IPAX Linz

Clinical study report

TITLE PAGE

An open label, single arm monocentric phase II study to evaluate safety, tolerability, and preliminary efficacy of carrier-added 4-L-[131I]iodo-phenylalanine (131I-IPA), administered as sequential injections in patients with recurrent IDH1/2 high grade glioma (HGG) concomitantly to 2nd line external radiation therapy

IPAX - Linz

EudraCT No.: b2021-006426-43

Investigational Product(s): Manufacturer(s): Telix Pharmaceuticals Limited

Indication: Malignant brain tumor (Glioblastoma)

Study Design: An open label, single arm monocentric phase II study

Sponsor: Dr. Josef Pichler

Study Phase: 2

Study Start Date: 02. April 2022

Study Completion Date: 28. November 2024 (last patient

Principal Investigator: Dr. Josef Pichler

Report Version Number: 1.0

Report Date:

The study was carried out in accordance with Good Clinical Practice as required by the following items:

- This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Ethikkommission der Medizinischen Fakultät der Johannes Kepler Universität Linz
- Informed consent was obtained from all individual participants included in the study.

SIGNATURE PAGE

Protocol Title: An open label, single arm monocentric phase II study to evaluate safety, tolerability, and preliminary efficacy of carrier-added 4-L-[^{131}I]iodo-phenylalanine (^{131}I-IPA), administered as sequential injections in patients with recurrent IDH1/2 high grade glioma (HGG) concomitantly to 2nd line external radiation therapy

IPAX – Linz

Protocol Number: IPAX Linz protocol version 1.0 from 17.11.2021

EudraCT No.: b2021-006426-43

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

Principal Investigator:

Signed: _____ Date: Linz, 27.08.2025

1 SYNOPSIS

Name of Sponsor:	Dr. Josef Pichler	
Name of Final Product(s):	^{131}I-IPA	
Name of Active Ingredient(s):	[^{131}I]-L-4 iodophenylalanine	
Title of Study: An open label, single arm monocentric phase II study to evaluate safety, tolerability, and preliminary efficacy of carrier-added 4-L-[^{131}I]iodo-phenylalanine (^{131}I-IPA), administered as sequential injections in patients with recurrent IDH1/2 high grade glioma (HGG) concomitantly to 2nd line external radiation therapy		
Investigator and Study Site: Dr. Josef Pichler, Department of Internal Medicine and Neurooncology, Kepler University Hospital Neuromed Campus 4020 Linz, Wagner-Jauregg-Weg 15, AUSTRIA		
Publication (reference):		
Study Period (years): 2 years 7 months		
Phase of Development:		
Objectives: **Primary Objective** To assess the safety and tolerability of intravenous ^{131}I-IPA administered concomitantly to Re- XRT in recurrent HGG. **Secondary Objective** 1. To measure the quality of life, neurological outcome (NANO) before and after therapy 2. Response assessment using mRANO criteria 3. Time to Progression, Progression free Survival 4. Overall survival		
Methodology: This study was an open label, monocentric Phase II study with a consolidation cohort of 10 patients subsequent to the IPAX 1 trial, which included 10 patients in different dose regimen of 131I-IPA. Administration of intravenously ^{131}I-IPA sequentially with a dose of 4 GBq before and after 2nd line external radiation therapy (XRT). Radiotherapy treatment was applied with 30 Gy in 5 fractions for low volumes (tumor diameter up to 3 cm). For tumors > 3 to ≤ 5 cm the radiation dose will be 36 Gy in 18 fractions		
Number of Participants (planned and analyzed): 10 planned, 8 analyzed		

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria for all Participants:

- 1. Previously confirmed histological diagnosis of IDH1/2 wildtype HGG, with current clinical or imaging evidence for first or second recurrence according to modified RANO criteria (2017). History of standard therapy (debulking surgery, followed by radio-chemotherapy (50–60 Gy in 2 Gy fractions, temozolomide). Patients treated with Radiotherapy alone in 1st line according to the elderly GBM protocol could also be included.
- 2. Interval since end of 1st line XRT ≥6 months
- 3. Amino acid-based molecular imaging (preferably ^{18}F-FET-PET indicating pathologically increased amino acid uptake inside or in the vicinity of the tumor, clearly discernible from background activity
- 4. Surgery for relapsed tumor is allowed, if postoperative MRI and/or PET shows residual tumor in contrast enhanced MRI and/or ^{18}F-FET-PET.
- In recurrent tumor with no preceded surgery MRI lesion with contrast enhancement is the target.
- The target in re-operated tumors is residual tumor in CE-MRI or 18F-FET-PET with metabolic tumor residuum (TBR ≥ 2)
- 5. Current indication for repeat radiation therapy as discussed at the multidisciplinary neuro-oncological tumor board meeting
- 6. Gross tumor volume (GTV) of up to 5 cm diameter, clinical target volume (CTV) 0.5 cm margin and planning target volume (PTV) ≤ 0.5 cm margin
- 7. Male or female ≥18 years of age.
- 8. Karnofsky performance status (KPS) ≥70. Life expectancy of at least 16 weeks.
- 9. Hematological, liver and renal function test results as follows:
- • WBC: >3*109/L
- • Hemoglobin >80 g/L
- • PLT >100*109/L
- • ALT, ALP, AST: ≤5 times upper international limit of normal (UILN)
- • Bilirubin ≤3 times UILN
- • Serum creatinine: within normal limits or <120 µmol/L for patients aged 60 years or older
- • Urine protein dipstick: no protein
- 10. Female patients surgically sterile or postmenopausal for at least 2 years. Participants of generative potential agreeing to use effective contraception during the period of therapy and 6 months after the end of study.
- 11. Written informed consent

Exclusion Criteria for all Participants:

- 1. Primary XRT dose > 60 Gy
- 2. Doses to organs at risk defined by Yasar and Tugrul (2005) exceeded or reached by prior radiation therapy; e.g. cumulative total dose on the optical chiasm >54 Gy for 2 Gy/fraction, α/β=2
- 3. Multifocal distant recurrence, defined as tumor lesion outside the primary XRT field, as evidenced by amino acid-based PET imaging or MRI
- 4. Prior treatment with brachytherapy
- 5. Prior treatment with bevacizumab
- 6. History or evidence of delayed-type hypersensitivity (DTH)-dependent chronic infection (e.g. tuberculosis, systemic fungal or parasitic infection), potentially exacerbating under systemic corticoid therapy
- 7. Localization of tumor related to brain stem or axis, unless sufficient reserve capacity (e.g. remnant resection cavity, marked atrophy) to accommodate possible post–procedural tissue reactions, or pre-therapeutic consent for emergency trepanation
- 8. Hemostatic conditions, precluding catheterization or invasive procedures
- 9. Clinically significant illness or clinically relevant trauma within 2 weeks before the administration of the investigational product
- 10. Known impairment of liver or kidney function or known liver or kidney disease, such as hepatitis, cirrhosis, renal failure
- 11. Known human immunodeficiency virus (HIV) positive serology or chronically active hepatitis B or C

- 12. Ongoing toxicity > grade 2 NCI-CTC (version 4.03) from previous standard or investigational therapies
- 13. Administration of another investigational medicinal product within 90 days prior to screening
- 14. Expected non-compliance with longer-term admission at isolated nuclear medicine ward
- 15. In pre-menopausal women: Pregnant as evidenced by a positive pregnancy test, or breast-feeding
- 16. Patients with known phenylketonuria

Investigational Product(s), Dose and Mode of Administration, Manufacturer:

Dose level of 4.0 GBq, ^{131}I-IPA will be administered sequential before and 2 GBq at the end of radiotherapy (cumulative dose 6 GBq).

Unit doses of ^{131}I-IPA will be centrally provided for each scheduled administration sufficiently in advance (typically the day before planned administration).

^{131}I-IPA will be administered as an intravenous short infusion using an intravenous cannula, placed into the cubital vein of the non-dominant arm.

Manufacturer: Seibersdorf GmbH

Changes in Manufacturing: none

Duration of Treatment:

Dose level of 4.0 GBq, ^{131}I-IPA will be administered sequential before and 2 GBq at the end of radiotherapy (cumulative dose 6 GBq).

Criteria for Evaluation:
MRI of brain using mRANO criteria
FET-PET for evaluation of metabolic tumor burden
SPECT Scan for detection of IPA uptake in the target (tumor) and for dosimetry

Statistical Methods:

The statistical analyses in this study will primarily be descriptive.
Descriptive analyses will include:
• Mean, standard deviation, median and range for continuous variables,
• Median, range and frequency distribution for discrete (ordinal) variables,
• Frequency distribution for nominal variables

Summary and Conclusions:

Efficacy Results:

Primary Endpoint(s):

To assess the safety and tolerability of intravenous 131I-IPA administered concomitantly to Re- XRT in recurrent HGG

Secondary Endpoints(s):

1. To measure the quality of life before and after therapy

2. Response assessment using mRANO criteria

3. Time to Progression, Progression free Survival

4. Overall survival

Safety Results: 3 patients experienced an adverse event which was graduated as possible related

AE: 1 leucopenia grade 2

1 lymphopenia grade 3

1 thrombocytopenia grade 3

1 fatigue grade 2

No SAE

Safety conclusion: no relevant safety issues raised during the study. It was very well tolerated.		
Secondary endpoints:		
1. QOL results: descriptive analysis shows no relevant impact on quality of life due to the short duration of active treatment and less side effects. Only the isolation after ^{131}I-IPA injection causes some discomfort on the patients.		
2. Response assessment: no partial or complete response was observed. Best response was stable disease.		
3. Progression free Survival:		
mPFS from relapse before IPA start to next progression (PFS2)	14.9 weeks	12.1 – 25 weeks
mOS from 1. diagnosis	32.2 months	19.4 – 60.4 months
mOS from 1. relapse	11.9 months	6.1 – 23.8 months
Conclusions: Well tolerated therapy with low toxicity, signal for good OS.		
Date of the Report:		

Data Quality Assurance

All source documents were completed by the clinician (or other appropriate study personnel).

Data were handled in accordance with Good Clinical Practice, federal regulations, and instructions from CCR. All source documents were filled out completely by the examining personnel or the study coordinator and signed by the person collecting the data on that form. The source documents were reviewed, signed, and dated by the investigator.

Inhalt

3 List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
BASG	Bundesamt für Sicherheit im Gesundheitswesen (Austrian Federal Office for Safety in Health Care)
BBB	Blood-brain barrier
BL	Baseline
BN20	Brain cancer questionnaire (of EORTC)
Cmax	Maximum plasma concentration of study drug or maximum tumour concentration achieved
COWA	Controlled oral word association
CRA	Clinical Research Assistant / Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
CT	Computed tomography
CTV	Clinical target volume
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
EBRT	external beam radiation therapy
ECG	Electrocardiogram
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-Study
FAS	Full analysis set

FDA	Food and Drug Administration
FSRT	Fractionated stereotactic radiotherapy
FU	Follow-up
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GTV	Gross tumour volume
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HGG	High grade glioma
HIV	Human immunodeficiency virus
HRQOL	Health-Related Quality Of Life
HVLT-R	Hopkins verbal learning test-revised
131I-IPA	4-L-[131I]iodo-phenylalanine
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	International Ethics Committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional Review Board
ISF	Investigator's Site File
IV	Intravenous
KPS	Karnofsky performance status
LGG	Low grade glioma
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MGMT	O6-methylguanine-DNA methyltransferase
MIRD	Medical Internal Radiation Dose
MR	Magnetic resonance

MRI	Magnetic resonance imaging
MSDL	Most suitable dose level
MTD	Maximum tolerated dose
MTV	Metabolic tumour volume
NANO	Neurologic assessment in neuro-oncology
OLINDA	Organ Level Internal Dose Assessment
OS	Overall survival
PET	Positron-emission tomography
PFS	Progression-free survival
PI	Principle Investigator
PP	Per protocol
PPV	Positive predictive value
PsPD	Pseudo-progression
PTV	Planning target volume
QLQ	Quality of Life Questionnaire
q.s.	quantum satis
RANO	Response Assessment in neuro-Oncology
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SPECT	Single-photon emission computed tomography
SUV	Standard uptake value
SUV-R	Standard uptake value for reference tissue
Sv	Sievert
TAC	Time activity curve
TBD	To be determined
T1/2	Terminal half-life
tmax	Time of occurrence of maximum plasma/organ concentration of 131I-IPA
TMF	Trial Master File

TMT	Trail making test
TMZ	Temozolomide
TTP	Time to progression
UILN	Upper international limit of normal
VMAT	Volumetric modulated arc therapy
WBC	White blood cells
WHO	World Health Organisation
XRT	External radiation therapy

4 Ethics

4.1 Institutional Review Board

The protocol and any amendments were submitted for ethical review, and approval was obtained in writing from. Any changes to the protocol required IRB approval prior to implementation unless proceeding with the changes was in the best interest of the Participant's safety.

4.2 Ethical Conduct of the Study

The guidelines of the World Medical Association Declaration of Helsinki, the guidelines of GCP (CPMP/ICH/135/95) as well as the demands of national drug and data protection laws and other applicable regulatory requirements were strictly followed.

4.3 Participant Information and Consent

Informed consent was an ongoing process that began with the first contact with a prospective participant and continued until the study was completed. The consent form provided information about the study and what was involved in participating in the study, the risks, the benefits, Participant rights, and documented the Participant's agreement to participate. All procedures, Participant obligations, and Participant rights were explained to the Participant in easily understood language. During the explanation of the study and during the actual study, the Participant was entitled to privacy and respect. The investigator or a designee presented the information and administered the consent. This person understood the protocol and was able to answer questions about the investigational agent(s). The investigator/designee presenting the study encouraged the prospective Participant to ask questions during this introduction to the study and anytime during his/her participation. Following the information presentation, the investigator/designee made certain that the Participant understood the study before the consent form was signed and before final enrollment in the study.

A copy of the current IRB-approved consent form was used to obtain informed consent from the Participant. The consent form must have been signed by the Participant before participation in any study related activities. A copy of the signed and dated consent form was provided to the Participant. Signed consent forms remained in each Participant's study file and were available for verification by study monitors at all times.

5 Investigators and Study Administrative Structure

Responsibility	Name	Affiliation / Address
Sponsor/Study Manager	Dr. Josef Pichler	Konsiliardienst Innere Medizin und Neuroonkologie Kepler Universitätsklinikum GmbH, Neuromed Campus 4020 Linz, Wagner-Jauregg-Weg 15 AUSTRIA T +43 (0)5 7680 87 - 24211, F +43 (0)5 7680 87 - 28554 josef.pichler@kepleruniklinikum.at
Coordinating CRO/Medical Monitoring	Martin Ziermayr, MEd MSc MBA	JOHANNES KEPLER UNIVERSITÄT LINZ Medizinische Fakultät Med. Campus I Gebäude ADM, 8. OG, Raum 812 Krankenhaustraße 5 4020 Linz, T +43 732 2468 3303 martin.ziermayr@jku.at
Manufacturer of study drug	Seibersdorf Labor GmbH	2444 Seibersdorf Austria Tel: +43-505503485 Fax: +43-505503473
Clinical Operations Project Manager	Sooma Jafari	Telix Pharmaceuticals Limited Homebased in Brisbane - QLD sooma.jafari@telixpharma.com

6 Introduction

6.1 Background Information

Cancer cells have a considerably larger nutrient consumption than non-malignant cells. This is also the case for malignant gliomas which show a higher uptake of amino acids in comparison with normal brain tissue. The uptake typically increases with the malignancy grade, and is particularly high in GBM. Amino acid transporter proteins actively transport amino acids across the blood-brain barrier (BBB) into tumor cells. Thus, they are prime targets for radio-imaging and targeted radiotherapy of gliomas in general and for GBM in particular.

4-iodo-*L*-phenylalanine (IPA) is a derivative of the naturally occurring essential amino acid *L*-phenylalanine, containing an iodine atom in position 4 (para-position) of the phenyl ring. In ^{131}I-IPA, the iodine atom of a fraction of the molecules of the medicinal product is radioactive iodine (^{131}I), whereas the iodine atom of the majority of the molecules (i.e. the carrier) is a stable iodine atom (^{127}I). Due to its mode of beta decay, ^{131}I is known to cause mutation and death in cells that it penetrates, and other cells up to several millimeters away, making it an ideal candidate for imaging and treating inoperable GBM lesions. In addition to this physical effect, an intrinsic cytostatic effect on GBM cells of IPA was demonstrated in pre-clinical studies, as well as a radio-sensitizing activity, synergistic to both, the intramolecular radiolabel, and external field radiation therapy (XRT).

Phenylalanine marked with different radioactive isotopes of iodine has been investigated in patients with glioma: ^{123}I-*L*-phenylalanine (^{123}I-IPA) was used as a radiotracer for glioma imaging using single photon emission computed tomography (SPECT) (Hellwig 2008, 2010). A high specificity and good sensitivity for glioma tissue, for both low-grade gliomas (LGG) and high-grade gliomas (HGG) was seen, irrespective of whether the blood-brain-barrier (BBB) was disturbed or not. In addition, a prolonged tumor retention, compared to the established amino acid-based tracers such as ^{11}C-methionine (^{11}C-MET) or ^{18}F-fluoroethyl-tyrosine (^{18}F-FET) was observed. In a pilot study, ^{124}I-*p*-iodo-*L*-phenylalanine (^{124}I-IPA) was administered to a 73-year-old patient with primary GBM. It was reported to improve accurate diagnosis, and to allow for postoperative treatment control, up to 6 days after injection (Farmakis et al. 2008). Due to its prolonged retention in GBM tissue, the administration of therapeutically active radiation doses becomes possible, using IPA as a molecular carrier. For this purpose, IPA was labelled with the therapeutic beta emitter ^{131}I, which is established as potentially curative treatment of thyroid cancer in nuclear medicine for many years. In preclinical models of GBM, ^{131}I-IPA was observed to improve survival and to possess the potential to histologically eradicate established experimental GBM in vivo (Samnick et al. 2009). Subsequently, ^{131}I-IPA was first tested in two patients with long-standing, extensively pre-treated gliomas. The patients underwent single intravenous injections of 2 and 4 GBq of c.a. ^{131}I-IPA, respectively. Tumor targeting was verified by ^{131}I-IPA single-photon emission computed tomography (SPECT). Metabolic and morphological changes indicative of tumor response were assessed by sequential -FET positron emission tomography (PET) and contrast-enhanced magnetic resonance imaging (MRI). Further monitoring included clinical condition, safety, laboratory, quality of life, and dosimetry. Both patients tolerated the treatment well, and there was no evidence of acute or delayed organ toxicity. ^{131}I-IPA accumulated in the tumor recurrences identified by MRI/^{18}F-FET. In patient 1, PET showed progressively decreasing maximum standardized uptake values (SUVmax) over 10 months, indicating metabolic response, paralleled by reduced tumor volume on MRI. Patient 2, followed-up for 3 months after therapy, showed stable disease on MRI and PET (Baum et al. 2011).

^{131}I-IPA was tested in a phase I/II clinical trial (the IPAX-1 study) for the treatment of recurrent glioma (Pichler J.et al, 2024). It has designated orphan status in the European Union and in the United States for the indication treatment of glioma. Orphan Drug Designation for ^{131}I-IPA for the “treatment of glioma” was granted by European Medicines Agency (EMA) in 2007 (Designation number EU/3/06/363) and in the US by Food and Drug Administration (FDA) in 2011 (Designation number 10-3287) IPAX 1 study has been completed.

Further details can be found in the investigator's brochure which contains comprehensive information on the study drug.

7 OBJECTIVES

7.1 Primary Objective

To assess the safety and tolerability of intravenous ^{131}I-IPA administered concomitantly to Re- XRT in recurrent HGG.

7.2 Secondary Objectives

1. To measure the quality of life, neurological outcome (NANO) before and after therapy
2. Response assessment using mRANO criteria
3. Time to Progression, Progression free Survival
4. Overall survival

8 Investigational Plan

8.1 Overall Study Design and Plan – Description

Study Design

This study was an open label, monocentric Phase II study with a consolidation cohort of 10 patients subsequent to the IPAX 1 trial, which includes 10 patients in different dose regimen of ^{131}I-IPA. Administration of intravenously ^{131}I-IPA sequentially with a dose of 4 GBq before and after 2nd line external radiation therapy (XRT). Radiotherapy treatment was applied with 30 Gy in 5 fractions for low volumes (tumor diameter up to 3 cm). For tumors > 3 to ≤ 5 cm the radiation dose was 36 Gy in 18 fractions.

8.2 Discussion of Study Design

Justification of the Design

In preclinical models of GBM, ^{131}I-IPA has been shown to exert the most promising cytotoxic effect on glioma cells, when combined with simultaneous XRT. Since the effective radiation doses from ^{131}I-IPA achieved in tumor tissue only amount to about 1 Gy (Verburg 2013), the intrinsic radiation sensitizing and cytostatic activities of IPA seem to be critical for the overall antineoplastic effect.

Based on experience from previous studies a single intravenously administered dose of 2 to 7 GBq of (^{131})IPA, resulted in radiation absorbed doses to the blood of 0.80-1.47 Gy (Verburg et al. 2013). In the IPAX1 trial doses of 2 GBq were used as a single or fractionated dose with favourable tolerability profile (data are preliminary and not published yet), Dosimetry studies in these patients are outlined in the table1.

Table 1

Normalised Absorbed Dose (mGy/MBq)

Organ	Single Dose Regimen (2.0 GBq)	Fractionated Dose Regimen (3 x 0.67 GBq)
Kidney	0.0022	0.0086
Liver	0.0139	0.0128
Spleen	0.0124	0.0036
Effective Dose Equivalent	0.2377	0.1660
Effective Dose	0.1537	0.1167

Total Absorbed Dose (mGy)

Organ	Single Dose Regimen (2.0 GBq)	Fractionated Dose Regimen (3 x 0.67 GBq)
Kidney	4.33	5.74
Liver	27.73	8.55
Spleen	24.84	2.43
Effective Dose Equivalent	475.33	111.22
Effective Dose	307.33	78.17

Hence, we decided to use a fractionated dose of 4 GBq given sequentially before and 2 GBq at the end of radiotherapy (cumulative dose of 6 GBq).

After (131)IPA therapy, patients were treated with hypo-fractionated EBRT in six fractions of 5 Gy (n = 4) or in eleven fractions of 2 Gy in one case in the study of Verburg et al 2013.

There are several clinical studies in the literature on re-irradiation of gliomas. The majority of these studies is retrospective, performed with a variety of techniques and a wide range of doses, emphasizing on the fact that no standard approach exists (Nieder et al 2006).

In a review of Nieder et al 2016 the limitation of data on the optimal dose is discussed and reflects the lack of universally agreed dose-constraints for re-irradiation. Fraction sizes of 3-5 Gy appear to be well tolerated in limited-volume recurrences (<75 ml) as long as the total dose is limited to 30-35 Gy.

So we choose different to the IPAX1 trial a fractionated stereotactic radiotherapy with distinct dosages and fraction sizes dependent on tumor volume. For tumors with low volume, defined as tumor diameter of up to 3 cm, application of a dosage of 30 Gy in 5 fractions was planned. For tumors with a diameter from > 3 to ≤ 5 cm FSRT was performed with 36 Gy in 18 fractions.

Rationale of the Study

Despite aggressive surgical treatment, high-dose radiotherapy and temozolomide, the vast majority of patients with primary high-grade gliomas show disease progression within two years of initial diagnosis. Treatment options at recurrence are palliative in nature and aim at extending survival whilst maintaining quality of life, and may consist of re-resection, second line chemotherapy, re-irradiation, or combinations of these. Although several delivery approaches and fractionation schemes have been used, re-irradiation is a therapeutic approach that has long been available for the treatment of recurrent gliomas. A recent review of re-irradiation outcomes in a total of >300 recurrent GBM published by 11 different institutions using diverse radiation modalities, regimens and adjuncts (e.g. hyperbaric oxygen), reported a median PFS following re-irradiation ranging from 3–8.4 (median 5.0) months (Nieder et al. 2008). A retrospective study by Fogh et al. reported that hypofractionated re-irradiation in 147 patients with recurrent high-grade gliomas could achieve a median overall survival of 11 months. The prolonged survival was particularly observed in younger patients with smaller residual tumors, and was independent of re-resection or the combined use of chemotherapy (Fogh 2010).

This and other studies indicate that re-irradiation is an acceptable treatment option for selected patients with progressive malignant gliomas, and could provide at least several months of additional survival with a favorable adverse event profile (Pollack 2010). At present, there is no standardized re-irradiation scheme in recurrent GBM.

The MGMT promoter regulates the expression of a DNA repair enzyme, which – when inactivated by epigenetic methylation – increases the efficacy of DNA-targeted therapies, such as alkylating chemo- or radiation therapy (Esteller 2000). Previous research had suggested that, in newly diagnosed GBM treated with standard radio-chemotherapy with temozolomide (TMZ), time to progression (TTP) and overall survival (OS) are significantly longer in patients with positive MGMT promoter methylation status (MGMT+), compared to those with a negative (MGMT-) one (TTP 23.7 vs. 9.2 months, $p < 0.0001$; OS 43.6 vs. 16.8 months, $p < 0.0001$). About 35% of GBM patients are reported to be MGMT+ (Brandes 2008). However, according to a more recent publication, overall survival or progression-free survival were no longer in the group with methylated MGMT-promoter as compared to patients without that methylation (Combs 2011). In this study MGMT promoter status will only be recorded for analyses.

Using human GBM cell lines, stereotactically implanted into the brains of partially immune-competent RNU rats as a model of human GBM, ^{131}I-IPA has been demonstrated to possess the potential to eradicate established experimental GBM tumors in vivo, and to considerably prolong survival of treated (as compared to non-treated) control animals. In the same model, animals treated with a combination of ^{131}I-IPA with simultaneous external radiation therapy (XRT) showed further improved survival, compared to either ^{131}I-IPA or XRT alone, which indicates a synergistic effect of ^{131}I-IPA + XRT combination therapy (Samnick 2009). ^{131}I-IPA as a monotherapy is well tolerated, and able to induce an anti-tumor response in glioma (Baum, 2011). ^{131}I-IPA + XRT combination therapy in five compassionate use patients with intractable GBM was reported to be well tolerated, and meriting further systematic evaluation (Verburg 2013). In a further patient with primarily inoperable bi-hemispheric GBM, ^{131}I-IPA + XRT combination therapy induced radiological changes on MRI consistent with PP six weeks after end of XRT. Subsequent histological verification confirmed complete eradication of viable glioma tissue in biopsy specimens from five different tumor regions (data on file). Given the pre-clinically and clinically reported synergistic effect of ^{131}I-IPA with XRT, this study of ^{131}I-IPA in humans with recurrent HGG will explore the combination of 2nd line XRT with addition of intravenously ^{131}I-IPA. The aims of this study include the evaluation of safety, tolerability as well as the exploration of preliminary efficacy of intravenous ^{131}I-IPA administered concomitantly to 2nd line XRT in recurrent HGG.

Inclusion of patients with HGG and not only GBM takes into account the new WHO classification of brain tumors which classifies tumors in an integrated diagnosis with molecular markers. Grade IV tumors are classified in reliance of IDH1/2 status. Rationale for inclusion of patients with different 1st line treatment is the lower dose delivered in older patients following the treatment schedule for elderly patients with unmethylated tumors. These patients received radiotherapy alone but are candidates for re-irradiation in recurrence (Wick et al 2012; Malmström et al 2012).

Benefit-Risk Assessment

Substance doses of IPA up to 175 times higher than proposed for the present study were not found to induce toxicity in rats. Clinically, more than 100 patients have received IPA, labelled with 123I (Samnick et al. 2002, Hellwig et al. 2008, Hellwig et al. 2010), 131I (Baum et al. 2011, EMEA/COMP/96512/2006) or 124I (Farmakis et al. 2008) in mass doses of up to 4 mg. In the context of named-patient use cases, the following adverse effects after intravenous ^{131}I-IPA administration have been observed; nausea and vomiting, drop in platelet count (Verburg et al., 2013). A NOAEL level for IPA of 15 mg/kg in rats, corresponding to a human equivalent dose of 2.42 mg/kg support a mass dose of up to 121 mg/dose for an adult of 50 kg body weight. Based on these findings, as well as on the case studies reported by Verburg (Verburg et al. 2013), it can be assumed that intravenous doses of ^{131}I-IPA are safe and well tolerated.

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

Inclusion Criteria for all Participants

- Only Participants who met the following inclusion criteria were eligible for enrollment in this study.

1. Previously confirmed histological diagnosis of IDH1/2 wildtype HGG, with current clinical or imaging evidence for first or second recurrence according to modified RANO criteria (2017). History of standard therapy (debulking surgery, followed by radio-chemotherapy (50–60 Gy in 2 Gy fractions, temozolomide). Patients treated with Radiotherapy alone in 1st line according to the elderly GBM protocol could also be included.
2. Interval since end of 1st line XRT ≥6 months
3. Amino acid-based molecular imaging (preferably ^{18}F-FET-PET indicating pathologically increased amino acid uptake inside or in the vicinity of the tumor, clearly discernible from background activity
4. Surgery for relapsed tumor is allowed, if postoperative MRI and/or PET shows residual tumor in contrast enhanced MRI and/or ^{18}F-FET-PET.

   In recurrent tumor with no preceded surgery MRI lesion with contrast enhancement is the target.

   The target in re-operated tumors is residual tumor in CE-MRI or ^{18}F-FET-PET with metabolic tumor residuum (TBR ≥ 2)
5. Current indication for repeat radiation therapy as discussed at the multidisciplinary neuro-oncological tumor board meeting
6. Gross tumor volume (GTV) of up to 5 cm diameter, clinical target volume (CTV) 0.5 cm margin and planning target volume (PTV) ≤ 0.5 cm margin
7. Male or female ≥18 years of age.
8. Karnofsky performance status (KPS) ≥70. Life expectancy of at least 16 weeks.
9. Hematological, liver and renal function test results as follows:
   - WBC: >3*109/L

- Hemoglobin >80 g/L
- PLT >100*109/L
- ALT, ALP, AST: ≤5 times upper international limit of normal (UILN)
- Bilirubin ≤3 times UILN
- Serum creatinine: within normal limits or <120 µmol/L for patients aged 60 years or older
- Urine protein dipstick: no protein

10. Female patients surgically sterile or postmenopausal for at least 2 years. Participants of generative potential agreeing to use effective contraception during the period of therapy and 6 months after the end of study.
11. Written informed consent

8.3.2 Exclusion Criteria

Exclusion Criteria for all Participants

No Participant could participate in the study if they met any of the following criteria:

1. Primary XRT dose > 60 Gy

2. Doses to organs at risk defined by Yasar and Tugrul (2005) exceeded or reached by prior radiation therapy; e.g. cumulative total dose on the optical chiasm >54 Gy for 2 Gy/fraction, α/β=2

3. Multifocal distant recurrence, defined as tumor lesion outside the primary XRT field, as evidenced by amino acid-based PET imaging or MRI

4. Prior treatment with brachytherapy

5. Prior treatment with bevacizumab

6. History or evidence of delayed-type hypersensitivity (DTH)-dependent chronic infection (e.g. tuberculosis, systemic fungal or parasitic infection), potentially exacerbating under systemic corticoid therapy

7. Localization of tumor related to brain stem or axis, unless sufficient reserve capacity (e.g. remnant resection cavity, marked atrophy) to accommodate possible post–procedural tissue reactions, or pre-therapeutic consent for emergency trepanation

8. Hemostatic conditions, precluding catheterization or invasive procedures

9. Clinically significant illness or clinically relevant trauma within 2 weeks before the administration of the investigational product

10. Known impairment of liver or kidney function or known liver or kidney disease, such as hepatitis, cirrhosis, renal failure

11. Known human immunodeficiency virus (HIV) positive serology or chronically active hepatitis B or C

12. Ongoing toxicity > grade 2 NCI-CTC (version 4.03) from previous standard or investigational therapies

13. Administration of another investigational medicinal product within 90 days prior to screening

14. Expected non-compliance with longer-term admission at isolated nuclear medicine ward

15. In pre-menopausal women: Pregnant as evidenced by a positive pregnancy test, or breast-feeding

16. Patients with known phenylketonuria

8.3.3 Removal of Participants from Therapy or Assessment

A Participant may have withdrawn or been withdrawn from the study for the following reasons:

- If a Participant withdrew or was withdrawn prior to completion of the study, the reason for this decision was recorded in the case report forms (CRFs). The remaining follow-up safety evaluations were conducted if the Participant agreed.

- Patients may decide to withdraw from the study at any time for any reason without prejudice to their further medical care. The investigator may withdraw a patient for any of the following reasons:

- Adverse event (AE): if patient is unwilling to continue because of an AE or if continued participation of the patient would be an unnecessary risk to the patient's health, in the opinion of the investigator

  Non-compliance

  Protocol deviation

  Pregnancy

  Lost to follow-up

8.4 Treatments

8.4.1 Treatments Administered

Difference to the dosages stated in the protocol is described in Section 8.4.2.1 and 9.7.2 Protocol deviations per patient.

Table 2

Patient number	2nd line RTX	1. IPA dose/2. IPA dose
01	36Gy/18	1.7GBq/0
02	36Gy/18	1.77GBq/0
03	36Gy/18	2.4/2.5 GBq
04	36Gy/18	4.4/2.2 GBq
05	36Gy/18	3.76/no
06	36Gy/18	4.3/1.9
09	30Gy/5	4.0/1.95
11	30Gy/5	3.98/2.0

8.4.2 Investigational Product

8.4.2.1 Study drug 131I-IPA

Chemical Properties

The chemical name for the drug substance is [^{131}I]-L-4-iodophenylalanine, or (S)-2-Amino-3-(4-131iodophenyl) propanoic acid. ^{131}I-IPA has a relative molecular mass of 291.09 g/mol, and the structural formula is as follows:

Pharmaceutical Properties

^{131}I-IPA is formulated as a solution for injection in glass vials for single intravenous use. The ^{131}I-IPA therapeutic drug product is manufactured as a “ready-to-use medicine". The composition of ^{131}I-IPA solution for injection includes the active pharmaceutical ingredient in a buffered solution without other excipients, as follows:

Table3 Composition of ^{131}I-IPA ("ready for administration")

Table 2 Composition of ^{131}I-IPA ("ready for administration") Name of ingredients	**Quantity/25 mL**	**Quantity/mL**	**Function**
^{127}I-IPA (cold)	8.0–12.0 mg	0.32–0.48 mg	Excipient
Ascorbic acid	272.5 mg	10.9 mg	Excipient
Sodium ascorbate	817.5 mg	32.7 mg	Excipient

Ethanol	up to 2.8 mL	up to 0.11 mL	Excipient but not part of diluent solution
Water for injection	q.s to 25.0 mL	q.s. to 1 mL	Excipient
Final product			
^{131}I-IPA	667–6875 MBq at end of synthesis	27–275 MBq at end of synthesis	Active substance

Amount of Doses and Timing of Dose in the Study

Dose level of 4.0 GBq, ^{131}I-IPA was administered sequential before and 2 GBq at the end of radiotherapy (cumulative dose 6 GBq).

Unit doses of ^{131}I-IPA were centrally provided for each scheduled administration sufficiently in advance (typically the day before planned administration).

^{131}I-IPA was administered as an intravenous short infusion using an intravenous cannula, placed into the cubital vein of the non-dominant arm.

The difference to the dosages stated in the protocol was due to protocol deviations (file notes were made for description) and delivery difficulties of the product.

8.4.3 Prior and Concomitant Therapy

Table 4

Prior and Concomitant Therapy							
patient 01	drug	dose	unit	start	stop	indication	status at withdrawel
	Levetiracetam	2x500	mg	21.04.2021	na	seizure	ongoing
	Dexamethason	4	mg	14.12.2022	na	brain edema	ongoing
	Natriumperchlorat	3x20	gtt	05.11.2022	04.01.2023	prophylaxis	
patient 02	drug	dose	unit	start	stop	indication	status at withdrawel
	Levetiracetam	2x1000	mg	na.12.201	na	seizure	ongoing
	Lacosamid	2x100	mg	na.10.2022	na	seizure	ongoing
	Dexamethason	4	mg	15.12.2022	10.01.2023	brain edema	
	Dexamethason	2	mg	11.01.2023	17.01.2023	brain edema	
	Natriumperchlorat	3x20	gtt	18.11.2022	19.12.2022	prophylaxis	
	Dexamethason			18.01.2023	na	brain edema	ongoing
patient 03	drug	dose	unit	start	stop	indication	status at withdrawel
	Levetiracetam	2x500	mg	18.08.2020	na	brain edema	ongoing
	Natriumperchlorat	3x20	gtt	25.02.2023	12.04.2023	prophylaxis	
	Dexamethason	6	mg	27.03.2023	na	brain edema	ongoing
patient 04	drug	dose	unit	start	stop	indication	status at withdrawel
	Escitalopram	10	mg	14.03.2022	na	depression	ongoing
	Levetiracetam	2x1500	mg	01.02.2019	na	seizure	ongoing
	Ramipril	1x2.5	mg	01.02.2019	na	hypertension	ongoing
	Dabigatran	2x150	mg	01.02.2019	na	oral antigoagulation	ongoing
	Pantoprazol	1x40	mg	18.08.2022		prophylaxis	ongoing
	Natriumperchlorat	3x20	gtt	13.03.2023	10.05.2023	prophylaxis	

patient 05	drug	dose	unit	start	stop	indication	status at withdrawel
	Natriumperchlorat	3x20	gtt	17.07.2021	31.07.2021	prophylaxis	
patient 06	drug	dose	unit	start	stop	indication	status at withdrawel
	Natriumperchlorat	3x20	gtt	17.07.2023	30.08.2023	prophylaxis	
	Levetiracetam	2x1000	mg	22.09.2022	na	seizure	ongoing
	Pantoprazol	1x40	mg	10.09.2022	na	prophylaxis	ongoing
	Dexamethason	1x4	mg	23.10.2023	30.10.2023	brain edema	
	Dexamethason	1x2	mg	31.10.2023	20.11.2023	brain edema	
	Dexamethason	1x1	mg	21.11.2023	20.12.2023	brain edema	
patient 09	drug	dose	unit	start	stop	indication	status at withdrawel
	Cetiricin	as needed	mg	05.06.2024	na	atopic rhinits	ongoing
	Vitamin D	1x10	gtt	05.06.2024	na	prophylaxis	ongoing
	Azelastin hydrochlorid	as needed	spray	05.06.2024	na	atopic rhinitis	ongoing
	CBC capsules	1x1	caps.	05.06.2024	na	self medication	ongoing
	Natriumperchlorat	3x20	gtt	17.06.2024	15.07.2024	prophylaxis	
patient 11	drug	dose	unit	start	stop	indication	status at withdrawel
	Natriumperchlorat	3x20	gtt	26.08.2024	30.09.2024	prophylaxis	

8.5 Efficacy and Safety Variables

8.5.1 Table 5 Schedule of Assessments

Examination/Evaluation	**Screening**	**Treatment**								**Follow Up**			
Time point	**BL**												
Day	**-14 to -1**	**0**	**1**						**End of RTX**	**Week 4 After RTX**	**3 monthly FU**	**Early withdrawal**	**EOS visit**
h*		pre dose	dose	post dose	24	48	72	96 (A)					
Informed Consent	X												
Review Inclusion/Exclusion criteria	X												
General													
Medical History/interim history	X									X	X	X	X
MGMT promoter methylation status	X												
Physical Exam	X									X	X	X	X
Vital Signs	X									X	X	X	X
Neurological exam (NANO status)	X									X	X	X	X
Haematology	X	X						X		X			
Serum Chemistry	X	X						X		X			
Urine analysis	X	X						X		X			
Pregnancy Test	X												
12-Lead ECG	X									X			
EORTC QLQ-C30/BN20	X									X	X	X	X
Concomitant Medications	X	X						X		X	X	X	X

Baseline findings/Adverse Events	X	X						X		X	X	X	X
Outcome imaging													
[^{18}F]-FET PET	X									X	X	X	X
MRI with contrast	X									X	X	X	X
Treatment & dosimetry imaging													
XRT, 2nd line								X					
^{131}I-IPA infusion sequential			X						X				
^{131}I-IPA Brain SPECT/SPECT-CT (B)					X				X				
^{131}I-IPA whole body planar imaging (C)				X	X	X	X	X					
Hospitalisation (D)		X	X	X	X	X	X	X	X				

(A) or earlier as possible due to local radiation safety regulations

(B) SPECT imaging at 24 hours p. inf. as far as feasible
(C)Whole body planar imaging at 0.5 (±0.25), 24, 48 (±8) & once 96 hours as far as feasible in line with local radiation safety regulations,

(D) as long as necessary dependent on local radiation safety regulations

8.5.2 Efficacy Assessments

8.5.2.1 Morphological and Functional Imaging

Efficacy was assessed by morphological imaging of the brain, using contrast-enhanced cerebral MRI scans and cerebral ^{18}F-FET PET obtained at the defined time points (table 1).

Radiological and clinical response was defined as follows according to current mRANO criteria.

8.5.2.2 Survival

Patients' survival status was tracked throughout the study. Whether there is tumor progression or not was assessed using MRI and ^{18}F-FET-PET imaging, as well as all available clinical information. Increase of any one of the response parameters with or without prior improvement was defined as progression. Progression-free-survival was defined as the time period from date of progression of the tumor that leads on to inclusion in the study to the time of diagnosis of further progression.

Overall survival (OS) was calculated from date of progression of the tumor that leads on to inclusion in the study to death.

8.5.2.3 Functional Performance

The functional performance of patients was measured using physical status including vital signs and Karnofsky performance status (KPS) and Quality of life assessment.

Patients' performance was also assessed using standardized neurological status, examination neurologic assessment in neuro-oncology (NANO) status.

8.5.3 Safety Assessments

Baseline Findings

A baseline finding was defined as any untoward medical condition in a study patient who has signed the informed consent form but not yet received the first dose of the study drug. This included conditions stabilized by treatment. By definition, a baseline finding cannot be causally related to study drug; however, it may be causally related to the study (e.g. caused by study-conduct-related investigations).

Differentiation between Medical/surgical History and Baseline Findings: Conditions which started before signature of informed consent and for which no symptoms or treatment were present until the first administration of study drug (e.g. seasonal allergy without acute complaints), were recorded as medical/surgical history.

Conditions which started before signature of informed consent and for which symptoms or treatment were present between signature of informed consent and first administration of study drug (e.g. allergic pollinosis) were recorded as baseline findings.

Differentiation between Baseline Findings and Adverse Events: Conditions (e.g. abnormal physical examination findings, symptoms, diseases, laboratory, electrocardiogram [ECG]) present before the first administration of study drug were documented as baseline findings.

Conditions which started or deteriorated after the first administration of study drug were documented as adverse events.

8.5.4 Categories, Assessments and Documentation of Baseline Findings

The date and time of the first acute occurrence of the event was documented as the onset.

If the baseline finding was "continuing" into the treatment phase, no AE had to be recorded if after start of study treatment the event had the same or milder pattern and intensity. If the finding worsened in terms of either the pattern or intensity after study drug administration, the event was documented as an AE.

If the event was concluded, this was recorded in the CRF ("resolved"). If the event vanished but re-occurred during treatment, an AE with a start date of its re-occurrence was entered.

All baseline findings were assessed and documented by the investigator according to the following categories:

• Seriousness: for each baseline finding, the seriousness was determined. If serious, the baseline finding was handled in the same way as an SAE

• Intensity

• Specific drug treatment

• Specific non-drug treatment

8.5.5 Appropriateness of Measurements

All efficacy and safety measurements were standard, reliable, and widely recognized as appropriate.

8.5.6 Endpoints

8.5.6.1 Primary Endpoint(s)

To assess the safety and tolerability of intravenous ^{131}I-IPA administered concomitantly to Re- XRT in recurrent HGG

8.5.6.2 Secondary Endpoint(s)

1. To measure the quality of life before and after therapy

2. Response assessment using mRANO criteria

3. Time to Progression, Progression free Survival

4. Overall survival

8.6 Data Quality Assurance

All source documents were completed by the clinician (or other appropriate study personnel).

Data were handled in accordance with Good Clinical Practice, federal regulations, and instructions from CCR. All source documents were filled out completely by the examining personnel or the study coordinator and signed by the person collecting the data on that form. The source documents were reviewed, signed, and dated by the investigator.

8.6.1 Data Recording

8.6.1.1 Case Report Form (CRF)

Case report forms were supplied for recording all study data from each patient. It was the responsibility of the investigator to ensure that the CRFs are fully completed and that the data therein are supported by source documentation at the study center. The ‘Completion of Study’ page of the CRF were signed by the principal investigator at the end of the study confirming that he/she is satisfied with its completion and accuracy. A CRF was completed for every patient who signed an informed consent and entered the study. Study monitors must never write in the CRF.

8.6.1.2 Missing Data

If any information was not available, and it was considered by the investigator that it will never be available (e.g. the weight on a particular visit was not recorded), the investigator scored out the question box in the CRF and, if appropriate, explained on the CRF, why the investigation was missed out (e.g. the patient was not well enough to undergo the procedure). This entry was signed and dated.

8.7 Drug Logistics and Accountability

^{131}I-IPA solution for injection was supplied in glass vials in appropriate packaging (lead-shielded containers). The labels of the packaging supplied by TELIX Pharmaceuticals included the following information as a minimum:

• Name and address of sponsor

• Study number

• Name of study drug and formulation

• Dose strength

• Batch number

• Expiry date

• Storage instructions

• “For Clinical Trial Use only”.

8.7.1 Medication Numbering

A system of medication numbering in accordance with all requirements of Good Manufacturing Practice (GMP) and any applicable regulatory requirement was used. This ensured that for each patient, any dose of study drug can be identified and traced back to the original bulk ware of the active ingredients.

Lists linking all numbering levels were maintained by the institutions in charge of study drug packaging

8.7.2 Supply, Storage, Dispensation and Return

^{131}I-IPA solution for injection was manufactured, handled and stored in accordance with GMP. Production, transport and delivery was organized by the Sponsor or a designee.

Upon receipt of all required documentation, e.g. written approval from the independent ethics committee (IEC)/institutional review board (IRB) and regulatory authority, as appropriate, the coordinating investigator received patient dose orders from the sites. Patient registration occurred at least one week in advance before the planned ^{131}I-IPA administration date. The investigators at the different center delegated ordering of ^{131}I-IPA solution for injection to the coordinating investigator, overseeing eligibility and planned treatment dates. The coordinating investigator organized (or have organized by a designee) direct delivery to the center to the attention of the radiopharmacist. ^{131}I-IPA for injection was provided by Telix International Pty Ltd and used unchanged from the original state. Receipt and use of ^{131}I-IPA was limited to institution holding an appropriate handling permit by their competent national or regional authority.

^{131}I-IPA solution for injection was kept in a secure, restricted-access location at room temperature and in accordance with applicable regulatory requirements at the radiopharmacy of the respective Nuclear Medicine Department.

^{131}I-IPA doses was accompanied by an individual certificate of analysis for each batch. Upon verification of the correct radioactive dose, as specified by the study protocol, the

radiopharmacist handed over the investigational product in a syringe, kept in a lead-shielded container, to the nuclear medicine investigator, or a designated and suitably qualified deputy for administration. This syringe was labelled by the radiopharmacist according to institutional standards.

Unused quantities of the ^{131}I-IPA solution for injection were disposed at the site, according to the applicable regulations for radioactive waste from medical institutions.

8.7.3 Drug Accountability

The investigator (or pharmacist) confirmed receipt of the study drug in writing and used the study drug only within the framework of this clinical study and in accordance with this study protocol. He/she kept a record of the study drug dispensed.

Receipt, distribution and return of the study drug was properly documented giving the following information: study protocol number, sender, receiver, date, mode of transport, quantity, batch number, expiration date and retest date, if applicable. The drug accountability records was monitored at regular points.

8.8 Therapies other than Study Drug

8.8.1 Prior and Concomitant Therapy

Patients were not permitted to enter the study if they have taken any radiopharmaceutical (within a period corresponding to 8 half-lives of the radionuclide used for labelling the respective radiopharmaceutical) prior to the administration of ^{131}I-IPA. Patients were excluded from the study if they have received any other investigational medicinal product (IMP) within 90 days prior to the planned administration of study drug, and patients were permitted to take any other IMP from the screening visit to the end of follow up.

During the study period, other concomitant medication was permitted at the discretion of the investigator. There is no evidence or theoretical likelihood that ^{131}I-IPA has an effect on other concomitant medications.

Vitamins, herbal preparations and other nutritional supplements were permitted during this study.

Prior medications (within 28 days from planned dosing visit at Day 0) and all medications (including herbal medications) taken from Day 0 until EOS were recorded. At each visit, the investigator asked the patient whether any medication was taken since the previous visit. The reason for treatment, generic name, administration form, strength, dose, frequency of dosing, route of administration, start date and, if applicable, stop date was recorded in source documents and the CRF.

8.8.2 Post-study Therapy

Following completion of this study, the patients were treated according to clinical practice at the discretion of the investigator. This included treatment of the tumor disease as well as any conditions that raised during the trial. Description of these conditions and treatments will be provided in the study report as appropriate, provided the patient consents to information collection after end of study.

8.9 Statistical Methods

8.9.1 Statistical and Analytical Plans

8.9.1.1 Analysis Sets

The Full analysis set (FAS) consist of all patients who comply with the inclusion and the exclusion criteria and were included in the study, irrespective of whether or not they have received ^{131}I-IPA.

The Safety analysis set (SAF) consist of all patients of the FAS who received at least one administration of ^{131}I-IPA.

The Efficacy analysis set consist of all patients of the SAF, who:

• Have received ^{131}I-IPA + XRT combination therapy and for whom sufficient follow-up data (imaging, clinical) are available to assess either response (morphological, metabolic) or survival parameters (PFS, OS).

• do had not major protocol deviations

8.9.1.2 Statistical Analyses

Statistical analyses was performed after database lock, after all study data including the EOS visit have been collected and cleaned.

The statistical analyses in this study are primarily descriptive.

Descriptive analyses will include:

• Mean, standard deviation, median and range for continuous variables,

• Median, range and frequency distribution for discrete (ordinal) variables,

• Frequency distribution for nominal variables

8.9.1.3 Determination of Sample Size

It was planned to include up to 10. The potential risk to humans is low in this study. Nevertheless, the number of patients should be as low as possible for ethical reasons, in particular in view of the radiation exposure, since at present, the efficacy of the product remains to be established in humans. The chosen number of glioma patients appears to be a reasonable compromise to address the study purposes, in particular to get sufficient information on the safety and to avoid unnecessary application of radiation.

8.10 Changes in the Conduct of the Study or Planned Analyses

The original IRB-approved protocol IPAX Linz protocol version 1.0 was dated 17.11.2021. There were no amendments.

9 Study Participants

It was anticipated to recruit approximately 10 male or female patients ≥18 years old with previously diagnosed IDH1/2 wildtype HGG, who are scheduled for 2nd line XRT, due to diagnosis of recurrence or progression of their disease. Disease progression was defined according to modified RANO Criteria 2017 (Ellingson et al. 2017).

9.1. Demographic and other Baseline Characteristics

The following demographic characteristics were recorded:

• date of birth or age, depending on local EC requirements

• weight, height

9.2 Medical and Surgical History

Medical/surgical history and medical conditions present before the administration of ^{131}I-IPA were recorded at the screening visit.

9.3 Prior and Concomitant Medication

Prior and concomitant medication were recorded at screening and throughout the study, beginning on Day 0, until the EOS visit.

9.4 Baseline Imaging

Routine structural imaging of the brain using contrast enhanced MRI (T1, T2 weighed), as routinely performed at the institution for the investigation of HGG, not older than 30 days, calculated from the date of first dose was available from routine work-up (diagnosis of recurrence). Subjects also received baseline imaging using [^{18}F]-FET PET imaging, available from routine work-up, not older than 30 days at the first ^{131}I-IPA dose.

The imaging methodology were conducted according to the institutional routine practice.

9.5 History of Glioma

In order to participate in the study, the patients must have diagnosis of recurrent IDH1/2 wildtype HGG. Diagnosis of HGG was based on clinical and/or imaging criteria, with histological confirmation of the diagnosis, and there was a current clinical, imaging or histological evidence for recurrence, requiring therapy. The patients' Karnofsky performance status was ≥70%, and they should have a life expectancy of at least 16 weeks.

9.6 Pregnancy Tests and Assessment of Postmenopausal Status

Part of the blood samples taken for the clinical laboratory tests at screening and on day 14 were used to perform a serum β-HCG pregnancy test in women of childbearing potential. Alternatively, a urine pregnancy test was performed. In postmenopausal patients < 55 years, a permanent postmenopausal status must be proven through history of hysterectomy or last spontaneous bleeding at least 2 years before start of the study.

9.7 Protocol Deviations

9.7.1 Screen failures

Patient 07: screening baseline MRI showed no tumor after resection 2 months prior screening

9.7.2 Protocol deviations per patient

Patient 4: Patient 4 was included in the study even though he had already experienced his third relapse. This was a decision made by the PI (sponsor) because the patient was in excellent health condition and had not yet received any other treatment other than surgery.

Patient 08: The patient was withdrawn from study because of delivery problems with the IMP. The manufacturer of the study drug Seibersdorf Labor GmbH has unexpected problem to get an important drug ingredient on the global market. This issue is a protocol violation (drug non-compliance) according pt. 4.4.2 of the study protocol.

Patient 10: The patient was withdrawn from study because of delivery problems with the IMP. The manufacturer of the study drug Seibersdorf Labor GmbH has unexpected problem to get an important drug ingredient on the global market. This issue is a protocol violation (drug non-compliance) according pt. 4.4.2 of the study protocol.

Patient 01: The ^{131}IPA infusion at the end of RTX couldn`t be administered according to protocol because of delivery problems with the IMP. The manufacturer of the study drug Seibersdorf Labor GmbH has an unexpected problem to get an important drug ingredient on the global market.

CAPA: To avoid the same issue in the future, the PI will already clarify the availability of IMP with the manufacturer Siebersdorf GmbH before any IMP administration will be planned. This issue was documented in the source data and in the CRF as well.

Patient 02: The 131IPA infusion at the end of RTX couldn`t be administered according to protocol because of delivery problems with the IMP. The manufacturer of the study drug Seibersdorf Labor GmbH has an unexpected problem to get an important drug ingredient on the global market.

CAPA: To avoid the same issue in the future, the PI will already clarify the availability of IMP with the manufacturer Siebersdorf GmbH before any IMP administration will be planned. This issue was documented in the source data and in the CRF as well.

Patient 5: the 2nd ^{131} IPA dose was not administered as a decision of the investigator because of safety reasons with hematological toxicity raised after 1st dose and this finding was assessed as possible related to the first drug application.

Patient 01, 02, 03: these patients received a reduced dose before RTX.

Reason for deviation: Start of therapy with first patient was delayed due to regulatory problems, first protocol draft version from October 2021with 2 GBq dose before RTX was communicated with Nuclear Medicine Department and they used this draft for the first three patients. The protocol submitted to EC was the final version one month later with 4 GBq before and 2 GBq after RTX. Despite this deviation of dose outlined in the final protocol no safety problems will arise with a lower dose. In patient 03 ordering of the lower dose cannot be changed before start, so the patient receives 2 GBq before and 2 GBq after RTX, but with this change we are in a safe range.

1. CAPA: the three patients were already informed about this protocol deviation but they have already confirmed to continue the study.

2. Correct protocol version was provided to all participating centers.

9.7.3 General Protocol deviation

Whole body planar imaging was deleted due to the discretion of the treating physician. But this investigation was rated as feasible/possible as outlined in the schedule of assessment 3.4 Study Flow Chart (Table 1): *(C)Whole body planar imaging at 0.5 (±0.25), 24, 48 (±8) & once 96 hours as far as feasible in line with local radiation safety regulations.*

10 Efficacy Evaluation

10.1 Demographic and Other Baseline Characteristics

Table 6 baseline characteristics per included person

patient	01	02	03	04	05	06	09	11
Age at diagnosis	66	48	56	55	61	66	33	61
Tumor extent at baseline mm^2	663	738	930	420	47	221	300	110
KPS	90	90	100	70	90	90	80	100
MGMT Methylation /yes /no	yes	no	no	no	no	no	yes	yes
Primary treatment								
RTX 60 Gy	yes	yes	yes	yes	yes	yes	yes	yes
Concomitant TMZ	yes	yes	yes	yes	yes	yes	yes	yes
Adj TMZ	yes	yes	no	yes	yes	yes	yes	yes
+Tumor treating Fields	-	-	-	-	-	-	yes	yes
Treatment before start of IPA	-	Re-op	Re-op	Re-op	-	-	-	Re-op
Time between 1. diagnosis and 1. relapse in months (PFS1)	21.4	7.9	21.5	36.3	9	7.8	25.8	10.6

Table 7 Clinical characteristics in patients with recurrent glioblastoma

	N=8	Range
	mean	
Age at diagnosis	55.7	33 - 66
KPS	88.7	70 - 100
Tumor extent at baseline mm2	428	47 - 930
	median	
PFS1	16.0 months	7.8 – 36.3
Time between 1. relapse and start of IPA in weeks	8.8 weeks	4.4 – 56.8
Time from MRI baseline to 1. FU MRI in weeks	9.0 weeks	7.0 – 12.0
	N =8	
MGMT Methylated/unmethylated	3/5	
Primary treatment		
RTX 60 Gy	8	
Concomitant TMZ	8	
Adj TMZ	7	
+Tumor treating Fields	2	
Re-Op before IPA treatment	5	1 - 2

10.2 Measurements of Treatment Compliance

^{131}I-IPA was administered by study personnel at the site. A record of the number of ^{131}I-IPA doses dispensed to each patient was maintained and reconciled with study treatment and compliance records. Details of each study drug administration were recorded in appropriate source documents.

10.3 Efficacy Results and Tabulations of Individual Participant Data

Table 8

N=8	median	range
Time between 1. diagnosis and Relapse before inclusion	15.5 months	7– 36 months
Time between relapse and start of therapy	6 weeks	4.4 – 10.7 weeks
mPFS from relapse before IPA start to next progression (PFS2)	14.9 weeks	12.1 – 25 weeks
mOS from 1. diagnosis	32.2 months	19.4-60.4 months
mOS from 1. relapse	11.9 months	6.1 – 23.8 months

Table 9 Time between 1. diagnosis and relapse before inclusion

patient	initial diagnosis	1. Relapse	PFS months
01	19.12.2020	07.10.2022	21
02	24.01.2022	21.09.2022	7
03	25.08.2020	07.06.2022	21
04	06.02.2019	08.02.2022	36
05	15.09.2022	14.06.2023	8
06	21.09.2022	16.05.2023	7
09	25.02.2022	16.04.2024	25
11	16.03.2023	01.02.2024	10

Table 10 Number of relapses and re-Op in all patients

Relapses before IPA treatment	1. Relapse after initial diagnosis before inclusion	re_op_before_IPAX	2. Relapse after Re-Op	3. Relapse after Re-Re-Op	Relapse_MR_Date before inclusion
1	07.10.2022	no			07.10.2022
1	07.09.2022	17.10.2022			07.09.2022
2	07.06.2022	22.07.2022	31.01.2023		31.01.2023
3	08.02.2022	25.02.2022, and 18.11.2022	27.10.2022	01.02.2023	01.02.2023
1	14.06.2023	no			14.06.2023
1	16.05.2023	no			16.05.2023
1	16.04.2024	03.05.2024			16.04.2024
2	01.02.2024	20.02.2024 and 29.07.2024	12.07.2024		12.07.2024

Table 11 Time between relapse and start of therapy

patient	Relapse MRI	start therapy	weeks delay
01	07.10.2022	07.11.2022	4.4
02	07.09.2022	21.11.2022	10.7
03	31.01.2023	27.02.2023	3.8
04	01.02.2023	13.03.2023	5.7
05	14.06.2023	17.07.2023	4.7
06	16.05.2023	17.07.2023	8.8
09	16.04.2024	17.06.2024	8.8
11	12.07.2024	26.08.2024	6.4

Table 12 Time between relapse before IPA therapy and next progression (PFS 2)

patient	1.relapse	2. relapse	weeks
01	07.10.2022	04.01.2023	12.7
02	07.09.2022	18.01.2023	19
03	31.01.2023	26.04.2023	12.1
04	01.02.2023	10.05.2023	14
05	14.06.2023	06.12.2023	25
06	16.05.2023	20.09.2023	18.1
09	16.04.2024	05.08.2024	15.8
11	12.07.2024	16.10.2024	13.7

Table 13 mOS from relapse before inclusion until death/last FU (OS2)

11.9 months (95 % CI 3.966-20.834) months

patient	Relapse_MR_Date before inclusion	date_death/ last FU	months
01	07.10.2022	28.07.2023	9,8
02	07.09.2022	30.08.2023	11,4
03	31.01.2023	13.06.2023	12,4
04	01.02.2023	24.01.2024	23,8
05	14.06.2023	04.01.2025	19
06	16.05.2023	alive/13.08.2025	n.r.
09	16.04.2024	17.10.2024	6,1
11	12.07.2024	30.04.2025	9.6

Table 14 mOS from initial diagnosis to death (OS1)

32.2 months (CI 95 % 30.937-33.463)

patient	initial diagnosis	Death/Last FU	months
01	19.12.2020	28.07.2023	31,7

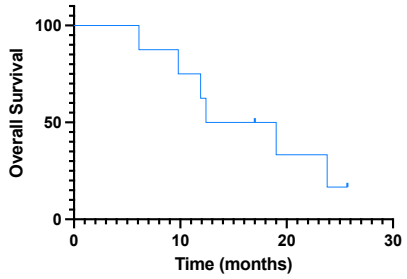
02	24.01.2022	30.08.2023	19,4
03	25.08.2020	13.06.2023	34,1
04	06.02.2019	24.01.2024	60,4
05	15.09.2022	04.01.2025	28,1
06	21.09.2022	alive/13.08.2025	n.r.
09	25.02.2022	17.10.2024	32,2
11	16.03.2023	30.04.2025	25.4

Table 15 Treatment applied on individual patient

Patient	2nd line RTX Gy/fractions	^{131}I-IPA dose 1st/2nd
01	36Gy/18	1.7GBq/0
02	36Gy/18	1.77GBq/0
03	36Gy/18	2.4/2.5 GBq
04	36Gy/18	4.4/2.2 GBq
05	36Gy/18	3.76/no
06	36Gy/18	4.3/1.9
09	30Gy/5	4.0/1.95
11	30Gy/5	3.98/2.0

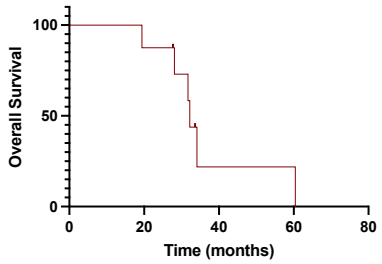
Figure 1

OS 2 (first progression – death)



Median OS2: 11.9 months (95 % CI 3.966-20.834), Deaths 7/8; censored 1/8, Last follow up June 2025

OS 1 (initial diagnosis – death)



Median OS1: 32.2 months (CI 95 % 30.937-33.463), Deaths:7/8; censored 1/8, Last follow up June 2025

10.3.1 Tabulation of Individual Response Data

Table 1 MRI response (according to mRANO)

PD clinical: clinical deterioration without confirmed morphological progression (patient refused): PD systemic: extracerebral metastasis

Table 16

patient number	Relapse_MR_Date	Start_IPA_therapy	MRI_baseline	1FU-MRI	assessment cm2	2FU-MRI	assessment cm2
	before inclusion		date	date	SD/PD/PR/CR	date	SD/PD/PR/CR
01	07.10.2022	07.11.2022	24.10.2022	04.01.2023	PD	EOS	
02	07.09.2022	21.11.2022	16.11.2022	18.01.2023	PD	EOS	
03	31.01.2023	27.02.2023	22.02.2023	26.04.2023 not done/pat refused	PD clinical	EOS	
04	01.02.2023	13.03.2023	01.03.2023	10.05.2023	PD	02.08.2023	PD
05	14.06.2023	17.07.2023	12.07.2023	13.09.2023	SD	06.12.2023	PD
06	16.05.2023	17.07.2023	28.06.2023	20.09.2023	PD	20.12.2023	PD
09	16.04.2024	17.06.2024	05.06.2024	24.07.2024	PD systemic SD cerebral	02.09.2024	PD systemic, SD cerebral
11	12.07.2024	26.08.2024	21.08.2024	16.10.2024	PD	28.11.2024	PD

Table 17 FET-PET response (classified using PET-RANO criteria, which are not defined in the protocol because they were published only after the protocol was finalized, but are now standard for response assessment with FET-PET in gliomas)

patient number	BL_FET_PET	1FU_FET_PET	PET RANO 1.0	2FU_FET_PET	PET RANO 1.0
	date	date	SD/PD/PR/CR	date	SD/PD/PR/CR
001	02.11.2022	04.01.2023	PD		
002	16.11.2022	18.01.2023	PD		
003	22.02.2023	not done			
004	01.03.2023	10.05.2023	PD		
005	12.07.2023	13.09.2023	SD	06.12.2023	PD
006	28.06.2023	20.09.2023	SD	20.12.2023	PD
009	05.06.2024	24.07.2024	SD	Not done/ systemic PD	
011	21.08.2024	16.10.2024	PD		

10.4 Efficacy Conclusions

Safety and tolerability:

Treatment was well tolerated with no serious adverse events. 3 patients experienced an adverse event deemed possibly-related to ^{131}I-IPA only (1 leucopenia grade 2; 1 lymphopenia grade 3 and 1 thrombocytopenia grade 3). 1 patient experienced fatigue grade 2 deemed possibly-related to XRT. Detailed adverse event information is outlined in table 3.

Quality of life: Descriptive analysis shows no relevant impact on quality of life due to the short duration of active treatment and less side effects. Only the isolation after ^{131}I-IPA injection causes some discomfort on the patients.

Best response was stable disease, but overall survival was quite good.

Theranostic approach with ^{131}I-IPA and its companion diagnostic, 18F-FET, is a novel and promising approach with a favorable safety and tolerability profile for GBM patients. The findings of this study support the potential for higher administered doses of ^{131}I-IPA to treat recurrent GBM in combination with re-RT. This theranostic approach should be pursued further in prospective randomized controlled studies.

11. Safety Evaluation

11.1 Extent of Exposure

The extent of radioactive exposure is determined by the half-life of iodine-131 and is dependent on the dose of ^{131}J-IPA, as specified in the IB. External radiotherapy was performed using standard photon radiation.

11.2 Adverse Events

11.2.1 Brief Summary of Adverse Events

No serious adverse event occurred, 3 patients experienced an adverse event (1 leucopenia grade 2, 1 lymphopenia grade 3, 1 thrombocytopenia grade 3, 1 fatigue grade 2).

11.2.2 Analysis of Adverse Events

Table 18

AE: 3 patients	adverse event deemed possibly-related to ^{131}I-IPA only	adverse event deemed possibly-related to XRT
	1 leucopenia grade 2 1 lymphopenia grade 3 1 thrombocytopenia grade 3	1 fatigue grade 2

11.2.3 Listing of Adverse Events by Participant

Table 19

patient	AE Term	AE grade	Start date	End Date	Ongoing after EOS	Action taken
04	lymphopenia	2	10.05.2023	na	yes grade 1	none
	leucopenia	2	10.05.2023	na	yes grade 1	none
05	platelet count decreased	3	16.08.2023	13.09.2023	no	2nd dose not applied
	lymphopenia	3	16.08.2023	na	yes grade 2	2nd dose not applied
	leucopenia	2	13.09.2023	09.10.2023	no	2nd dose not applied
06	fatigue	2	25.08.2023	na	yes grade 1	none

11.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No serious adverse events occurred.

7 of 8 patients died due to underlying GBM disease. At time of report 1 patients stayed alive.

11.4 Clinical Laboratory Evaluation

11.4.1 Listing of Individual Laboratory Measurements by Participant and Each Abnormal Laboratory Value

Patient 01: BL to end of study (PD) lab values

Auftragsnummer			L2210240096		L2301040057	
Datum			24.10.2022		04.01.2023	
Uhrzeit			08:42		07:55	
Hämatologie - Blutbild (NMC)						
3.6 - 10.5	G/L	Leukozyten	9.3		15.3	HH
130 - 350	G/L	Thrombozyten	471	H	457	H
3.85 - 5.20	T/L	Erythrozyten	4.15		4.06	
11.8 - 15.8	g/dL	Hämoglobin	11.8		12.2	
35.0 - 45.5	%	Hämatokrit	37.2		38.1	
80.0 - 101.0	fL	MCV	89.7		93.7	
27.0 - 34.0	pg	MCH	28.5		30.0	
31.5 - 36.0	g/dL	MCHC	31.8		32.0	
11.5 - 14.7	%	RDW-CV	12.6		14.3	
5.9 - 9.9	fL	MPV	8.5		8.2	
1.5 - 7.7	G/L	Neutroph. Gra	5.9		13.4	HH
1.1 - 4.0	G/L	Lymphozyten a	2.1		1.1	
0.1 - 0.9	G/L	Monozyten abs	0.7		0.7	
0.0 - 0.5	G/L	Eosinophile G	0.2		0.1	
0.0 - 0.2	G/L	Basophile Gr.	0.1		0.0	
0.0 - 0.4	G/L	LUC abs.	0.2		0.1	
42.0 - 77.0	%	Neutroph. Gra	64.1		87.4	HH
20.0 - 44.0	%	Lymphozyten r	22.7		7.1	LL
2.0 - 9.5	%	Monozyten rel	8.0		4.3	
0.5 - 5.5	%	Eosinophile G	2.4		0.5	
0.0 - 1.8	%	Basophile Gr.	0.6		0.1	
0.0 - 4.0	%	LUC rel.	2.2	*	0.5	*
Hämostaseologie - Globaltests						
		Therapie:	siehe Kom.	*	siehe Kom.	*
78 - 123	%	PTZ (Prothrom	130	H	130	H
		INR	x	*	x	*
22 - 29	sek	aPTT	24		22	
14 - 21	sek	Thrombinzeit	15		16	
170 - 420	mg/dL	Fibrinogen	354		332	
79 - 120	%	AT III Aktivi	111		118	
Klinische Chemie - Niere/Elektrolyt						
136 - 145	mmol/L	Natrium	141		137	
3.5 - 4.6	mmol/L	Kalium	x	*	3.8	*
98 - 107	mmol/L	Chlorid	103		101	
2.20 - 2.55	mmol/L	Calcium	2.46		2.33	
0.81 - 1.45	mmol/L	Phosphat			0.80	L
0.51 - 0.95	mg/dL	Kreatinin	0.68		0.73	
90 - 160	mL/min/1	GFR (CKD-EPI)	> 90	*	89	L*
8 - 23	mg/dL	BUN	13		20	
2.4 - 5.7	mg/dL	Harnsäure	4.6			

Klinische Chemie - Leber/Pankreas				
10 - 35	U/L	ASAT (GOT)	x *	x *
10 - 35	U/L	ALAT (GPT)	18	15
6 - 42	U/L	Gamma-GT	14	15
35 - 104	U/L	Alk.Phosphata	97	72
5320 - 12920	U/L	Cholinesteras	8202	7045
0.00 - 1.20	mg/dL	Bilirubin	0.33	0.39
13 - 60	U/L	Lipase	38	42
13 - 53	U/L	Pankreas-Amyl	41	53
Klinische Chemie - Glukosestoffwech				
60 - 140	mg/dL	Glucose postp	84	118
Proteindiagnostik				
64.0 - 87.0	g/L	Totalprotein	77.7	64.0
3500.00 - 52	mg/dL	Albumin		3620.00
Urinstreifen				
		Mittelstrahlh	eingelangt	eingelangt
1.010 - 1.03		Spez.Gew./U T	1.005 L	1.017
5.0 - 8.0		pH /U Teststr	5.5	< =5.0/L
0 - 24	/µL	Leuko /U Test	25 H	75 HH
		Nitrit /U ql.	neg	POS HH
0 - 4	/µL	Hgb(Ery) /U T	neg	10 H
0 - 20	mg/dL	Tot.Prot./U T	neg	neg
0 - 49	mg/dL	Glucose/U Tes	neg	neg
0 - 5	mg/dL	Keton /U Test	neg	neg
0.0 - 0.2	mg/dL	Bilirubin/U T	neg	neg
0.0 - 1.9	mg/dL	Urobilin./U T	norm	norm
0 - 19	mg/dL	Ascorbin. /U	0	0
		Urinfarbe	hellgelb	hellgelb
Urinsediment				
		Erythrozyten		vereinzelt
		Leukozyten /U	vereinzelt	mäßig
		Bakterien /US		massenhaft
		Rundepithelie		vereinzelt

Patient 02: BL to end of study (PD) lab values

Auftragsnummer			L2211160459	L2301180112
Datum			16.11.2022	18.01.2023
Uhrzeit			14:09	08:26
Hämatologie - Blutbild (NMC)				
4.1 - 11.8	G/L	Leukozyten	3.9 L	5.2
130 - 350	G/L	Thrombozyten	226	113 L*
4.01 - 5.29	T/L	Erythrozyten	3.84 L	3.72 L
12.4 - 16.1	g/dL	Hämoglobin	12.4	12.5
35.4 - 46.3	%	Hämatokrit	37.2	37.8
80.1 - 95.3	fL	MCV	96.9 H	101.4 HH
27.0 - 32.9	pg	MCH	32.2	33.6 H
32.6 - 36.5	g/dL	MCHC	33.3	33.2
11.5 - 14.7	%	RDW-CV	13.3	14.6
5.9 - 9.9	fL	MPV	6.8	6.8
2.1 - 7.7	G/L	Neutroph. Gra	2.7	4.3
1.2 - 3.5	G/L	Lymphozyten a	0.7 LL	0.6 LL
0.2 - 0.7	G/L	Monozyten abs	0.4	0.3
0.0 - 0.5	G/L	Eosinophile G	0.1	0.0
0.0 - 0.1	G/L	Basophile Gr.	0.0	0.0
0.0 - 0.4	G/L	LUC abs.	0.1	0.1
42.0 - 77.0	%	Neutroph. Gra	67.6	82.2 H
20.0 - 44.0	%	Lymphozyten r	18.7 L	11.0 LL
2.0 - 9.5	%	Monozyten rel	9.4	4.9
0.5 - 5.5	%	Eosinophile G	1.3	0.5
0.0 - 1.8	%	Basophile Gr.	0.4	0.2
0.0 - 4.0	%	LUC rel.	2.6 *	1.2 *
Differentialblutbild manuell (NMC)				
40 - 70	%	Segmentkern.		
20 - 44	%	Lymphozyten r		
2 - 10	%	Monozyten rel		
1 - 6	%	Eosinoph.Gr.r		
		Kommentar Dif		
Hämostaseologie - Globaltests				
		EXTEM		
		INTEM		
		FIBTEM		
		APTEM		
		Therapie:	siehe Kom. *	siehe Kom. *
78 - 123	%	PTZ (Prothrom	114	> 150 HH
		INR	x *	x *
22 - 29	sek	aPTT	27	24
14 - 21	sek	Thrombinzeit	15	16
170 - 420	mg/dL	Fibrinogen	465 H	260
79 - 120	%	AT III Aktivi	113	127 H
Klinische Chemie - Entzündungsmarke				
0.0 - 0.5	mg/dL	CRP		
1 - 20	mm/h	Blutsenkung		

Klinische Chemie - Niere/Elektrolyt						
136 - 145	mmol/L	Natrium	135	L	138	
3.5 - 4.6	mmol/L	Kalium	4.0		4.5	
98 - 107	mmol/L	Chlorid	98		100	
2.15 - 2.50	mmol/L	Calcium	2.30		2.34	
0.81 - 1.45	mmol/L	Phosphat	1.26		1.57	H
0.51 - 0.95	mg/dL	Kreatinin	0.71		0.73	
90 - 160	mL/min/1	GFR (CKD-EPI)	> 90	*	> 90	*
6 - 20	mg/dL	BUN	12		20	
2.4 - 5.7	mg/dL	Harnsäure				
Klinische Chemie - Leber/Pankreas						
10 - 35	U/L	ASAT (GOT)	12		15	
10 - 35	U/L	ALAT (GPT)	9	L	16	
6 - 42	U/L	Gamma-GT	11		15	
35 - 104	U/L	Alk.Phosphata	94		64	
5320 - 12920	U/L	Cholinesteras	8057		7905	
0.00 - 1.20	mg/dL	Bilirubin	0.27		0.21	
13 - 60	U/L	Lipase	35		54	
13 - 53	U/L	Pankreas-Amyl	44		63	H
Klinische Chemie - Hämolysemarker						
135 - 250	U/L	LDH				
Klinische Chemie - Glukosestoffwech						
60 - 100	mg/dL	Glucose				
60 - 140	mg/dL	Glucose postp	106		111	
Klinische Chemie - Fettstoffwechsel						
120 - 200	mg/dL	Cholesterin				
50 - 200	mg/dL	Triglyceride				
Proteindiagnostik						
64.0 - 87.0	g/L	Totalprotein	72.3		69.4	
3500.00 - 52	mg/dL	Albumin	4350.00		4250.00	
Harnchemie						
0.0 - 20.0	mg/dL	Glucose /U	11.0			
Molekulare Infektionsdiagnostik						
	pos/neg	COVID Antigen				

Patient 03: BL to end of study (PD) lab values

Auftragsnummer			L2302220148		
Datum			22.02.2023		
Uhrzeit			09:17		
Hämatologie - Blutbild (NMC)					
4.1 - 11.8	G/L	Leukozyten	5.7		
130 - 350	G/L	Thrombozyten	250		
4.01 - 5.29	T/L	Erythrozyten	4.47		
12.4 - 16.1	g/dL	Hämoglobin	13.0		
35.4 - 46.3	%	Hämatokrit	37.9		
80.1 - 95.3	fL	MCV	84.8		
27.0 - 32.9	pg	MCH	29.1		
32.6 - 36.5	g/dL	MCHC	34.3		
11.5 - 14.7	%	RDW-CV	12.7		
5.9 - 9.9	fL	MPV	7.5		
2.1 - 7.7	G/L	Neutroph. Gra	3.7		
1.2 - 3.5	G/L	Lymphozyten a	1.5		
0.2 - 0.7	G/L	Monozyten abs	0.3		
0.0 - 0.5	G/L	Eosinophile G	0.0		
0.0 - 0.1	G/L	Basophile Gr.	0.0		
0.0 - 0.4	G/L	LUC abs.	0.1		
42.0 - 77.0	%	Neutroph. Gra	64.3		
20.0 - 44.0	%	Lymphozyten r	26.7		
2.0 - 9.5	%	Monozyten rel	6.1		
0.5 - 5.5	%	Eosinophile G	0.8		
0.0 - 1.8	%	Basophile Gr.	0.3		
0.0 - 4.0	%	LUC rel.	1.9	*	
Hämostaseologie - Globaltests					
		Therapie:	siehe Kom.	*	
78 - 123	%	PTZ (Prothrom	111		
		INR	x	*	
22 - 29	sek	aPTT	25		
14 - 21	sek	Thrombinzeit	16		
170 - 420	mg/dL	Fibrinogen	370		
79 - 120	%	AT III Aktivi	120		
Klinische Chemie - Niere/Elektrolyt					
136 - 145	mmol/L	Natrium	134	L	
3.5 - 4.6	mmol/L	Kalium	4.2	*	
98 - 107	mmol/L	Chlorid	100		
2.15 - 2.50	mmol/L	Calcium	2.39		
0.81 - 1.45	mmol/L	Phosphat	1.03		
0.51 - 0.95	mg/dL	Kreatinin	0.57		
90 - 160	mL/min/1	GFR (CKD-EPI)	> 90	*	
6 - 20	mg/dL	BUN	10		

Klinische Chemie - Leber/Pankreas				
10 - 35	U/L	ASAT (GOT)	x	*
10 - 35	U/L	ALAT (GPT)	18	
6 - 42	U/L	Gamma-GT	11	
35 - 104	U/L	Alk.Phosphata	71	
5320 - 12920	U/L	Cholinesteras	8305	
0.00 - 1.20	mg/dL	Bilirubin	0.46	
13 - 60	U/L	Lipase	32	
13 - 53	U/L	Pankreas-Amyl	29	
Klinische Chemie - Glukosestoffwech				
60 - 140	mg/dL	Glucose postp	89	
Proteindiagnostik				
64.0 - 87.0	g/L	Totalprotein	72.4	
3500.00 - 52	mg/dL	Albumin	4400.00	
Urinstreifen				
		Mittelstrahlh	eingelangt	
1.010 - 1.03		Spez.Gew./U T	1.022	
5.0 - 8.0		pH /U Teststr	6.0	
0 - 24	/µL	Leuko /U Test	25	H
		Nitrit /U ql.	neg	
0 - 4	/µL	Hgb(Ery) /U T	10	H
0 - 20	mg/dL	Tot.Prot./U T	neg	
0 - 49	mg/dL	Glucose/U Tes	neg	
0 - 5	mg/dL	Keton /U Test	5	
0.0 - 0.2	mg/dL	Bilirubin/U T	neg	
0.0 - 1.9	mg/dL	Urobilin./U T	norm	
0 - 19	mg/dL	Ascorbin. /U	0	
		Urinfarbe	gelb	
Urinsediment				
		Erythrozyten	vereinzelt	
		Schleimfäden	vereinzelt	

Patient 04: BL to end of study (PD) lab values

Treatment applied from 13.03.2023 – 12.04.2023

Auftragsnummer			L2303010487		L2305100088		L2305100201	
Datum			01.03.2023		10.05.2023		10.05.2023	
Uhrzeit			14:04		08:19		10:30	
Hämatologie - Blutbild (NMC)								
3.8 - 10.3	G/L	Leukozyten	4.8				2.8	LL
130 - 350	G/L	Thrombozyten	274				213	
4.57 - 5.98	T/L	Erythrozyten	4.99				4.31	L
13.9 - 17.7	g/dL	Hämoglobin	16.6				14.6	
39.6 - 51.8	%	Hämatokrit	47.0				41.5	
80.1 - 95.3	fL	MCV	94.2				96.5	H
27.6 - 33.2	pg	MCH	33.2				33.8	H
33.0 - 37.2	g/dL	MCHC	35.2				35.0	
11.5 - 14.7	%	RDW-CV	11.4	L			12.9	
5.9 - 9.9	fL	MPV	7.6				6.8	
1.8 - 7.0	G/L	Neutroph. Gra	3.2				2.0	
1.1 - 3.1	G/L	Lymphozyten a	1.2				0.5	LL
0.2 - 0.7	G/L	Monozyten abs	0.2				0.2	
0.0 - 0.5	G/L	Eosinophile G	0.1				0.0	
0.0 - 0.1	G/L	Basophile Gr.	0.0				0.0	
0.0 - 0.4	G/L	LUC abs.	0.0				0.0	
42.0 - 77.0	%	Neutroph. Gra	66.5				71.3	
20.0 - 44.0	%	Lymphozyten r	25.9				17.6	L
2.0 - 9.5	%	Monozyten rel	4.6				8.4	
0.5 - 5.5	%	Eosinophile G	1.7				0.6	
0.0 - 1.8	%	Basophile Gr.	0.6				0.6	
0.0 - 4.0	%	LUC rel.	0.7	*			1.5	*
Hämostaseologie - Globaltests								
		Therapie:	siehe Kom.	*			siehe Kom.	*
78 - 123	%	PTZ (Prothrom	78				78	
		INR	x	*			x	*
22 - 29	sek	aPTT	42	H			45	H
14 - 21	sek	Thrombinzeit	> 160	HH*			> 160	HH
170 - 420	mg/dL	Fibrinogen	426	H			332	
79 - 120	%	AT III Aktivi	107				101	
Klinische Chemie - Niere/Elektrolyt								
136 - 145	mmol/L	Natrium	139				134	L
3.5 - 4.6	mmol/L	Kalium	3.9	*			4.0	*
98 - 107	mmol/L	Chlorid	103					
2.20 - 2.55	mmol/L	Calcium	2.42	*			2.38	
0.81 - 1.45	mmol/L	Phosphat	1.10					
0.67 - 1.17	mg/dL	Kreatinin	0.86		0.85		0.82	
90 - 160	mL/min/1	GFR (CKD-EPI)	> 90	*	> 90	*	> 90	*
8 - 23	mg/dL	BUN	8	*			13	

Klinische Chemie - Leber/Pankreas							
10 - 50	U/L	ASAT (GOT)	19	*		x	*
10 - 50	U/L	ALAT (GPT)	21			13	
10 - 71	U/L	Gamma-GT	18			17	
40 - 129	U/L	Alk.Phosphata	74			67	
5320 - 12920	U/L	Cholinesteras	7910				
0.00 - 1.20	mg/dL	Bilirubin	0.64				
13 - 60	U/L	Lipase	25			25	
13 - 53	U/L	Pankreas-Amyl	29			30	
Klinische Chemie - Glukosestoffwech							
60 - 100	mg/dL	Glucose				100	
60 - 140	mg/dL	Glucose postp	91				
Proteindiagnostik							
64.0 - 87.0	g/L	Totalprotein	74.2			69.5	
3500.00 - 52	mg/dL	Albumin	4240.00				
Urinstreifen							
		Mittelstrahlh	eingelangt			eingelangt	
1.010 - 1.03		Spez.Gew./U T	1.018			1.035	
5.0 - 8.0		pH /U Teststr	5.5			5.5	
0 - 24	/µL	Leuko /U Test	neg			neg	
		Nitrit /U ql.	neg			neg	
0 - 4	/µL	Hgb(Ery) /U T	10	H		10	H
0 - 20	mg/dL	Tot.Prot./U T	neg			neg	
0 - 49	mg/dL	Glucose/U Tes	neg			neg	
0 - 5	mg/dL	Keton /U Test	neg			neg	
0.0 - 0.2	mg/dL	Bilirubin/U T	neg			neg	
0.0 - 1.9	mg/dL	Urobilin./U T	norm			norm	
0 - 19	mg/dL	Ascorbin. /U	0			0	
		Urinfarbe	hellgelb			gelb	
Urinsediment							
		Sediment					
		Erythrozyten				vereinzelt	
		Leukozyten /U	vereinzelt				
		Schleimfäden				vereinzelt	

Patient 05: BL to end of study (PD) lab values

Treatment applied from 17.07.2023 – 11.08.2023

Auftragsnummer			L2307120168		L2308170241		L2309130137	
Datum			12.07.2023		17.08.2023		13.09.2023	
Uhrzeit			10:39		12:19		09:45	
Hämatologie - Blutbild (NMC)								
3.7 - 10.3	G/L	Leukozyten	3.4	L*	3.9	*	2.4	LL*
130 - 350	G/L	Thrombozyten	177		41	LL	117	L
4.57 - 5.98	T/L	Erythrozyten	4.64		4.68		4.25	L
13.9 - 17.7	g/dL	Hämoglobin	15.0		15.1		13.9	
39.6 - 51.8	%	Hämatokrit	44.2		43.6		41.3	
80.1 - 95.3	fL	MCV	95.2		93.1		97.3	H
27.6 - 33.2	pg	MCH	32.3		32.3		32.7	
33.0 - 37.2	g/dL	MCHC	34.0		34.7		33.7	
11.5 - 14.7	%	RDW-CV	13.4		12.9		14.8	H
5.9 - 9.9	fL	MPV	7.0		7.8		7.3	
1.7 - 7.0	G/L	Neutroph. Gra	2.4	*	2.7	*	1.5	L*
1.0 - 3.1	G/L	Lymphozyten a	0.5	LL*	0.5	LL*	0.3	LL*
0.2 - 0.7	G/L	Monozyten abs	0.3		0.3		0.4	
0.0 - 0.5	G/L	Eosinophile G	0.1		0.1		0.1	
0.0 - 0.1	G/L	Basophile Gr.	0.0		0.0		0.0	
0.0 - 0.4	G/L	LUC abs.	0.1		0.2		0.1	
42.0 - 77.0	%	Neutroph. Gra	71.5		70.2		62.2	
20.0 - 44.0	%	Lymphozyten r	13.8	L	13.2	L	13.7	L
2.0 - 9.5	%	Monozyten rel	10.0	H	8.3		16.0	HH
0.5 - 5.5	%	Eosinophile G	1.9		3.2		3.5	
0.0 - 1.8	%	Basophile Gr.	0.5		0.1		0.2	
0.0 - 4.0	%	LUC rel.	2.2	*	5.0	H*	4.4	H*
Differentialblutbild manuell (NMC)								
40 - 70	%	Segmentkern.			59			
0 - 10	%	Stabkernige r			4			
0 - 1	%	Metamyeloz. r			2	H		
20 - 44	%	Lymphozyten r			25			
2 - 10	%	Monozyten rel			7			
1 - 6	%	Eosinoph.Gr.r			2			
0 - 2	%	Basophile Gr.			1			
		Kommentar Dif			siehe Kom.	*		
Hämostaseologie - Globaltests								
		Therapie:	siehe Kom.	*			siehe Kom.	*
78 - 123	%	PTZ (Prothrom	91				98	
		INR	x	*			x	*
21 - 28	sek	aPTT	27	*			26	*
14 - 21	sek	Thrombinzeit	17				16	
0 - 20	ng/mL	PIVKA						
170 - 420	mg/dL	Fibrinogen	230				286	
79 - 119	%	AT III Aktivi	98	*			107	*

Auftragsnummer			L2307120168	L2308170241	L2309130137	L2309130214
Datum			12.07.2023	17.08.2023	13.09.2023	13.09.2023
Uhrzeit			10:39	12:19	09:45	11:26
Klinische Chemie - Niere/Elektrolyt						
136 - 145	mmol/L	Natrium	138		141	
3.5 - 4.6	mmol/L	Kalium	4.2		4.6 *	
98 - 107	mmol/L	Chlorid	103		104	
2.20 - 2.54	mmol/L	Calcium	2.33 *		2.42 *	
0.81 - 1.45	mmol/L	Phosphat	0.95		1.12	
0.67 - 1.17	mg/dL	Kreatinin	1.11		1.38 H	
90 - 160	mL/min/1	GFR (CKD-EPI)	75 L*		58 L*	
8 - 23	mg/dL	BUN	11		13	
3.4 - 7.0	mg/dL	Harnsäure				
Klinische Chemie - Leber/Pankreas						
10 - 50	U/L	ASAT (GOT)	24		x *	
10 - 50	U/L	ALAT (GPT)	13		19	
10 - 71	U/L	Gamma-GT	27		28	
40 - 129	U/L	Alk.Phosphata	45		54	
5320 - 12920	U/L	Cholinesteras	7382		7819	
0.00 - 1.20	mg/dL	Bilirubin	0.53		0.42	
13 - 60	U/L	Lipase	45		54	
13 - 53	U/L	Pankreas-Amyl	37		38	
Klinische Chemie - Hämolysemarker						
135 - 250	U/L	LDH				
Klinische Chemie - Glukosestoffwech						
60 - 100	mg/dL	Glucose				
60 - 140	mg/dL	Glucose postp	98		105	
Klinische Chemie - Fettstoffwechsel						
120 - 200	mg/dL	Cholesterin				
50 - 200	mg/dL	Triglyceride				
Proteindiagnostik						
64.0 - 87.0	g/L	Totalprotein	71.8		75.0	
3500.00 - 52	mg/dL	Albumin	4390.00		4450.00	
Urinstreifen						
		Mittelstrahlh	eingelangt			eingelangt
1.010 - 1.03		Spez.Gew./U T	1.028			1.012
5.0 - 8.0		pH /U Teststr	< =5.0/L			6.0
0 - 24	/µL	Leuko /U Test	neg			neg
		Nitrit /U ql.	neg			neg
0 - 4	/µL	Hgb(Ery) /U T	neg			neg
0 - 20	mg/dL	Tot.Prot./U T	neg			neg
0 - 49	mg/dL	Glucose/U Tes	neg			neg
0 - 5	mg/dL	Keton /U Test	neg			neg
0.0 - 0.2	mg/dL	Bilirubin/U T	neg			neg
0.0 - 1.9	mg/dL	Urobilin./U T	norm			norm
0 - 19	mg/dL	Ascorbin. /U	0			0
		Urinfarbe	gelb			hellgelb

Patient 06: BL to end of study (PD) lab values

Treatment applied from 15.07.2023 – 14.08.2023

Auftragsnummer			L2307060222	L2309200051
Datum			06.07.2023	20.09.2023
Uhrzeit			11:38	07:48
Hämatologie - Blutbild (NMC)				
3.6 - 10.5	G/L	Leukozyten	9.6	4.9
130 - 350	G/L	Thrombozyten	296	208
4.00 - 5.65	T/L	Erythrozyten	4.97	4.68
12.5 - 17.2	g/dL	Hämoglobin	14.8	14.4
37.0 - 49.0	%	Hämatokrit	44.0	42.7
80.0 - 101.0	fL	MCV	88.5	91.2
27.0 - 34.0	pg	MCH	29.7	30.8
31.5 - 36.0	g/dL	MCHC	33.6	33.8
11.5 - 14.7	%	RDW-CV	12.4	13.2
5.9 - 9.9	fL	MPV	7.4	6.9
1.5 - 7.7	G/L	Neutroph. Gra	6.5	2.7
1.1 - 4.0	G/L	Lymphozyten a	2.1	1.3
0.1 - 0.9	G/L	Monozyten abs	0.7	0.4
0.0 - 0.5	G/L	Eosinophile G	0.2	0.3
0.0 - 0.2	G/L	Basophile Gr.	0.0	0.0
0.0 - 0.4	G/L	LUC abs.	0.1	0.2
42.0 - 77.0	%	Neutroph. Gra	67.0	55.1
20.0 - 44.0	%	Lymphozyten r	21.9	26.9
2.0 - 9.5	%	Monozyten rel	7.2	8.1
0.5 - 5.5	%	Eosinophile G	2.4	5.7 H
0.0 - 1.8	%	Basophile Gr.	0.1	0.5
0.0 - 4.0	%	LUC rel.	1.4 *	3.7 *
Hämostaseologie - Globaltests				
		Therapie:	siehe Kom. *	siehe Kom. *
78 - 123	%	PTZ (Prothrom	125 H	120
		INR	x *	x *
22 - 29	sek	aPTT	26	24
14 - 21	sek	Thrombinzeit	17	16
170 - 420	mg/dL	Fibrinogen	245	252
79 - 120	%	AT III Aktivi	86	105
Klinische Chemie - Niere/Elektrolyt				
136 - 145	mmol/L	Natrium	141	142
3.5 - 4.6	mmol/L	Kalium	4.7 H	3.7
98 - 107	mmol/L	Chlorid	105	107
2.20 - 2.54	mmol/L	Calcium	2.37 *	2.36 *
0.81 - 1.45	mmol/L	Phosphat	0.74 L	0.92
0.67 - 1.17	mg/dL	Kreatinin	1.09	1.07
90 - 160	mL/min/1	GFR (CKD-EPI)	74 L*	75 L*
8 - 23	mg/dL	BUN	20	16

Klinische Chemie - Leber/Pankreas				
10 - 50	U/L	ASAT (GOT)	28	27
10 - 50	U/L	ALAT (GPT)	29	25
10 - 71	U/L	Gamma-GT	25	19
40 - 129	U/L	Alk.Phosphata	71	66
5320 - 12920	U/L	Cholinesteras	8293	8002
0.00 - 1.20	mg/dL	Bilirubin	0.23	0.33
13 - 60	U/L	Lipase	36	34
13 - 53	U/L	Pankreas-Amyl	33	33
Klinische Chemie - Glukosestoffwech				
60 - 140	mg/dL	Glucose postp	110	83
Proteindiagnostik				
64.0 - 87.0	g/L	Totalprotein	72.5	73.3
3500.00 - 52	mg/dL	Albumin	4210.00	4310.00
Tumormarker				
0.00 - 4.10	µg/L	PSA gesamt (E		
Urinstreifen				
		Mittelstrahlh	eingelangt	eingelangt
1.010 - 1.03		Spez.Gew./U T	1.012	1.009 L
5.0 - 8.0		pH /U Teststr	< =5.0/L	5.5
0 - 24	/µL	Leuko /U Test	neg	neg
		Nitrit /U ql.	neg	neg
0 - 4	/µL	Hgb(Ery) /U T	neg	neg
0 - 20	mg/dL	Tot.Prot./U T	neg	neg
0 - 49	mg/dL	Glucose/U Tes	neg	neg
0 - 5	mg/dL	Keton /U Test	neg	neg
0.0 - 0.2	mg/dL	Bilirubin/U T	neg	neg
0.0 - 1.9	mg/dL	Urobilin./U T	norm	norm
0 - 19	mg/dL	Ascorbin. /U	0	0
		Urinfarbe	hellgelb	hellgelb

Patient 09: BL to end of study (PD) lab values

Auftragsnummer			L2406050092	L2408060210
Datum			05.06.2024	06.08.2024
Uhrzeit			08:34	11:21
Hämatologie - Blutbild (NMC)				
3.7 - 10.3	G/L	Leukozyten	6.8	5.3
130 - 350	G/L	Thrombozyten	251	187
4.57 - 5.98	T/L	Erythrozyten	5.17	3.36 LL
13.9 - 17.7	g/dL	Hämoglobin	16.1	10.5 LL
39.6 - 51.8	%	Hämatokrit	47.2	31.0 LL
80.1 - 95.3	fL	MCV	91.3	92.2
27.6 - 33.2	pg	MCH	31.1	31.3
33.0 - 37.2	g/dL	MCHC	34.1	33.9
11.5 - 14.7	%	RDW-CV	12.3	14.7
5.9 - 9.9	fL	MPV	8.1	9.1
1.7 - 7.0	G/L	Neutroph. Gra	3.6	3.8
1.0 - 3.1	G/L	Lymphozyten a	2.1	0.7 LL
0.2 - 0.7	G/L	Monozyten abs	0.5	0.5
0.0 - 0.5	G/L	Eosinophile G	0.4	0.1
0.0 - 0.1	G/L	Basophile Gr.	0.1	0.0
0.0 - 0.4	G/L	LUC abs.	0.2	0.2
42.0 - 77.0	%	Neutroph. Gra	53.2	71.1
20.0 - 44.0	%	Lymphozyten r	30.9	13.1 L
2.0 - 9.5	%	Monozyten rel	7.4	10.3 H
0.5 - 5.5	%	Eosinophile G	5.4	2.0
0.0 - 1.8	%	Basophile Gr.	0.8	0.2
0.0 - 4.0	%	LUC rel.	2.2 *	3.4 *
Hämostaseologie - Globaltests				
		Therapie:	siehe Kom. *	siehe Kom. *
78 - 123	%	PTZ (Prothrom	113	94
		INR	x *	x *
21 - 28	sek	aPTT	25 *	24 *
14 - 21	sek	Thrombinzeit	19	16
170 - 420	mg/dL	Fibrinogen	290	
79 - 119	%	AT III Aktivi	113	
Klinische Chemie - Entzündungsmarke				
0.0 - 0.5	mg/dL	CRP		13.8 HH
1 - 15	mm/h	Blutsenkung		90 HH
Klinische Chemie - Niere/Elektrolyt				
136 - 145	mmol/L	Natrium	142	136
3.5 - 4.6	mmol/L	Kalium	3.8	3.7
98 - 107	mmol/L	Chlorid	105	98
2.15 - 2.50	mmol/L	Calcium	2.49	2.20
0.81 - 1.45	mmol/L	Phosphat	1.14	
0.67 - 1.17	mg/dL	Kreatinin	1.02	0.98
90 - 160	mL/min/1	GFR (CKD-EPI)	> 90 *	> 90 *
6 - 20	mg/dL	BUN	16	
Klinische Chemie - Kardiale Marker				
0 - 190	U/L	CK		36

Auftragsnummer				L2406050092		L2408060210
Datum				05.06.2024		06.08.2024
Uhrzeit				08:34		11:21
0.67 - 1.17	mg/dL	Kreatinin		1.02		0.98
90 - 160	mL/min/1	GFR (CKD-EPI)		> 90	*	> 90 *
6 - 20	mg/dL	BUN		16		
Klinische Chemie - Kardiale Marker						
0 - 190	U/L	CK				36
Klinische Chemie - Leber/Pankreas						
10 - 50	U/L	ASAT (GOT)		26		27
10 - 50	U/L	ALAT (GPT)		88	H	50
10 - 71	U/L	Gamma-GT		68		170 H
40 - 129	U/L	Alk.Phosphata		72		
5320 - 12920	U/L	Cholinesteras		12369		6811
0.00 - 1.20	mg/dL	Bilirubin		0.44		
13 - 60	U/L	Lipase		47		
13 - 53	U/L	Pankreas-Amyl		43		
Klinische Chemie - Hämolysemarker						
135 - 250	U/L	LDH				223
Klinische Chemie - Glukosestoffwech						
60 - 140	mg/dL	Glucose postp		97		103
4.8 - 6.0	%	Hämoglobin A1				5.7
29 - 42	mmol/mol	Hämoglobin A1				39
Proteindiagnostik						
64.0 - 87.0	g/L	Totalprotein		77.5	*	
3500.00 - 52	mg/dL	Albumin		4720.00	*	
Endokrinologie - Schilddrüsendiagno						
0.27 - 4.20	µU/mL	TSH				4.16
Urinstreifen						
		Mittelstrahlh				
1.010 - 1.03		Spez.Gew./U T				
5.0 - 8.0		pH /U Teststr				
0 - 24	/µL	Leuko /U Test				
		Nitrit /U ql.				
0 - 4	/µL	Hgb(Ery) /U T				
0 - 20	mg/dL	Tot.Prot./U T				
0 - 49	mg/dL	Glucose/U Tes				
0 - 5	mg/dL	Keton /U Test				
0.0 - 0.2	mg/dL	Bilirubin/U T				
0.0 - 1.9	mg/dL	Urobilin./U T				
0 - 19	mg/dL	Ascorbin. /U				
		Urinfarbe				
Urinsediment						
		Erythrozyten				
		Leukozyten /U				
		Bakterien /US				
		Schleimfäden				
		Amorphe Krist				

Patient 11: BL to end of study (PD) lab values

Auftragsnummer			L2408210353		L2410160316		L2411250655	
Datum			21.08.2024		16.10.2024		25.11.2024	
Uhrzeit			12:52		12:48		17:16	
Hämatologie - Blutbild (NMC)								
4.0 - 11.8	G/L	Leukozyten	4.2		2.1	LL	12.1	H
130 - 350	G/L	Thrombozyten	224		156		192	
4.01 - 5.29	T/L	Erythrozyten	4.33		3.77	L	4.13	
12.4 - 16.1	g/dL	Hämoglobin	12.4		11.5	L	12.8	
35.4 - 46.3	%	Hämatokrit	37.7		34.5	L	38.0	
80.1 - 95.3	fL	MCV	87.1		91.3		91.9	
27.0 - 32.9	pg	MCH	28.6		30.4		31.0	
32.6 - 36.5	g/dL	MCHC	32.8		33.3		33.7	
11.5 - 14.7	%	RDW-CV	13.5		16.1	H	14.0	
5.9 - 9.9	fL	MPV	6.5		7.3		6.8	
2.0 - 7.7	G/L	Neutroph. Gra	2.7		1.5	L	11.6	HH
1.1 - 3.4	G/L	Lymphozyten a	0.8	L	0.3	LL	0.2	LL
0.2 - 0.6	G/L	Monozyten abs	0.2		0.1	L	0.2	
0.0 - 0.5	G/L	Eosinophile G	0.4		0.0		0.0	
0.0 - 0.1	G/L	Basophile Gr.	0.0		0.0		0.0	
0.0 - 0.4	G/L	LUC abs.	0.1		0.1		0.0	
42.0 - 77.0	%	Neutroph. Gra	64.7		74.9		95.8	HH
20.0 - 44.0	%	Lymphozyten r	18.1	L	13.4	L	2.0	LL
2.0 - 9.5	%	Monozyten rel	4.9		6.7		1.9	L
0.5 - 5.5	%	Eosinophile G	8.5	H	0.5		0.0	L
0.0 - 1.8	%	Basophile Gr.	1.0		0.6		0.1	
0.0 - 4.0	%	LUC rel.	2.7	*	4.0	*	0.2	*
Hämostaseologie - Globaltests								
		Therapie:	siehe Kom.	*	siehe Kom.	*	siehe Kom.	*
78 - 123	%	PTZ (Prothrom	120		143	H	143	H
- 3.5		INR	x	*	0.9	*	0.9	*
21.6 - 28.7	sek	aPTT	22.8	*	22.4		20.3	L
14 - 21	sek	Thrombinzeit	18				17	
170 - 420	mg/dL	Fibrinogen	318				337	
79 - 120	%	AT III Aktivi	114	*			117	
Klinische Chemie - Entzündungsmarke								
0.0 - 0.5	mg/dL	CRP					0.1	
0.0 - 7.0	pg/mL	Interleukin-6						
1 - 30	mm/h	Blutsenkung					8	
Klinische Chemie - Niere/Elektrolyt								
136 - 145	mmol/L	Natrium	140				140	
3.5 - 4.6	mmol/L	Kalium	4.0				4.0	
98 - 107	mmol/L	Chlorid	104				103	
2.20 - 2.54	mmol/L	Calcium	2.35				2.29	
0.51 - 0.95	mg/dL	Kreatinin	0.87		0.83		0.98	H
90 - 160	mL/min/1	GFR (CKD-EPI)	75	L*	79	L*	65	L*
8 - 23	mg/dL	BUN	13		12		15	
2.4 - 5.7	mg/dL	Harnsäure			4.4		8.0	H

Auftragsnummer			L2408210353	L2410160316	L2411250655
Datum			21.08.2024	16.10.2024	25.11.2024
Uhrzeit			12:52	12:48	17:16
Klinische Chemie - Leber/Pankreas					
10 - 35	U/L	ASAT (GOT)	13	17	23
10 - 35	U/L	ALAT (GPT)	12	16	17
6 - 42	U/L	Gamma-GT	68 H	31	27
35 - 104	U/L	Alk.Phosphata	87	77	81
5320 - 12920	U/L	Cholinesteras		6912	7565
0.00 - 1.20	mg/dL	Bilirubin		0.48	0.30
13 - 60	U/L	Lipase	21	17	17
13 - 53	U/L	Pankreas-Amyl	24	22	19
Klinische Chemie - Hämolysemarker					
135 - 250	U/L	LDH			158
Klinische Chemie - Glukosestoffwech					
60 - 100	mg/dL	Glucose	93		153 HH
Klinische Chemie - Fettstoffwechsel					
120 - 200	mg/dL	Cholesterin			221 H
50 - 200	mg/dL	Triglyceride			81
Proteindiagnostik					
64.0 - 87.0	g/L	Totalprotein	69.3	67.2	71.7
Endokrinologie - Schilddrüsendiagno					
0.27 - 4.20	µU/mL	TSH		2.35	
0.92 - 1.68	ng/dL	Freies T4		0.96	
80 - 200	ng/dL	T3		112	
2.00 - 4.40	pg/mL	Freies T3		3.19	
Levetiracetam-Spiegel					
		Letzte Medika			
10.0 - 40.0	µg/mL	Levetiracetam			
	mg/d	Tagesdosis			
		Dosis-Schema			
50.0 - 85.0	kg	Körpergewicht			
	mg/kg/d	Dosis/kg Körp			
Urinstreifen					
		Mittelstrahlh	eingelangt	eingelangt	
1.010 - 1.03		Spez.Gew./U T	1.010	1.012	
5.0 - 8.0		pH /U Teststr	7.5	7.0	
0 - 24	/µL	Leuko /U Test	500 HH	neg	
		Nitrit /U ql.	neg	neg	
0 - 4	/µL	Hgb(Ery) /U T	10 H	neg	
0 - 20	mg/dL	Tot.Prot./U T	neg	neg	
0 - 49	mg/dL	Glucose/U Tes	neg	neg	
0 - 5	mg/dL	Keton /U Test	neg	neg	
0.0 - 0.2	mg/dL	Bilirubin/U T	neg	neg	
0.0 - 1.9	mg/dL	Urobilin./U T	norm	norm	
0 - 19	mg/dL	Ascorbin. /U	0	0	
		Urinfarbe	hellgelb	hellgelb	
Urinsediment					
		Sediment		siehe Kom. *	
		Erythrozyten	vereinzelt		
		Leukozyten /U	reichlich		
		Bakterien /US	mäßig		

11.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

No relevant findings.

11.6 Long Term Follow Up

1 patient is still alive after finishing the CSR.

11.7 Safety Conclusions

No relevant safety issues raised during the study, only in one patient treatment was withhold due to hematologic adverse event. No related SAE or death occurred.

12 Discussion and Overall Conclusions

The very low toxicity of this therapy is a positive aspect that is important for patients with a palliative therapy approach. Quality of life was only affected by the progression of the disease. The periods of isolation after IPA administration were well tolerated by the patients and kept to a minimum.

The side effects of a second radiotherapy are not different from those in studies with re-XRT alone.

The discrepancy between PFS and OS cannot be explained immediately. The short progression-free period after IPA treatment followed by XRT is similar to the data with lomustine in recurrent GBM treatment. One possible explanation could be pseudo-progression, which can be ruled out by subsequent MRI with further progression and FET-PET

studies. Another explanation could be the benefit of third-line therapy with bevacizumab, which 6 of 8 patients received.

Apart from the positive preliminary data on survival and tolerability, many limitations of this study must be taken into account. The small number of patients does not allow conclusive proof of effectiveness. Different dosages of IPA due to delivery difficulties cause heterogeneous therapies.

Two patients received hypofractionated radiotherapy with 6 Gray in 5 fractions for small tumor volumes with equally good tolerability. One patient died not related of the brain tumor recurrence but because of systemic metastases, which were verified as metastases of the glioblastoma. This manifestation with peritoneal, lung and bone metastases is very unusual and a secondary malignancy was ruled out in a 36-year-old otherwise healthy patient. The brain tumor was stable until death.

We have a delay of 28-44 days from MRI indicating relapse and start of therapy. A long period of time in which the tumor might grow. Half of the patient in our series indicated progression in the period between relapse MRI and baseline MRI. Logistic challenges with the production and supply of the IMP must be considered in a rapid growing tumor, so these timelines are essential.

Conclusion

Despite the many limitations in this study, we find this form of therapy to be a potentially new and promising approach, as the patients in this study were not a positively selected population but had many prognostically unfavorable factors and still showed a good outcome. We believe that this therapeutic approach should be pursued further in prospective controlled studies.

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