patients with the diagnosis of low-grade glioma and the indication for radiotherapy will be evaluated and screened for the protocol. All patients fulfilling the inclusion and exclusion criteria will be informed about the study.

4.1 Inclusion criteria

- ✓ Age › 18 years
- ✓ histologically proven low-grade glioma

- ✓ indication for definitive or adjuvant radiotherapy
- ✓ ability to understand character and personal consequences of the clinical trial
- ✓ written informed consent

4.2 Exclusion criteria

- previous cerebral irradiation
- contraindication for contrast-enhanced MRI
- neurofibromatosis
- participation in another clinical trial with competing objectives

4.3 Patient registration

The study center keeps a logbook in which all patients who meet the selection criteria are recorded consecutively and documented in a registration form. If not included in the study, the reason is documented. All patients who fulfill the selection criteria, who have been informed and have given their consent to participate in the study, are registered as recruited at the study center. For this purpose, the registration form and the signed informed consent are handed over or faxed to the study center. In the study center, the registration form is checked for completeness and the patient is recorded in the logbook.

The informed consent of each patient takes place through a conversation between the study physician and the patient before inclusion in the study. The physician has to give the patient sufficient time for reflection and opportunity for further inquiries and must be convinced that the informed consent was understood by the patient. All questions of the patient must be answered and any ambiguities eliminated. The consent of the patient must explicitly refer to the collection and processing of personal data. Therefore, patients are explicitly informed about the purpose and scope of the survey and the use of this data, in particular health data. The storage of full names, dates of birth, addresses, and telephone numbers in the study center will be recorded in writing.

The patient may withdraw consent at any time and without giving any reason and discontinue the study. In such a case, he should be asked to give the reason for the termination, but pointed out that he does not have to do this.

4.4 Withdrawal of patients

A subject may voluntarily discontinue participation in this study at any time at their own request. The investigator may also, at his/her discretion, withdraw the subject from the

study at any time. In addition, study treatment will be discontinued if unmanageable toxicity is documented, or if the Principal Investigator decides to terminate the trial. A subject will be withdrawn from the protocol if, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being.
If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. In case of withdrawal of a subject at his/ her own request, the reason should be asked for as extensively as possible and documented. All efforts will be made to follow up the subjects and, all examinations scheduled for the final trial day will be performed as far as possible on all patients and documented.
All ongoing Adverse Events (AEs)/ Serious Adverse Events (SAEs) of withdrawn patients have to be followed up until no more signs and symptoms are verifiable or the subject is on stable condition.

4.5 Specification of safety parameters

Reasons for a preliminary discontinuation of the trial might be:

- Principal investigators decision due to unacceptable risks or toxicity after careful benefit-risk-consideration
- Consideration to discontinue after any grade 5 toxicity, after 2 consecutive grade 4 toxicities, after 5 consecutive grade 3 toxicities
- New scientific findings during trial period
- Major delay in recruitment
- Major problems with quality of acquired data that cannot be resolved
- Timely recognition of a significant superiority or inferiority of one of the treatment arms as defined by the terms of the interim analysis
- Neglecting legal or ethical regulations

5 Radiation therapy

Patients will be treated with proton beam therapy up to 54 Gy RBE. The prescribed dose will be delivered in active scanning technique at one of the participating centers using a fractionation of either 30 x 1.8 Gy RBE or 27 x 2 Gy RBE with five fractions per week. Patients in the control arm are treated according to the current clinical standard in the respective facilities.

5.1 Treatment planning

For treatment planning, patients will be immobilized using an individually manufactured head mask. Both CT as well as contrast enhanced MR-imaging will be performed for optimal target definition. CT slice thickness should be 1 mm. Treatment planning MRI should be performed with 3T not earlier than 4 weeks prior to radiotherapy. Minimum required sequences are:

- T1 MPRAGE with and without contrast enhancement, slice thickness ~ 1mm
- 3D FLAIR / dark fluid TIRM, slice thickness ~ 1mm

Treatment planning in the control arm is performed with the available treatment planning system at each participating center (e.g. Siemens Syngo TPS, Raysearch Raystation) using a fixed RBE of 1.1. Each plan should aim for a dose distribution as homogenous and as conformal as possible. The number and directions of beams are adapted to the patient anatomy. Single beam plans must be avoided whenever possible. The optimization strategy in the conventional treatment planning arm is not determined by the protocol. In principal both Single Beam Optimization/Single Field Uniform Dose or IMPT could be used. Model-based NTCP is calculated after plan approval, however, no further adjustments are to be made to the approved treatment plan.

Re-planning in the experimental arm is performed with Raysearch Raystation, a commercially available treatment planning software with CE certification as medical medical product, using identical beam directions and normal tissue constraints as the initial treatment plan. Compared to the initial treatment plan, the following optimization objectives are modified and added, respectively:

1. the optimization objectives that control the maximum dose in the target volume employ a variable, LETd-dependent model for RBE that allows us to include the RBE-variations predicted by the NTCP model

2. the periventricular volume, defined as the volume closer than 4 mm to the ventricular wall, is included into the optimization with a constraint on its Equivalent Uniform Dose (EUD) and with the variable RBE model described above. Thereby, the combined effect of the RBE variation and increased sensitivity of the periventricular volume, as predicted by the NTCP model, is included.

The effectiveness of the re-planning is verified by a second NTCP computation.

5.2 Target volume definition

Target volume definition is based on international consensus guidelines. The following target volumes must be delineated:

- **GTV**: gross tumor volume is defined as the hyperintense area on T2/FLAIR/TIRM sequences at the time of treatment planning.
- **GTV_initial**: in case of postoperative radiotherapy gross tumor volume is defined as the hyperintense area on T2/FLAIR/TIRM sequences before surgery.
- **Tumorbett:** in case of postoperative radiotherapy the tumor bed is defined as overlap of resection cavity and initial GTV.
- **CTV:** the clinical target volume is defined as GTV plus an isotropic margin of 1 cm.
- **PTV:** the planning target volume is defined as CTV plus a margin of 3 mm.
- **Overlap:** defined as the overlap of Ventrikelsaum and PTV outside the GTV

5.3 Organs at risk

The following organs at risk should be defined according to international accepted standards (see EPTN International Neurological Contouring atlas at https://www.cancerdata.org/. To facilitate future comparison of the structures, enable template based planning or automated plan evaluation and dose-volume-histogram analysis the proposed uniform nomenclature is to be used:

- Auge li.
- Auge re.
- Chiasma
- Hippocamous li.
- Hippocampus re.

- Hirn
- Hirnstamm
- Hypophyse
- Hypothalamus li.
- Hypothalamus re.
- InnenOhr li.
- InnenOhr re.
- Linse li.
- Linse re.
- Rueckenmark
- Sehnerv li.
- Sehnerv re.
- Traenendruese li.
- Traenendruese re.
- Ventrikel
- Ventrikelsaum (=Ventrikel + 6 mm)

To avoid inacceptable radiation induced toxicity the maximum dose to organs at risk must not exceed the TD 5/5 (toxic dose causing 5% severe complications in 5 years). For further details see detailed results of QUNATEC analysis (https://www.redjournal.org/issue/S0360-3016(10)X0002-5).

5.4 Assessment of toxicity

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for toxicity and adverse event reporting. A copy or the CTCAE can be accessed from the CTEP home page (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

Safety and toxicity of the study treatment will be evaluated by clinical neurological examination as well as neuro-imaging studies (MRI or CT).

5.4.1 Patient reported outcome

This trial will assess patient reported outcomes of the common terminology criteria for adverse events (PRO-CTCAE). PRO-CTCAE is a patient-reported outcome measurement

system developed by the National Cancer Institute to capture symptomatic adverse events in patients on cancer clinical trials.

5.5 Assessment of quality of life

Quality of life will be assessed prior to radiation, at the end of treatment and during follow-up. Quality of life will be assessed using EORTCs (brain specific) questionnaires for quality of life of cancer patients (QLQ-C30 and QLQ-BN20).

5.6 Plan for treatment or care after the trial

After completion of trial treatment, no further adjuvant treatment is scheduled or recommended. Any systemic treatment or chemotherapy or any other treatment applied is not part of the clinical trial.

For tumor progression, treatment alternatives will be evaluated and discussed in the interdisciplinary setting considering options of neurosurgical resection, systemic treatment such as chemotherapy, a second course of radiation therapy, or other.

6 Clinical examinations (trial visits)

6.1 Overview

Treatment schedule	baseline visit	weekly during RT	end of RT	FU 1 6 weeks post RT	FU 2 3 months post RT	FU 3 6 months post RT	FU 4 9 months post RT	FU 5 12 months post RT	FU 6 15 months post RT	FU 7 18 months post RT	FU 8 21 months post RT	FU 9 24 months post RT
Informed consent	√											
Inclusion / exclusion criteria	√											
Demographic information	√											
Anamnesis/ clinical examination	√			√	√	√	√	√	√	√	√	√
randomization	√											
AEs und SAEs	√	√	√	√	√	√	√	√	√	√	√	√
Symptoms/toxicity	√	√	√	√	√	√	√	√	√	√	√	√
MRI	√			√	√	√	√	√	√	√	√	√
QLQ-C30 & QLQ-BN20	√		√			√		√				√
PRO-CTCAE	√	√	√	√	√	√	√	√	√	√	√	√
(Cognitive assessment)	√		√			√		√				√

The number of trial visits and the extent of their examinations is equivalent to standard care. Trial related additional expense is a result of the neurocognitive testing. The MoCA test is designed to take less than 15 min. Completing the PRO-CTCAE form takes less than 5 min. Additional time is needed for completing the quality of life questionnaires which takes approx. additional 20 min per visit. In total, the additional time expense for the patient sums up to 40 min on five trial visits and 5 min at the remaining visits.

6.2 Base line examination

- Anamnesis and clinical examination
- Assessment of QoL
- Assessment of toxicity (CTCAE)
- Assessment of patient reported outcome (PRO-CTCAE)

6.3 Weekly examination during radiotherapy

- Assessment of toxicity (CTCAE)
- Assessment of patient reported outcome (PRO-CTCAE)

6.4 End of radiotherapy

- Assessment of QoL
- Assessment of toxicity (CTCAE)
- Assessment of patient reported outcome (PRO-CTCAE)

6.5 Follow-up

Trial follow-up starts six weeks after completion of radiotherapy. Further follow-up exams are scheduled every three months for a period of two years. The following parameters will be assessed:

- Contrast-enhanced MRI of the brain
- Clinical status
- Toxicity (according to CTCAE 5.0)
- Patient reported outcome of CTCAE (PRO-CTCAE)
- Quality of life (only after 6, 12 and 24 months)

7 Assessment of efficacy parameters

7.1 Assessment of efficacy parameters

7.1.1 Radiation induced contrast enhancement

All MRI scans will be evaluated by two independent radiologists. Any new contrast enhancement seen outside the GTV but inside the treated high-dose volume (defined as the 80% isodose) is classified as potentially radiation induced. In case of detection of new contrast enhancing lesions, the corresponding series will be imported into the treatment planning system, merged with the initial treatment planning CT and delineated as new volume of interest. The dose distribution will be updated by re-calculating dose volume histograms enabling an in-depth dosimetric and volumetric analysis and correlation with beam parameters. Furthermore, the localization will be checked against the prediction of the NTCP-model.

7.1.2 Progression free survival

Progression-free survival (PFS) is one of the secondary endpoints of the trial. Progression-free survival will be counted from the first day of radiotherapy treatment until the date of the first event of either progression or death due to any cause. Patients alive without progressive disease at the time of data analysis will be censored at the time of the most recent follow-up visit. Radiological responses will be classified as follows:

Complete remission (CR): Remission of all solid tumor lesions on CT or MRI without worsening of neurologic status

Partial remission (PR): at least 50% remission of the solid tumor lesion on CT or MRI without increase in steroid medication and without worsening of the neurologic status

Stable disease (SD): Remission of the solid tumor on CT or MRI of less than 50% or progression of the solid tumor on CT or MRI of less than 25%, without increase in steroid medication of worsening of the neurologic status

Progressive disease (PD): Increase in solid tumor of 25% or more or development of a new lesion

Progression-free survival and its distinction from radiation induced contrast enhancement will be assessed as defined hereunder:

Follow-up assessments (including MRI or CT) will be performed as described until disease progression (even after the end of the study). Special attention should be given so as to avoid tissue reaction to radiation treatment to be classified as tumor or disease progression. Such variations in post-radiotherapy imaging may continue for months, and may be accompanied by clinical signs and symptoms. In addition, surgical procedures may cause increased contrast uptake which should be differentiated from tumor progression. The clinical follow-up must dictate how the initial progression of the lesion should be labeled. If the course of events shows that true progression indeed occurred, the date of the first increased is to be considered as the date of progression. The principal investigator may be contacted for further discussion on a case by case basis.

7.1.3 Overall survival

Overall survival (OS)is one of the secondary endpoints of the trial. The duration of survival is the time interval between initial diagnosis (date of the neuropathology report) and the date of death due to any cause. Patients not reported dead or lost to follow-up will be censored at the date of the last follow-up examination.

8 Assessment of safety parameters

8.1 Adverse events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product or treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or treatment, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before clinical trial start

- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator. Each AE developing during study treatment or within 30 days after completion of study treatment should be documented up to 6 months after completion of study treatment. The investigator is responsible to perform and consider all required therapeutic measures and methods to follow-up this condition. An event, which occurs in conjunction or association with tumor progression will not be considered an AE or subsequently as an SAE unless more severe than expected.

Following examples will also not be considered as an AE:

- A medical or surgical procedure (the condition that led to the procedures is an AE)
- Situations in which an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or conditions(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless they are more severe than expected for the subject's condition

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale as defined in CTCAE v5.0:

Grade 1	mild AE
Grade 2	moderate AE
Grade 3	severe AE
Grade 4	life-threatening AE or AE causing disablement
Grade 5	death related to AE

The grading of all AEs listed in the CTCAE v5.0 will be based on the information therein. The grading of all other AEs, i.e. those who are not listed will be performed by a responsible investigator, based on the definition given above.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

- AEs are classified as "non-serious" or "serious".

8.2 Serious adverse events

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity

Examples of SAEs that do not need to be reported:

- Medical or surgical procedures (i.e. endoscopy, appendectomy); the condition that leads to the procedure may be an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to the hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated

Any SAE that occurs outside the SAE detection period (after the 30-day period) considered to be reasonably related to the investigational treatment or study participation have to be documented and reported.

This must be done within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator. The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgement to determine the relationships. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational treatment will be considered and investigated.

8.3 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the known common side effects after radiation therapy according to the CTCAE criteria. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

8.4 Coherency between AEs and trial treatment

The investigator will evaluate each AE that occurred after administration of investigational medicinal product regarding the coherency with the administration of the investigational medicinal product possibly:

Related	There is a reasonable possibility that the event may have been caused by the trial treatment. A certain event has a strong temporal relationship and an alternative cause is unlikely
Probable	An AE that has a reasonable possibility that the event is likely to have been caused by the trial treatment. The AE has a timely relationship and follows a known pattern of response, but a potential alternative cause may be present.
Possible	An AE that has a reasonable possibility that the event may have been caused by the trial treatment. The AE has a timely relationship to the

	trial treatment; however, the pattern of response is untypical, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event
Unlikely	Only a remote connection exists between the trial treatment and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event
Not related	An AE that does not follow a reasonable temporal sequence related to the trial treatment and is likely to have been produced by the subject's clinical state, other modes of therapy or other known etiology

8.5 Outcome of AEs

The outcome of an AE at the time of the last observation will be classified as:

Recovered/resolved:	all signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation
Recovering/resolving:	the intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution
Not recovered/not resolved	signs and symptoms of an AE are mostly unchanged at the time of the last interrogation
Recovered/resolved with sequel	actual signs and symptoms of an AE disappeared but there are sequels related to the AE
Fatal	resulting in death. If there are more than one adverse event only the adverse event leading to death (possibly related) will be characterized as 'fatal'
Unknown	the outcome is unknown or implausible and the information cannot be supplemented or verified

9 Quality assurance

9.1 Central review of treatment plans

To ensure consistent quality of the treatment plans a central review of the first three treatment plans in the control arm and of every treatment plan in the experimental arm will be performed prior to first irradiation. Data will be exchanged using the HIRO research data base.

The plans will be assessed by the coordinating investigators of the participating centers. At least the following criteria will be evaluated:

- definition of target volumes
- definition of OARs
- dose prescription
- target coverage for CTV and PTV
- dose constraints for OARs
- beam arrangement

9.2 Dummy run

The Dummy Run will ensure that the contouring and treatment planning is consistent with the protocol requirements. The Dummy Run will include a submission of contouring, dose planning, and optimised re-planning for evaluation. Based on this, the study coordinators will evaluate if the centre is ready to participate and at least the above-mentioned quality criteria are met. In case of deviations from the specifications of the protocol the coordinating investigators will discuss the results and the dummy run might be repeated.

10 Documentation

10.1 Data management

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to a paper form or an electronic data record or both, depending on the data collection method used at each participating center. All findings including clinical and laboratory data will be documented by the investigator or an authorized member of the study team in the

subject's medical record and in the CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data.

10.2 Patient Identification Log

All patient-related data are recorded in a pseudonymized form. Each patient is uniquely identified by a patient identification number. The investigator maintains a patient identification list in which the patient identification numbers are associated with the full patient name. This list must be kept absolutely confidential and must not leave the testing center. The patient identification list must be archived for at least 30 years after the end of the study.

All clinical data entered in the HIRO database in the eCRFs, treatment plans and imaging will be sent exclusively pseudonymized.

10.3 Data Acquisition/ Case Report Forms

The data is collected, managed and processed electronically in the in-house HIRO research database. In the case of revocation of the consent, the data may continue to be used, as long as there is no request for complete deletion of the data.

It is the responsibility of the principal investigator to conduct the study in accordance with applicable legal provisions and the study protocol, and that the data is entered correctly and completely in the eCRFs.

All data collected in this study must be documented by authorized persons in the eCRFs. Access to the database must be authorized in writing by the principal (Signature Log). Only authorized persons are granted access to the database. Access authorization may not be passed to third parties.

Data in the HIRO database will be checked by programmed value ranges, validity and consistency checks. If necessary, queries may arise that are made using the HIRO database and authorized persons. Based on the queries, the study physician / study nurse can review and answer or correct the resulting discrepancies.

The eCRFs must be completed promptly and then checked by the investigator.

After completion of the study and after entry of all relevant data and clarification of the queries, the data base will be closed.

10.4 Archiving of Study Documents

The originals of all central study documents, including documentation sheets, are kept at the Study Center for at least 30 years after the final report has been prepared.

The principal investigator of the study center keeps the administrative documents (correspondence with the ethics committee, study administration, study center), the patient identification list, the signed declarations of consent, copies of the CRFs and the general study documentation (protocol, amendments) for the above-mentioned time.

Original data of the patients (medical records) must be kept for the required archiving period of the study center, but not less than 30 years.

10.5 Confidentiality

The data obtained in the course of the trial will be treated pursuant to the Federal Data Protection Law (Bundesdatenschutz- bzw. Landesdatenschutzgesetz, BDSG-neu, LDSG and the General Data Protection Regulation (DSGVO).

During the clinical trial, patients will be identified solely by means of their year of birth, and an individual identification code (Subject ID). Trial findings stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The subject consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the subject-related data collected during the trial ensuring the data protection law.

The investigator will maintain a subject identification list (subject IDs with the corresponding subject names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data will not be included into the trial.

11 Sample Size

Sample size calculation is based on the primary endpoint "cumulative incidence of contrast enhancing brain lesions (CEBL) observed within 24 months after PRT".

Our previous analysis showed that the primary endpoint is negative binomial distributed and that an 86 % cumulative incidence CBL negative binomial event rate, p_{conv}, as well as dispersion parameter of $\Phi = 0.2597$ can be assumed in the conventional group. On the bases of additional experiments, a 60 % reduction of the probability for at least one lesion in the model-aided experimental group is assumed, corresponding to a negative binomial event rate $p_{aided} = 0.18$ when assuming the same dispersion parameter in both groups.

For a fixed sample size design, the sample size required to achieve a power of $1 - \beta$ of 80% for the one-sided negative binomial regression at a significance level of $\alpha = 0.025$ in conventional and experimental group and a randomization allocation ratio of 1 as well as the above-mentioned assumptions, amounts to $2 * 46 = 92$. It can be expected that including covariates of prognostic importance in the negative binomial regression model as defined for the confirmatory analysis (see section 13.3) will increase the power as compared to no included covariates.

As the individual results for the primary endpoint are collected within 24 months, there is a possibility of some patients not surviving the observation period, becoming lost to follow-up or withdrawing their informed consent. If a patient discontinues from the study prematurely without having a full observation time (e.g. due to death, loss to follow, or withdrawal of informed consent) but was observed for at least one year after randomization, the primary outcome variable will be set to the number of lesions observed until the last available follow-up visit. If a patient has a follow-up less than one year after randomization, the primary endpoint will be set to missing. In order to take this potential loss of information into account, a premature death rate of 8% and a drop-out rate of 10% (loss to follow or withdrawal of informed consent) after 12 months is assumed. Thus, an overall "drop-out" rate of 18% after 12 months is assumed, and therefore the total sample size required for a fixed design amounts to $n = 92 + 22 = 114$ patients (57 per group).

A group-sequential design with interim analysis allowing to prematurely stop the trial for efficacy or futility, using O´Brien-Fleming-type alpha and beta spending functions, is

performed. This will allow to prematurely declare the treatment as effective in case of a substantially large treatment effect, as well as to stop the trial in case the treatment does not prove to be effective. The interim analysis is conducted after half of the patients did reach the primary endpoint (see the detailed description of the procedure applied for the interim analysis in section 13.3 below). Additionally, the study can be stopped in the interim analysis due to futility (boundaries for interim and final analysis are given in section 13.4). These assumptions would lead to a sample size of 98 (49 per group) without consideration of drop-outs. With an assumed 18% drop-out rate 120 patients (60 per group) are needed to achieve a power of 80%.

It should be noted that the interim analysis will likely take place after the total number of 120 patients have been enrolled. While in such a case, it is not possible to reduce the total number of enrolled patients, the follow-up time of the trial might be reduced, thus allowing to save resources and costs.

Calculations were performed with R packages gscounts for sample size calculations and MASS for estimation of the dispersion parameter. R version 3.6.3 was used.

12 Statistical Analyses

12.1 Primary objective and study design

The primary endpoint of this clinical trial is the cumulative incidence of CEBLs within 24 months after PRT measured by quarterly contrast enhanced MRI of the brain.

A group-sequential design with interim analysis according to O'Brien-Fleming type alpha and beta spending decision boundaries is performed to not withhold a possible effective treatment to the control group as well as the general trial population in case of a large beneficial treatment effect, and to prevent harm for the patients in case the experimental treatment should prove to be ineffective at interim. The interim analysis is conducted after n = 49 patients did reach the primary endpoint within 24 months, which is half of the planned total sample size not considering dropouts or premature deaths. No sample size recalculation is performed at the interim analysis. Furthermore, descriptive statistics for progression-free-survival and overall survival will be given at the interim analysis. This design allows early stopping of the trial under control of the overall type I error rate, or,

alternatively, a stop for futility. Results of the interim analysis will be presented to the Data Safety and Monitoring Board (DSMB) who will advise the Steering Committee of the trial to either terminate or to continue the trial.

12.2 Hypothesis

To formalize the statistical approach, the following notation will be used:

p_{conv}/p_{aided}: cumulative incidence CEBL negative binomial rate within 24 months in the conventional / model-aided experimental group. The following test problem is defined:

$$H_0: p_{\text{aided}} \geq p_{conv} \quad \text{vs.} \quad H_1: p_{\text{aided}} < p_{conv},$$

which will be assessed at a one-sided significance level of 2.5 %.

12.3 Analysis

12.3.1 Analysis sets

The allocation of each patient to the different analysis populations will be defined and explained in further detail in the statistical analysis plan (SAP) prior to the analysis.

Full Analysis Set (FAS): All patients who fulfilled the inclusion and exclusion criteria and hence were included into the trial. The term “ITT-analysis” is used for an analysis applying ITT principles to all patients of the FAS.

Per Protocol Set (PP): All patients from the FAS, excluding patients with major protocol violations. During the interim analysis, deviations from the protocol will be assessed as „minor” or „major”. „Major” protocol violations will be discussed with the coordinating investigator.

Safety Set: All patients from the FAS who received at least one fraction of radiotherapy. Patients will be allocated to the treatment they actually received.

12.3.2 Confirmatory analysis of the primary endpoint

The null-hypothesis is tested with a two-level negative binomial regression model including the covariates treatment, prescribed dose, and the random factor center. An overall one-sided significance level of $\alpha = 0.025$ is applied. Confirmatory analysis of the primary endpoint will be primarily based on the FAS which is consistent with the intention-to-treat (ITT)-principle by including all patients who were randomized to one of the study

groups. If a patient discontinues from the study prematurely without having a full observation time (e.g. due to death, loss to follow, or withdrawal of informed consent) but was observed for at least one year after randomization, the primary outcome variable will be set to the number of lesions observed until the last available follow-up visit. If a patient has a follow-up less than one year after randomization, the primary endpoint will be set to missing. An evaluation of the PP and safety set is performed additionally and the results are compared with those of the ITT analysis. Additionally, multiple sensitivity analyses of the primary endpoint will be performed by applying alternative methods dealing with missing data such as:

- Complete-case analysis, which means that the primary outcome of all patients with an incomplete 24 month follow up will be set to missing and neglected for the primary analysis.
- Analysis based on the FAS. If a patient discontinues from the study prematurely without having a full observation time, missing data for the primary outcome variable will be replaced by using multiple imputation by means of fully conditional specification method (van Buuren, 2006). The variables treatment, dose, center, lesions observed until censoring, and observation time will be included in the imputation model, which will use predictive mean matching to impute missing primary outcome data.
- Analysis based on the FAS of the primary endpoint using the non-parametric van Elteren test stratified by center, where the number of CEBLs is set to infinity for all deceased patients. If a patient discontinues from the study prematurely without having a full observation time due to loss to follow-up, missing data for the primary outcome variable will be replaced by using multiple imputation by means of fully conditional specification method (van Buuren, 2006). The variables treatment, dose, center, lesions observed until censoring, and observation time will be included in the imputation model, which will use predictive mean matching to impute missing primary outcome data.

12.3.3 Analysis of the secondary endpoints

The secondary endpoints overall survival and progression-free survival will be analyzed using Kaplan-Meier-Curves. The 1-year and 2-year survival rates as well as the median survival rate will be provided alongside two-sided 95%- confidence intervals. A Cox

regression frailty model adjusting for the fixed factors treatment and dose, and the frailty factor center will be conducted to compare the two treatment groups.
Missing values in the items of PRO-CTCAE, QLQ-C30 and QLQ-BN20 will be handled as described in the scoring manuals of the QoL measures. Further missing values will be documented and frequencies will be described with descriptive methods.
The secondary endpoint neurocognition (MoCA) will be analyzed using a non-parametric Van Elteren Test stratified for center.
The other secondary endpoints and the patients` characteristics will be displayed by descriptive measures grouped by treatment group. Continuous variables will be described using number non-missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum. In addition, t-test between treatment groups will be performed.
For binary or categorical variables absolute and relative frequencies will be provided. Furthermore, two-sided 95%- confidence intervals will be calculated and chi-square tests between treatment groups.

12.3.4 Safety analysis

For safety analysis, laboratory parameters, all AEs and all SAEs will be analyzed via descriptive statistical methods in the safety population. The safety analysis includes calculation of frequencies and rates of complications and serious adverse events together with corresponding 95%-confidence intervals. In addition, tolerability and dosing will be described by numbers of patients in whom treatment was given as planned, delayed or permanently stopped.

Further details of the analysis will be specified in the statistical analysis plan (SAP) which will be finalized before database closure. All analyses will be done using R version 3.6.3 or higher.

12.3.5 Homogeneity of the intervention groups

The homogeneity of the treatment groups will be described by comparison of the demographic data and the baseline values.

12.4 Interim analysis

A group-sequential design with interim analysis containing decision boundaries without sample size recalculation will be performed after availability of the results for the primary endpoint for a total of 49 randomized patients (i.e., 50% of the sample size).

The following type I error rates, decision boundaries for the interim and the final analysis are specified:

- Global one-sided type I error rate: $\alpha = 0.025$
- Boundary for the one-sided p-value for accepting the null-hypothesis within the interim analysis: $\alpha_0 = 0.2879$ (according to an O'Brien-Fleming type beta-spending approach). This rule is considered as a non-binding stopping rule for futility.
- One-sided local type I error rate for testing the null-hypothesis within the interim analysis: $\alpha_1 = 0.0015$ (according to an O'Brien-Fleming type alpha-spending approach)
- Boundary for the one-sided p-value for testing the null-hypothesis within the final analysis: $\alpha_2 = 0.0235$ (according to an O'Brien-Fleming type alpha-spending approach)

The trial will only be continued as planned after the interim analysis, if for the one-sided p-value p_1 of the interim analysis $p_1 \in]0.0015, 0.2879[$ holds true. Furthermore, descriptive progression-free-survival and overall survival will be analyzed at the interim analysis using Kaplan-Meier-Curves. The 1-year and 2-year survival rates as well as the median survival rate will be provided alongside two-sided 95%- confidence intervals.

In case the trial is prematurely stopped due to efficacy or futility, patients who are still under observation but were not yet included in the interim analysis will not be followed up as planned.

It should be noted that the interim analysis will likely take place after the total number of 120 patients have been enrolled. While in such a case, it is not possible to reduce the total number of enrolled patients, the follow-up time of the trial might be reduced, thus allowing to save resources and costs.

Results of the interim analysis will be presented to the Data Safety and Monitoring Board (DSMB) who will advise the Steering Committee of the trial to either terminate or to continue the trial.

Detailed procedures of the interim analysis will be specified in a separate interim Statistical Analyses Plan (SAP), which will be finalized before interim database lock.

12.4.1 Randomisation

Screened and eligible patients will be included into the trial once the study has been initiated. The patients will be randomized with the help of the web-based software randomizer.at (provided by the Institute for Medical Informatics, Statistics and Documentation; Medical University of Graz; https://www.randomizer.at). Block randomization stratified by center will be performed to ensure approximately equal sample sizes within the treatment groups.

13 Ethical, legal and administrative aspects

13.1 Good clinical practice/ declaration of Helsinki

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki (2013 Version of the Declaration of Helsinki, adopted at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

The trial will be carried out in keeping with local legal and regulatory requirements. The study plan will be submitted to the Institutional Review Board (IRB)/independent Ethics Committee (EC) of the Medical Faculty Heidelberg for approval. Patient recruitment will not start before the written approval by the ethics committee has been obtained.

13.2 Subject information and informed consent

Participation in this trial is voluntary for all patients – and only for those patients – who conform to the inclusion and exclusion criteria put down in this protocol. A study subject may at any point withdraw his/her consent and thus terminate his/her participation in the study without the need to specify reasons for doing so.

Participation in the clinical trial is voluntary for subjects. Before inclusion in the study, a potential subject will be thoroughly and in detail informed about the nature, the aims, the risks and benefits of the study before informed consent can be given. Detailed information shall be provided in a fashion and language understood by the patient. An informational

handout as well as an informed consent form – both documents conforming to ICH-GCP standards – will be provided to the patient before inclusion. Informed consent must be given only after an appropriate amount of time for consideration and then must be in writing and complemented with information about date and time of signature in the patient's own handwriting. Informed consent must be countersigned by the treating physician. If a patient is incapable of signing the informed consent form himself, the oral informed consent must be confirmed by the signature of a witness.

The personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and documented in the case report form.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must include the name of the investigator who informed the subject. The Informed Consent Form must be signed by the subject as well as the investigator giving informed consent.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue the study. Clinical subjects are completely free to refuse to enter the study or to withdraw from it at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator. This study includes no additional invasive or otherwise harmful or burdening procedures.

Upon withdrawal, patients will be asked if they agree with the use of the data obtained so far. The information about the withdrawal must be documented in the patient file as well as on the participant's informed consent form.

13.3 Responsibilities of investigator

The Principal Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions. The Principal Investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

The current trial is neither a clinical investigation of a drug according to the German Medicinal Products Act (Arzneimittelgesetz) nor a clinical investigation of a medical device according the Medical Device Regulation. The treatment planning software Raystation is a

commercially available software with CE label and currently used as standard treatment planning software in the clinical routine as well.

13.4 Approval of trial protocol and amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC). written favorable vote of the EC is a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes (see §10, (1) of German GCP-Regulation) will be submitted and must be approved by the EC.

The investigator and the Clinical Trial Center at the Department of Radiation Oncology, University Hospital of Heidelberg, Heidelberg, Germany, will keep a record of all communication with the EC and the regulatory authorities.

13.5 Registration of the trial

Prior to the beginning of the clinical phase (FSI) the coordinating/principal investigator will register the trial at Current Controlled Trials (http://www.controlled-trials.com/) or http://www.clinicaltrials.gov. Thus, the trial will be given a unique registration code (e.g. ISRCTN), which is a prerequisite for a publication in many peer-reviewed journals.

14 Agreements

14.1 Financing

An application for funding has been made for this clinical trial (clinical trials programme, DFG). Funding was requested for human resources such as treating physicians, medical physicists, study nurses, data management, biostatistics and project management. Furthermore funding for print costs, travel costs, monitoring, hardware and fees was applied for.

The Department of Radiation Oncology, University Hospital Heidelberg, INF 400, 69120 Heidelberg, and the Department of Radiation Oncology, university Hospital Dresden, Fetscherstr. 47, 01307 Dresden, will cover the additional costs of the clinical study.

Participation in this trial will cause no additional costs for the patient (compared to standard treatment).

All persons involved (including the principal investigator and coordinator) declare that there is no conflict of interest in connection with the implementation and evaluation of the study.

14.2 Reports

A report summarizing the results of the trial will be prepared within one years after closure of the data base by the Study Center of the Department of Radiation Oncology, University Hospital of Heidelberg, Germany.

14.3 Publication

All information concerning the trial is confidential before publication. Publication will be prepared under the lead of the study coordinator of the study. The first and last authorship are reserved for the principal investigator and the study coordinator of the study if both do not wish to transfer their authorship to a third person. All data will be published independently of the results of the trial.

15 Signatures

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:
- the current risk-benefit assessment of the investigational treatment
- the moral, ethical, and scientific principles governing clinical research as set out the principles of GCP and in the applicable version of Declaration of Helsinki.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational treatment.

Principal investigator

	28.10.2022
_____	_____
Dr. Semi Harrabi	date

Statistician

_____	_____
M.Sc. Christopher Büsch	date

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