NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) and SOC of the N²M² project. This report covers the results of the overall trial report. Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N²M²

Final Study Report (Synopsis) according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.0, February 2nd 2024
Investigational Product:	A: CD95L APG101, (B:Alectinib,) C: Idasanutlin, D: Atezolizumab, (E: Vismodegib,) F: CDK4 / CDK6 palbociclib, G: p-mTOR^{Ser2448} Temsirolimus
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 5.0 April 5th 2022

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail:Kaufmaennische-direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Umbrella trial: Initiation and Completion Dates:
First Patient in: May 17th 2018
Last Patient in: July 8th 2022
Last Patient Last Visit: February 22nd 2023
Data base lock: November 20th 2023

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	HEIDELBERG 5/2/24 Place, Date
Biostatistician	Lisa-Marie Lanz, M.Sc.	Weinheim, 06.02.24 Place, Date

List of abbreviations:

AE	Adverse Event
ALT	Alanine transaminase
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
DLT	Dose-limiting toxicity
ECG	Electrocardiography
EES	Efficacy Evaluable Set
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-glutamyltransferase
KPI	Kanrofsky Performance Index
MGMT	O-6-methylguanine-DNA methyltransferase
MTD	Maximum tolerated dose
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
RANO	Response assessment in neuro-oncology criteria
REES	Regular Efficacy Evaluable Set
RLT	Regime-limiting toxicity
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SP P1	Safety Population Phase I

Synopsis

Name of Sponsor/Company:

Heidelberg University Hospital
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:

APG101 (Asunercept), Alectinib, Idasanutlin, Atezolizumab, Vismodegib (Erivedge), Palbociclib (IBRANCE®) , Temsirolimus (Torisel®)

Name of Active Ingredient:

APG101, Alectinib, Idasanutlin (RO5503781/F17 (50 mg), RO5503781/F16 (200 mg), RO5503781/F13 (300 mg)), Atezolizumab, Vismodegib, Palbociclib, Temsirolimus

Title of Study:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Short Title/ Acronym:

N²M²

Protocol versions:

Umbrella protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)
Final 2.0, December 10th 2020 (Substantial Amendment)
Final 3.0, July 6th 2021 (Substantial Amendment)
Final 4.0 September 10th 2021 (Substantial Amendment)
Final 5.0 April 5th 2022 (Substantial Amendment)

Including the following subtrial protocols:

Subtrial A (APG101) protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)

Subtrial B (Alectinib) protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)

Subtrial C (Idasanutlin) protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)

Subtrial D (Atezolizumab) protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)
Final 2.0, April 5th 2022 (Substantial Amendment)
Subtrial E (Vismodegib) protocol:
Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)
Subtrial F (Palbociclib) protocol:
Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)
Final 2.0, September 10th 2021 (Substantial Amendment)
Final 2.1, April 5th 2022 (Substantial Amendment)
Subtrial G (Temsirolimus) protocol:
Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)

Study center(s) and Principle Investigator(s):

01 Prof. Wolfgang Wick/CI
Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg

02 Prof. Dr. med. Dietmar Krex
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden

03 Prof. Dr. Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin

04 Prof. Dr. med. Uwe Schlegel
Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum

05 Prof. Dr. med. Ulrich Herrlinger
Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn

06 Prof. Dr. med. Martin Glas
Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen

07 PD Dr. med. Michael Burger
Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt

08 Prof. Dr. Roland Goldbrunner
Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln

09 Prof. Dr. med. Florian Ringel
Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz

10 Prof. Dr. Michael Platten

	Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
11	Prof. Dr. med. Peter Hau Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg
12	Prof. Dr. med. Ralf Ketter, Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg
13	Prof. Dr. med. Ghazaleh Tabatabai, Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N^2M^2)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N^2M^2) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2*. Journal of Clinical Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090
- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N^2M^2 (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years):	**Phase of development**:
date of first enrolment: May 17th 2018 date of last enrolment: July 8th 2022 date of last completed: February 22nd 2023	I/IIa

Objectives:

Phase I:

The *primary Objective* of the phase I part of the trial was the determination of safety and tolerability of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial,
- Progression-free survival at six months (PFS-6) according to RANO criteria (Wen et al. 2010; Okada et al. 2015)

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N^2M^2 subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.
  As stated in the protocol, this objective is not analyzed in this final trial report, but will be addressed in future manuscripts.

Methodology:

The trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N^2M^2 project. The phase I part of the subtrial shall determine the MTD for the combination therapy IMP + RT with an accelerated rule based design for subtrials A, C and F or with a bayesian approach for subtrials B, D and E. No phase I was planned for subtrial G. Patients treated at the final dose of phase I, can also be evaluated in the phase IIa part of the trial.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily
- IMP:
  A: Weeks 1 to 26, weekly
  B: Weeks 1 to 26, 7x2
  C: Weeks 1, 5, 9, 13, 17, 21, 25, 5x1
  D: Weeks 1, 4, 7, 10, 13, 16, 19, 22, 25, weekly
  E: Weeks 1 to 26, daily, 7x1
  F: Weeks 1-3, 5-7, 12-14, 16-18, 20-22, 24-26, 7x1
  G: Weeks -1 to 26, weekly
  SOC: Weeks 1 to 6, 7x1, weeks 11, 15, 19, 23, 5x1
- AEs*: Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- Concomitant Medication*: Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- DLTs (only phase I): Week 1 – 6
- RLTs (phase I): Week 7 – 26
- RLTs (phase IIa)*: Week 1 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab (chemistry), Karnofsky Performance Index (KPI)): Screening, Attribution, Weeks 4, 8, 12, 16, 20, 24, 26
- Examinations (safety lab (hematology)): Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- EOS: Week 26

*: For subtrial G the examinations start at week -1.

Number of patients (planned and analyzed):

Number of patients planned: ≤374 (including 40 patients per subtrial planned for phase IIa) with SOC

Number of patients analyzed: 228

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials)
- Standard MRI ≤ 72 (+ 12 h) post-surgery according to the present national and international guidelines
- Availability of formalin-fixed, paraffin-embedded (FFPE) tissue and fresh-frozen tissue, as well as blood
- patients eligible for RT at 60 Gy in 2 Gy fractions according to the local Standard of Care
- Age: ≥18 years
- KPS ≥70%
- Life expectancy > 6 months
- All female patients with reproductive potential must have a negative pregnancy test (serum or urine) within 6 days prior to start of therapy. All female patients must be surgically sterile or must agree to use adequate contraception during the period of therapy and 6 months after the end of study treatment, or women must be postmenopausal for at least 2 years.
- Male patients willing to use contraception (condoms with spermicidal jellies or cream) upon study entry and during the course of the study and 3 months after the end of the study, have undergone vasectomy, or are practicing total abstinence. Sperm donation is not permitted for the same time interval.

For subtrial specific inclusion criteria (molecular markers) of patients allocated to subtrial C (idasanutlin), F (palbociclib) and G (temsirolimus), see the respective subtrial reports. For subtrials A (APG101), D (atezolizumab) and SOC (temozolomide) no specific molecular marker was defined (non-MATCH group). Patients who could not be included in one of the other subtrials were randomized in the non-MATCH group.

Investigational product, dose and mode of administration, batch number:

For information on the investigational products of the experimental arms, see the respective subtrial reports.

Reference therapy, dose and mode of administration, batch number:

Not applicable

Duration of treatment:

Up to 6 months.

Criteria for evaluation:

Phase I (not suitable for subtrial G and SOC):

Safety:

The *primary safety endpoint* was the determination of posterior probability of Dose Limiting Toxicity (DLT), defined as all adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA) ≥ Grade 3 according to the National Cancer Institute

Common Terminology Criteria for AE (CTCAE) v5.0 that are definitely, probably or possibly related to the administration of the IMP in combination with RT.

Secondary safety endpoint:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial for patients recruited for phase I.

Efficacy:

The *secondary efficacy endpoint* was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. See also the primary efficacy endpoint for phase IIa for more information.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without an event relevant for PFS (progression or death) at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events
- Karnofsky Index (KPI)
- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory parameters (hematology, chemistry, urinalysis), ECG

SOC:

Solely for validation of the nullhypothesis, patients treated according to standard of care (SOC) were observed for efficacy endpoint PFS-6. Treatment according to SOC compromises radiotherapy at 60 Gy in 2 Gy fractions plus concomitant temozolomide chemotherapy (75 mg/m² body surface) followed by six cycles of temozolomide maintenance therapy (150/200 mg/m² body surface).

The nullhypothesis is supposed to give the PFS-6 rate of SOC. Originally the rate was set to 40%. Due to data collected from 26 patients with 6 responders, the DSMC suggested to correct the rate (and thus p_0) to 23.1%.

Statistical methods:

Statistical analysis:

Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results (where appropriate) for all subtrials is presented in this umbrella report.

Phase I

Analysis of the safety endpoints:

- For the primary safety endpoint (DLTs), the different examined dose-levels are presented, together with the amount and type (Preferred Term (PT) and System Organ Class level) of DLTs, patients experienced at these dose levels. Summary tables present the number of patients observed with a DLT and the corresponding percentage. Exact 95% two-sided Clopper-Pearson CIs are presented.
- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CIs are presented. All patients who completed the combined treatment phase are included.

Analysis of the efficacy endpoint:

Progression-free survival at six months (PFS-6) according to RANO criteria as a binary endpoint is analyzed. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing.

Phase IIa

Analysis of the efficacy endpoints:

- The primary efficacy endpoint PFS-6 according to RANO criteria as a binary endpoint is analyzed with a one-sample one-sided Binomial test of the null hypothesis $H_0: p = 0.231$. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing, but for the calculation of the p-value those patients are assumed to be non-responders. α-level for the primary analysis is 10%.

  Response assessment is determined by combining information from the clinical trial site (local RANO Assessment, a status page in the eCRF showing the information if the patient experienced progression during the 6 months after study entry and survival follow-up in case of premature EOS) and central RANO assessment performed by central neuroradiology in Heidelberg. If the clinical trial site stated a progression on the status page, the patient is assumed to be a non-responder, irrespective of other information. Central RANO assessment is the preferred type of assessment, but if not available (or differing to a stated progression on the status page) other sources of information are used to determine the response status/assessment.
- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first) minus 1 day. Patients without an event relevant for PFS* at

the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.

- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

* Please note, that patients with a death event in the survival follow-up (without a preceding progression event) are only considered as having an event relevant for PFS, if regular information on disease assessment for that patient is available. Otherwise the patient is censored at the last date of disease assessment.

Analysis of the (secondary) safety endpoints:

- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CI are presented.
- Adverse Events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages.
- Karnofsky Index (KPI) is summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages).
- Vital Signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening), respiratory rate) are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented. This includes changes (differences) from the baseline assessment, except for body height.
- Clinical laboratory parameters (hematology, chemistry, urinalysis) and ECG are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented (for ECG: only for abnormal results). The number of patients with laboratory values that are below, within or above normal ranges are tabulated for each parameter. Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and of changes from baseline are presented for each parameter. The number and percentage of patients with normal and abnormal ECG results at baseline and follow-up are tabulated. ECG findings are tabulated by patient.

SUMMARY – STUDY POPULATION

SOC: A total of 64 patients were included in 13 trial sites. 54 patients were treated and are thus part of the Full Analysis Set (FAS). All 54 patients are available for the primary endpoint analysis (and thus are part of the Efficacy Evaluable Set (EES). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		Temozolomide FAS/EES N (%)
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	23 (42.6)
	(Premature) end of treatment reached prior to week 26	31 (57.4)
Reason(s) for premature end of treatment *	Disease progression (lack of clinical benefit)	28 (90.3)
	Death	2 (6.5)
		Temozolomide FAS/EES N (%)
	Withdrawal of informed consent (patients decision)	2 (6.5)
	Adverse event other than undue toxicity	1 (3.2)
	Investigator's opinion	1 (3.2)
	Lost to Follow-Up	1 (3.2)
	Other reason(s)	1 (3.2)
Other reasons include disease progression.		
Status at the End of the Study	Defined end of study at week 26 is reached	23 (42.6)
	Death	3 (5.6)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	9 (16.7)
	30 days safety follow-up is reached after premature EOT due to progression	10 (18.5)
	Premature study termination (and no safety follow-up was performed)	9 (16.7)
Reason(s) for premature study termination*	Withdrawal of informed consent	4 (44.4)
	Non-compliance	1 (11.1)
	Other Reason(s)	6 (66.7)
Other reasons include disease progression and personal reasons.		

* Documentation of multiple reasons were possible.

Demographics FAS/EES:

	All Patients	Male	Female
Sex, n (%)			
Male	36 (66.7)	36 (100)	0
Female	18 (33.3)	0	18 (100)
Age continuous (years), Mean (SD)	58.6 (7.79)	58.6 (8.03)	58.7 (7.52)

	All Patients	Male	Female
BMI (kg/m²), Mean (SD)*	27.0 (4.83)	27.7 (4.87)	25.7 (4.61)
Height (cm), Mean (SD)*	176.1 (9.82)	181.1 (7.28)	166.0 (5.52)
Weight (kg), Mean (SD)*	84.2 (19.20)	90.9 (18.05)	71.0 (14.16)
Age categorical (years), n (%)			
18-44	1 (1.9)	0	1 (5.6)
45-64	40 (74.1)	28 (77.8)	12 (66.7)
≥65	13 (24.1)	8 (22.2)	5 (27.8)
Ethnic Group, n(%)			
Caucasian/white	52 (96.3)	34 (94.4)	18 (100)
Oriental	2 (3.7)	2 (5.6)	0

Umbrella: Overall 301 patients were screened. 228 patients were treated. For details on demographics of all screened patients, see the following table:

Demographics Screening Umbrella:

	All Patients	Male	Female
Sex, n (%)			
Male	192 (63.8)	192 (100)	0
Female	109 (36.2)	0	109 (100)
Age continuous (years), Mean (SD)	58.9 (9.71)	59.0 (9.55)	58.8 (10.03)
BMI (kg/m²), Mean (SD)*	26.6 (4.64)	27.0 (4.08)	25.7 (5.41)
Height (cm), Mean (SD)*	174.0 (9.07)	178.6 (6.91)	166.0 (6.50)
Weight (kg), Mean (SD)*	80.7 (16.95)	86.3 (14.85)	71.0 (16.02)
Age categorical (years), n (%)			
18-44	21 (7.0)	12 (6.3)	9 (8.3)
45-64	193 (64.1)	128 (66.7)	65 (59.6)
≥65	87 (28.9)	52 (27.1)	35 (32.1)
Ethnic Group, n(%)			
Caucasian/white	296 (98.3)	188 (97.9)	108 (99.1)
Oriental	5 (1.7)	4 (2.1)	1 (0.9)

* For overall 10 patients neither weight nor height were documented.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

SOC:

The objective is the determination of efficacy of Temozolomide in conjunction with radiotherapy for patients with newly diagnosed MGMT-non-hypermethylated glioblastoma.

Primary endpoint is the PFS-6 rate (corresponds to response rate), defined as the proportion of patients free of progression at 6 months after study entry. The tested null hypothesis is $H_0: p_0 = 23.1\%$.

Secondary endpoints include progression-free survival (PFS) and overall survival (OS).

Primary endpoint: PFS-6:

In the following table response-status and RANO-assessment are shown together with the best available source of information for the Full Analysis Set (FAS)/the Efficacy Evaluable

Set (EES). Please note, that for this trial, patients are assessed as responders if stable disease, partial response or complete response is present after 6 months.

FAS/EES (N=54)	All Patients	Central RANO Assess-ment	Local RANO Assess-ment	Pro-gression accor-ding to status page	No pro-gression, but different anti-cancer therapy received
Response-Assessment					
Yes	10 (18.5)	9 (25.7)	1 (6.3)	0	0
No	44 (81.5)	26 (74.3)	15 (93.8)	2 (100)	1 (100)
RANO-Assessment					
Stable Disease (SD)	10 (18.5)	9 (25.7)	1 (6.3)	0	0
Progressive Disease (PD)	44 (81.5)	26 (74.3)	15 (93.8)	2 (100)	1 (100)

For the primary analysis the FAS is used. Overall, 18.52% (10/54) of these patients were assessed as responders (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [0.0925, 0.3143%]). 9 of them were confirmed by central RANO assessment. Best available assessment was “stable disease”. The corresponding p-value of the one-sided binomial test is $p = 0.831$.

As a sensitivity analysis, the same calculations were performed on the EES. For SOC, FAS and EES are equal thus sensitivity analysis does not differ from the primary analysis.

SOC:

Secondary endpoint: PFS
The secondary endpoint PFS is analyzed using the FAS and EES. The number of patients with an event relevant for PFS is 43. Median progression-free survival is 3.8 months for FAS and EES. For more information see the following table:

	FAS/EES
Number of Patients	54
Number of Patients with the Event (%)	43 (79.6)
25 Percent Point Estimate* (95% CI)	2.6 (2.4, 2.8)
Median* (95% CI)	3.8 (2.8, 5.7)
75 Percent Point Estimate* (95% CI)	6.6 (5.7, 8.3)
6-month event free rate** (95% CI)	0.310 (0.190, 0.438)
9-month event free rate** (95% CI)	0.042 (0.003, 0.172)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAS and EES. The number of patients with the event until database lock is 49 (FAS/EES 90.7%). Median overall survival is 12.1 months for FAS and EES. For more information see the following table:

	FAS/EES
Number of Patients	54
Number of Patient with the Event (%)	49 (90.7)
25 Percent Point Estimate* (95% CI)	9.8 (7.4, 10.6)
Median* (95% CI)	12.1 (10.6, 14.6)
75 Percent Point Estimate* (95% CI)	17.4 (14.4, 20.3)
6-month event free rate** (95% CI)	0.924 (0.810, 0.971)
9-month event free rate** (95% CI)	0.827 (0.693, 0.906)
12-month event free rate** (95% CI)	0.512 (0.368, 0.638)
18-month event free rate** (95% CI)	0.216 (0.116, 0.337)
24-month event free rate** (95% CI)	0.052 (0.010, 0.148)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed
Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results (where appropriate) for all subtrials is presented below.

Updated PFS/OS results:
Data for time-to-event endpoints is further collected after EOS of the respective subtrial until overall EOS of the umbrella trial. In case new information on PFS/OS after EOS of the respective subtrial is available, the data is presented below. No new PFS information is available.

Updated PFS/OS results for subtrial A:

OS:

	FAS/EES
Number of Patients (%)	26 (100)
Number of Patient with the Event (%)	19 (73.1)
25 Percent Point Estimate* (95% CI)	10.1 (6.2, 11.9)
Median* (95% CI)	13.0 (10.1, 19.3)
75 Percent Point Estimate* (95% CI)	20.4 (13.8,)
6-month event free rate** (95% CI)	0.962 (0.757, 0.994)
9-month event free rate** (95% CI)	0.808 (0.598, 0.915)
12-month event free rate** (95% CI)	0.577 (0.368, 0.739)
18-month event free rate** (95% CI)	0.385 (0.204, 0.563)
24-month event free rate** (95% CI)	0.220 (0.076, 0.410)

Updated PFS/OS results for subtrial D:

No new information.

Updated PFS/OS results for subtrial F:

No new information.

Updated PFS/OS results for subtrial G:

OS:

	FAS/EES
Number of Patients (%)	46 (100)
Number of Patient with the Event (%)	41 (89.1)
25 Percent Point Estimate* (95% CI)	10.8 (7.2, 11.9)
	FAS/EES
Median* (95% CI)	15.4 (11.7, 18.0)
75 Percent Point Estimate* (95% CI)	20.3 (17.6, 23.8)
6-month event free rate** (95% CI)	0.890 (0.755, 0.953)
9-month event free rate** (95% CI)	0.801 (0.652, 0.891)
12-month event free rate** (95% CI)	0.601 (0.443, 0.726)
18-month event free rate** (95% CI)	0.372 (0.233, 0.511)
24-month event free rate** (95% CI)	0.112 (0.039, 0.227)
30-month event free rate** (95% CI)	0.084 (0.023, 0.194)

SAFETY RESULTS:

For SOC no information on adverse events or laboratory data were collected.

For specific safety results of the subtrials, see the respective subtrial report.

CONCLUSION:

Subtrial A (APG101): The data from Subtrial A of the N^2M^2 trial show low efficacy for the primary endpoint (overall 15.4% patients without progression after 6 months). The subtrial was terminated due to futility compared to standard of care (H_0: p=23.1%).

The observed DLT-rate in patients receiving the starting dose (600mg) is 0% (0/3 patients) (95% two-sided Clopper-Pearson CI: [0, 0.708]). The observed RLT-rate in patients receiving the determined MTD 800mg is 0% (0/26 patients) (95% two-sided Clopper-Pearson CI: [0, 0.132]), thus tolerability of the MTD is confirmed.

Subtrial B (Alectinib): Due to the rareness of the molecular marker (Alk fusion/ point mutation) required for inclusion in this subtrial, no patients could be recruited.

Subtrial C (Idasanutlin): Due to the early sub-study termination prior to the start of phase II resulting in reduced sample size and correspondingly reduced power, any conclusions in regard to study objectives could not be demonstrated, especially dose-finding could not be finished and thus no optimal dose was found.

Subtrial D (Atezolizumab): The data from Subtrial D of the N^2M^2 trial does not show significant efficacy for the primary endpoint (overall 21.4% patients without progression after 6 months with H_0: p_0=23.1%). The corresponding p-value is $p = 0.660$.

For the primary safety endpoint of phase I concerning DLTs, in 22.2% (2/9) of the patients DLTs were observed (95% two-sided Clopper-Pearson CI: [0.028, 0.600]).

Overall 23.8% (10/42) patients experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.121, 0.395]) thus the DLT/RLT rate is below the unacceptable rate of 30%, but tolerability cannot be confirmed with a confidence of 95% according to the confidence interval.

Subtrial E (Vismodegib): Due to the rareness of the molecular marker (SHH activation) required for inclusion in this subtrial, no patients could be recruited.

Subtrial F (Palbociclib): The data from Subtrial F of the N^2M^2 trial does not show significant efficacy for the primary endpoint (overall 24.4% patients without progression after 6 months with H_0: p_0=23.1%). The corresponding p-value is $p = 0.4823$.

For the primary safety endpoint of phase I concerning DLTs, in 50.0% (3/6) of the patients receiving 125 mg DLTs were observed (95% two-sided Clopper-Pearson CI: [0.118, 0.882]) and 16.7% (1/6) of the patients receiving the determined MTD experienced a DLT (95% two-sided Clopper-Pearson CI: [0.004, 0.641]).

Overall 83.3% (5/6) patients receiving a dose of 125 mg experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.359, 0.996]) thus the probability is high that the tolerability is unacceptable. For the dose of 75 mg neither DLTs nor RLTs were observed (0/1 patients) (95% two-sided Clopper-Pearson CI: [0, 0.95]). For the determined MTD of 100 mg, overall 26.8% (11/41) of the patients experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.142, 0.429]), thus the DLT rate is below the unacceptable rate of 30%, but tolerability of the MTD cannot be confirmed with a confidence of 95% according to the confidence interval.

Subtrial G (Temsirolimus): The data from Subtrial G of the N^2M^2 trial shows efficacy for the primary endpoint (overall 39.1% patients without progression after 6 months) with a highly significant p-value of 0.0109 (α-level of this trial is 10%). This shows benefit compared to the assumed PFS-6 rate in standard of care ($p_0 = 23.1\%$).

The observed RLT-rate is 34.8% (95% Clopper-Pearson CI: [0.214, 0.502]), which is slightly above the predefined unacceptable rate for RLTs of 30%, thus, using the confidence interval, an acceptable safety profile can neither be confirmed nor denied. Most RLTs had severity grade 3, one RLT had severity grade 4. No RLTs resulted in death.

SOC (Temozolomide): The data from the SOC patients of the N^2M^2 trial shows low efficacy for the primary endpoint (overall 18.52% patients without progression after 6 months with H_0: p_0=23.1%). The corresponding p-value is $p = 0.831$. The outcome of all 54 patients shows that the final observed response rate for SOC is below the corrected p_0. The 95% confidence interval ([0.0925, 0.3143%]) shows that the observed rate is not significantly below the assumed rate of 23.1%.

Substantial amendments / interruptions or early termination:

Substantial amendments: substantial amendments of the umbrella trial are listed

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Updated Informed Consent Forms (ICF) due to EU GDPR and updated IBs and SmPCs	25.05.2018
02	Change of deputy at site 13	13.07.2018
03	Change of deputy site 06, 07, 09, 10 change of investigator at site 07	21.01.2019, 28.01.2019, 29.01.2019, 06.03.2019
04	Change of deputy at site 12	28.10.2019
05	Protocol amendment (v1.4), updated IBs, ICF	29.12.2019

Amendment No.	Content	Approval Date
06	Protocol amendment (v1.5), updated IBs, ICF, new site Leipzig (no. 14), change of deputy at site 08 and 02	12.11.2020, 19.11.2020, 04.12.2020, 28.01.2021
07	Protocol amendment (v2.0), updated IBs, ICF	12.01.2021
08	New deputy at site 03, change of address at site 11	25.03.2021, 08.04.2021
09	Protocol amendment (v3.0), updated IBs, ICF	03.08.2021
10	Protocol amendment (v4.0), updated IBs, ICF	08.10.2021
11	New deputy at site 13	17.03.2022
12	Protocol amendment (v5.0), updated IBs, ICF	18.05.2022
13	New deputy at site 06	03.06.2022
14	Change of investigator and deputy at site 04	07.10.2022

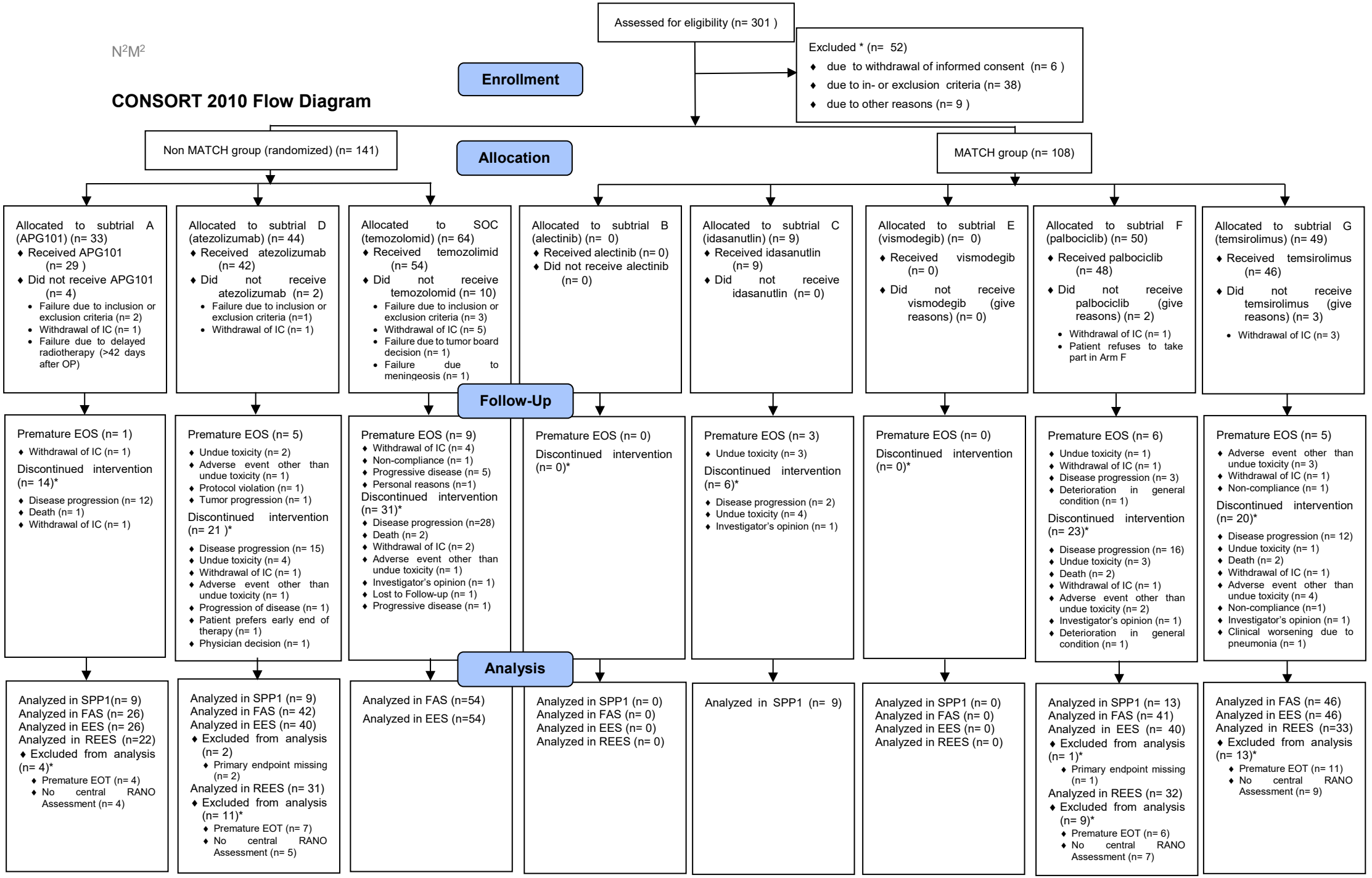
Paul Ehrlich Institute (PEI)

Amendment No.	Content	Approval Date
01	Change requests from ec from initial submission, IMPD Atezolizumab, updated IBs and SmPCs	10.04.2018
02	IMPD Alectinib and Idasanutlin	29.06.2019
03	Protocol amendment (v1.4), updated IBs, manufacturing documents Vismodegib	20.12.2019
04	Protocol amendment (v1.5), updated IBs, labels Idasanutlin	25.11.2020
05	Protocol amendment (v2.0), updated IB Idasanutlin, IMPD APG101	06.01.2021
06	Protocol amendment (v3.0), updated IBs	05.08.2021
07	Protocol amendment (v4.0), updated SmPCs	06.10.2021
08	Protocol amendment (v5.0), updated IBs, ICF	13.05.2022

Interruptions:
There was no interruption of the umbrella trial.

Date of the report:
February 2nd 2024

CONSORT 2010 Flow Diagram



*Multiple reasons for the same patient were possible

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol A

APG101 Plus Radiotherapy for Patients with Newly Diagnosed MGMT-unmethylated Glioblastoma

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. This report covers the results of subtrial A (APG101). Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N²M²

Final Sub-Study Report according to §13(9) GCP-V

Version Number/ Date:	Final 1, May 31st 2022
Investigational Product:	CD95L APG101
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 5.0 April 5th 2022 / N2M2 Subtrial A: CD95L APG101, 1.5, October 21st 2020

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Subtrial A (APG101): Initiation and Completion Dates:
First Patient in: October 22nd 2018
Last Patient in: November 17th 2020
Last Patient Last Visit: June 2nd 2021
Data base lock: May 17th 2022

Signatures

The present sub-study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	HEIDELBERG, 31/05/22 Place, Date
Biostatistician	Lanz Lisa-Marie Lanz, M.Sc.	Heidelberg, 01.06.2022 Place, Date

List of abbreviations:

AE	Adverse Event
ALT	Alanine transaminase
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
DLT	Dose-limiting toxicity
ECG	Electrocardiography
EES	Efficacy Evaluable Set
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-glutamyltransferase
KPI	Kanrofsky Performance Index
MGMT	O-6-methylguanine-DNA methyltransferase
MTD	Maximum tolerated dose
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
RANO	Response assessment in neuro-oncology criteria
REES	Regular Efficacy Evaluable Set
RLT	Regime-limiting toxicity
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SP P1	Safety Population Phase I

Synopsis

Name of Sponsor/Company:
Heidelberg University Hospital
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:
APG101 (Asunercept)

Name of Active Ingredient:
APG101

Title of Study:
Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol A: APG101 Plus Radiotherapy for Patients with Newly Diagnosed MGMT-unmethylated Glioblastoma

Short Title/ Acronym:

N^2M^2 – Subtrial A (APG101)

Protocol versions:

Umbrella protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)
Final 2.0, December 10th 2020 (Substantial Amendment)
Final 3.0, July 6th 2021 (Substantial Amendment)
Final 4.0 September 10th 2021 (Substantial Amendment)
Final 5.0 April 5th 2022 (Substantial Amendment)

Subtrial A (APG101) protocol:

Final 1.3, February 8th 2018 (First Authorization)
Final 1.4, October 23rd 2019 (Substantial Amendment)
Final 1.5, October 21st 2020 (Substantial Amendment)

Clinical trial sites and Principle Investigators of umbrella trial:

01 Prof. Wolfgang Wick/CI
Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg

02 Prof. Dr. med. Dietmar Krex
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden

03 Prof. Dr. Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin

04 Prof. Dr. med. Uwe Schlegel

	Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum
05	Prof. Dr. med. Ulrich Herrlinger Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn
06	Prof. Dr. med. Martin Glas Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen
07	PD Dr. med. Michael Burger Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt
08	Prof. Dr. Roland Goldbrunner Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln
09	Prof. Dr. med. Florian Ringel Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz
10	Prof. Dr. Michael Platten Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
11	Prof. Dr. med. Peter Hau Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg
12	Prof. Dr. med. Ralf Ketter, Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg
13	Prof. Dr. med. Ghazaleh Tabatabai, Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen
14	OA Dr. med. Clemens Seidel Universitätsklinikum Leipzig AöR, Klinik für Strahlentherapie und Radiologie, Stephanstraße 9a, 04103 Leipzig
All sites except 02, 06, 11 and 14 treated patients in subtrial A (APG101).	

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N^2M^2)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N^2M^2) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2*. Journal of Clinical

Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090

- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N²M² (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years) for subtrial A (APG101):	**Phase of development**:
Date of first enrollment: October 22nd 2018 Date of last enrollment: November 17th 2020 Date of last completed: June 2nd 2021 Early termination after treatment of 29 patients due to futility of the treatment compared to SOC.	I/IIa

Objectives:

Phase I:

The *primary Objective* of the phase I part of the trial was the determination of safety and tolerability of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial.
- Progression-free survival at six months (PFS-6) according to RANO criteria (Wen et al. 2010; Okada et al. 2015)

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N²M² subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.
  As stated in the protocol, this objective is not analyzed in this final trial report, but will be addressed in future manuscripts.

Methodology:

The trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. The phase I part of the subtrial shall determine the MTD for the combination therapy APG101 + RT with an accelerated rule based design. Patients treated at the final dose of phase I, can also be evaluated in the phase IIa part of the trial. For this subtrial no molecular marker was defined. Patients without a matching molecular marker were randomized in subtrials A, D or SOC.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily
- APG101: Weeks 1 to 26, weekly
- AEs: Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- Concomitant Medication: Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- DLTs (only phase I): Week 1 – 6
- RLTs (phase I): Week 7 – 26
- RLTs (phase IIa): Week 1 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab (chemistry), Karnofsky Performance Index (KPI)): Screening, Attribution, Weeks 4, 8, 12, 16, 20, 24
- Examinations (safety lab (hematology)): Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- EOS: Week 26

Number of patients (planned and analyzed in subtrial A):

Number of patients planned: ≤52 (40 of them planned to be analyzed for phase IIa)

Number of patients analyzed: 29

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials)

Investigational product, dose and mode of administration, batch number:

Drug Code: APG101 (human fusion protein)

Pharmaceutical formulation: Sterile concentrate for solution for infusion

Route of administration: i.v.

Storage conditions: 2 – 8°C

Manufacturer/Importer: Apogenix AG

Marketing Authorization number: not applicable

Dose: Three dose levels were available for examination (bold dose levels were actually administered): D0 (400mg), **D1 (600mg)**, **D2 (800mg)**

Batch numbers: 1019961, 1030564, 1039547, 1043971

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

Up to 6 months.

Criteria for evaluation:

Phase I:

Safety:

The *primary safety endpoint* was the determination of posterior probability of Dose Limiting Toxicity (DLT), defined as all adverse events (AEs) coded using Medical Dictionary for

Regulatory Activities (MedDRA) ≥ Grade 3 according to the National Cancer Institute Common Terminology Criteria for AE (CTCAE) v5.0 that are definitely, probably or possibly related to the administration of APG101 in combination with RT.

Secondary safety endpoint:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial for patients recruited for phase I.

Efficacy:

The *secondary efficacy endpoint* was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. See also the primary efficacy endpoint for phase IIa for more information.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without an event relevant for PFS (progression or death) at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events
- Karnofsky Index (KPI)
- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory Parameters (hematology, chemistry, urinalysis), ECG

Statistical methods:

Statistical analysis:

Subtrial A (APG101) of the Umbrella-trial N²M² passed the first interim analysis. For the second interim analysis, the response data did not fulfill the requirements for continuation to the final analysis and thus the subtrial was stopped.

Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results may be presented in the umbrella report.

Phase I

Analysis of the safety endpoints:

- For the primary safety endpoint (DLTs), the different examined dose-levels are presented, together with the amount and type (Preferred Term (PT) and System Organ Class level) of DLTs, patients experienced at these dose levels. Summary tables present the number of patients observed with a DLT and the corresponding percentage. Exact 95% two-sided Clopper-Pearson CIs are presented. Please note, that not all of the 3 dose-levels were examined. Starting dose was 600 mg.
- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CIs are presented. All patients who completed the combined treatment phase are included.

Analysis of the efficacy endpoint:

Progression-free survival at six months (PFS-6) according to RANO criteria as a binary endpoint is analyzed. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing.

Phase IIa

Analysis of the efficacy endpoints:

- The primary efficacy endpoint PFS-6 according to RANO criteria as a binary endpoint is analyzed with a one-sample one-sided Binomial test of the null hypothesis $H_0: p = 0.231$ Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing, but for the calculation of the p-value those patients are assumed to be non-responders. α-level for the primary analysis is 10%.
  Response assessment is determined by combining information from the clinical trial site (local RANO Assessment, a status page in the eCRF showing the information if the patient experienced progression during the 6 months after study entry and survival follow-up in case of premature EOS) and central RANO assessment performed by central neuroradiology in Heidelberg. If the clinical trial site stated a progression on the status page, the patient is assumed to be a non-responder, irrespective of other information. Central RANO assessment is the preferred type of assessment, but if not available (or differing to a stated progression on the status page) other sources of information are used to determine the response status/assessment.
- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first) minus 1 day. Patients without an event relevant for PFS* at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

* Please note, that patients with a death event (without a preceding progression event) are only considered as having an event relevant for PFS, if regular information on disease assessment for that patient is available. Otherwise the patient is censored.

Analysis of the (secondary) safety endpoints:

- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CI are presented.
- Adverse Events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages.
- Karnofsky Index (KPI) is summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages).
- Vital Signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening), respiratory rate) are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented. This includes changes (differences) from the baseline assessment, except for body height.
- Clinical laboratory parameters (hematology, chemistry, urinalysis) and ECG are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented (for ECG: only for abnormal results). The number of patients with laboratory values that are below, within or above normal ranges are tabulated for each parameter. Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and of changes from baseline are presented for each parameter. The number and percentage of patients with normal and abnormal ECG results at baseline and follow-up are tabulated. ECG findings are tabulated by patient.

Sub-Study populations

A total of 33 patients were included in 10 clinical trial sites. 29 patients were treated. 9 of these patients were treated in phase I and are thus part of the Safety Population Phase I (SP P1), 3 patients received 600mg (D1) and the remaining 6 patients were treated at the final dose of phase I (800mg, D2) and are thus also evaluable for phase IIa. Overall 26 patients received the final dose of phase I and thus part of the Full Analysis Set (FAS) and all of these 26 patients are available for the primary endpoint analysis (and are thus part of the Efficacy Evaluable Set (EES)). A total of 22 patients were treated at the final dose of phase I, had regular EOT (i.e. the patient had maximum treatment duration or premature EOT due to progression or death) and a central RANO assessment for PFS-6 is available (or the patient terminated treatment/study early due to death) and thus fulfill the criteria to be part of the Regular Efficacy Evaluable Set (REES). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		APG101 FAS/EES N (%)	APG101 SP P1 N (%)
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	12 (46.2)	3 (33.3)
	Premature end of treatment reached prior to week 26	14 (53.8)	6 (66.7)
Reason(s) for premature end of treatment *	Disease progression (lack of clinical benefit)	12 (85.7)	4 (66.7)
	Death	1 (7.1)	1 (16.7)
	Withdrawal of informed consent (patients decision)	1 (7.1)	1 (16.7)
Status at the End of the Study	Defined end of study at week 26 is reached	12 (46.2)	3 (33.3)
	Death	1 (3.8)	1 (11.1)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	12 (46.2)	4 (44.4)
	Premature study termination (and no safety follow-up was performed)	1 (3.8)	1 (11.1)
Reason(s) for premature study termination*	Withdrawal of informed consent	1 (100)	1 (100)

* Documentation of multiple reasons were possible.

Demographics FAS/EES:

	All Patients	Male	Female
Sex, n (%)			
Male	19 (73.1)	19 (100)	0
Female	7 (26.9)	0	7 (100)
Age continuous (years), Mean (SD)	59.0 (7.94)	59.4 (7.98)	57.9 (8.34)
BMI (kg/m²), Mean (SD)	25.8 (3.49)	26.9 (3.40)	22.8 (1.17)
Height (cm), Mean (SD)	175.7 (6.82)	177.4 (5.86)	171.1 (7.56)
Weight (kg), Mean (SD)	79.9 (12.41)	84.7 (10.30)	67.0 (7.46)
Age categorical (years), n (%)			
18-44	2 (7.7)	2 (10.5)	0
45-64	17 (65.4)	11 (57.9)	6 (85.7)
≥65	7 (26.9)	6 (31.6)	1 (14.3)
Ethnic Group, n(%)			
Caucasian/white	26 (100)	19 (100)	7 (100)

Demographics SP P1:

	All Patients	Male	Female
Sex, n (%)			
Male	5 (55.6)	5 (100)	0
Female	4 (44.4)	0	4 (100)

	All Patients	Male	Female
Age continuous (years), Mean (SD)	59.2 (10.28)	61.2 (3.19)	56.8 (15.92)
BMI (kg/m²), Mean (SD)	25.8 (3.76)	25.8 (1.76)	25.8 (5.79)
Height (cm), Mean (SD)	175.9 (9.48)	182.6 (2.88)	167.5 (7.72)
Weight (kg), Mean (SD)	79.8 (12.25)	86.1 (7.11)	72.0 (13.64)
Age categorical (years), n (%)			
18-44	1 (11.1)	0	1 (25.0)
45-64	5 (55.6)	4 (80.0)	1 (25.0)
≥65	3 (33.3)	1 (20.0)	2 (50.0)
Ethnic Group, n(%)			
Caucasian/white	9 (100)	5 (100)	4 (100)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The objective of Phase IIa part is the determination of efficacy of APG101 in conjunction with radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma.

Primary endpoint for phase IIa and secondary endpoint for phase I is the PFS-6 rate (corresponds to response rate), defined as the proportion of patients free of progression at 6 months after study entry. The tested null hypothesis (for phase IIa) is $H_0: p_0 = 23.1\%$.

Secondary endpoints for phase IIa include progression-free survival (PFS) and overall survival (OS).

Primary (Phase IIa)/secondary (Phase I) endpoint: PFS-6:

In the following 3 tables response-status and RANO-assessment are shown together with the best available source of information for the Full Analysis Set (FAS)/Efficacy Evaluable Set (EES), the Regular Efficacy Evaluable Set (REES) and the Safety Population Phase I (SP P1):

FAS/EES (N=26)	**All Patients**	**Central RANO Assessment**	**Local RANO Assessment**	**Progression according to trial site, not diagnosed with MRI**
Response-Status*				
Yes	4 (15.4)	4 (19.0)	0	0
No	22 (84.6)	17 (81.0)	3 (100)	2 (100)
Response-Assessment				
Stable Disease (SD)	4 (15.4)	4 (19.0)	0	0
Progressive Disease (PD)	22 (84.6)	17 (81.0)	3 (100)	2 (100)

REES (N=22)	**All Patients**	**Central RANO Assessment**	**Local RANO Assessment****
Response-Status*			
Yes	4 (18.2)	4 (19.0)	0
No	18 (81.8)	17 (81.0)	1 (100)

REES (N=22)	All Patients	Central RANO Assessment	Local RANO Assessment**
RANO-Assessment			
Stable Disease (SD)	4 (18.2)	4 (19.0)	0
Progressive Disease (PD)	18 (81.8)	17 (81.0)	1 (100)

SP P1 (N=9)	All Patients	Central RANO Assessment	Local RANO Assessment	Progression according to trial site, not diagnosed with MRI
Response-Status*				
Yes	1 (11.1)	1 (14.3)	0	0
No	8 (88.9)	6 (85.7)	1 (100)	1 (100)
Response-Assessment				
Partial Response (PR)	1 (11.1)	1 (14.3)	0	0
Progressive Disease (PD)	8 (88.9)	6 (85.7)	1 (100)	1 (100)

*: Patients are assessed as responders if stable disease, partial response or complete response is present after 6 months
**: This patient, in addition to the locally assessed progression, terminated study early due to death

For the primary analysis the FAS is used (in this case identical to the EES). Overall, 15.4% (4/26) of these patients were assessed as responders (95%-Clopper-Pearson CI: [4.36%, 34.87%]). All of them were confirmed by central RANO Assessment. Best available assessment was “stable disease”. The corresponding p-value of the one-sided binomial test is $p = 0.8825$

As a sensitivity analysis, the same calculations were performed on the REES. 18.2% (4/22) of these patients were assessed as responders (95%-Clopper-Pearson CI: [5.19%, 40.28%]). The corresponding p-value of the one-sided binomial test is $p = 0.7829$.

As secondary endpoint for Phase I, PFS-6 is analyzed using SP P1. 11.1% (1/9) of these patients (receiving 600 mg APG101) was assessed as responder (95%-Clopper-Pearson CI: [0.28%, 48.25%]) with partial response confirmed by central RANO Assessment. The corresponding p-value of the one-sided binomial test is $p = 0.906$.

Secondary endpoint: PFS
The secondary endpoint PFS is analyzed using the FAS/EES. The number of patients with an event relevant for PFS until database lock is 22/26 (84.6%). Median progression-free survival is 5.4 months. For more information see the following table:

Number of Patients (%)	26 (100)
Number of Patients with the Event (%)	22 (84.6)
25 Percent Point Estimate* (95% CI)	2.8 (2.6, 2.9)
Median* (95% CI)	5.4 (2.8, 5.8)

75 Percent Point Estimate* (95% CI)	6.2 (5.7, 6.5)
6-month event free rate** (95% CI)	0.299 (0.138, 0.480)
9-month event free rate** (95% CI)	0.064 (0.005, 0.243)
12-month event free rate** (95% CI)	0.064 (0.005, 0.243)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAS/EES. The number of patients with the event until database lock is 19/26 (73.1%). Median overall survival is 12.8 months. For more information see the following table:

Number of Patients (%)	26 (100)
Number of Patient with the Event (%)	19 (73.1)
25 Percent Point Estimate* (95% CI)	10.1 (6.2, 11.9)
Median* (95% CI)	12.8 (10.1, 18.5)
75 Percent Point Estimate* (95% CI)	19.3 (13.8, 20.4)
6-month event free rate** (95% CI)	0.962 (0.757, 0.994)
9-month event free rate** (95% CI)	0.808 (0.598, 0.915)
12-month event free rate** (95% CI)	0.577 (0.368, 0.739)
18-month event free rate** (95% CI)	0.345 (0.162, 0.538)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

SAFETY RESULTS:

For the Full Analysis Set the total drug exposure for all patients was 3671 days.

Overall 24 (92.3%) patients experienced at least one (all causality) AE (total number of AEs=138) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Nervous system disorders” and “General disorder and administration site conditions”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. 10 (38.5%) patients experienced at least one treatment related AE (total number of treatment-related AEs=27). The most frequent treatment related AEs in terms of system organ class were “Nervous system disorders” and “General disorder and administration site conditions”. 6 SAEs occurred in overall 6 (23.1%) patients. Most of these SAEs were reported in the system organ class “Infections and infestations”. No RLTs occurred.

For the Safety Population Phase I the total drug exposure for all patients was 1284 days.

All 9 patients experienced at least one (all causality) AE (total number of AEs=69, total number of AEs for patients with dosage 600 mg=26, total number of AEs for patients with dosage 800 mg=43) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class for patients receiving a dose of 600 mg as well as for patients receiving 800 mg were “Nervous system disorders”. 1 patient receiving 800 mg experienced one treatment related AE in the system

organ class “Gastrointestinal disorders”. No treatment related AEs were reported for patients receiving 600 mg.

No RLTs or DLTs were reported. 1 SAE in 1 patient (11.1%) receiving 800 mg was reported (assessed as unrelated to study treatment).

For detailed information see the following table:

	FAS N (%)	**SP P1 All patients N (%)**	**SP P1 600mg (D1) N (%)**	**SP P1 800mg (D2) N (%)**
Overview all AEs				
Any AE	24 (92.3)	9 (100)	3 (100)	6 (100)
Any SAE	6 (23.1)	1 (11.1)	0	1 (16.7)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	10 (38.5)	6 (66.7)	3 (100)	3 (50.0)
Any DLT	0	0	0	0
Any RLT	0	0	0	0
Patients discontinued study drug due to AEs	0	0	0	0
Patients with dose of study drug reduced or temporary discontinuation due to AE	6 (23.1)	4 (44.4)	1 (33.3)	3 (50.0)
Patients with AE resulting in death	0	0	0	0
Overview related AEs				
Any AE	10 (38.5)	1 (11.1)	0	1 (16.7)
Any SAE	0	0	0	0
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	0	0	0	0
Any DLT	0	0	0	0
Any RLT	0	0	0	0
Patients discontinued study drug due to AEs	0	0	0	0
Patients with dose of study drug reduced or temporary discontinuation due to AE	0	0	0	0
Patients with AE resulting in death	0	0	0	0
AEs by System Organ Class (MedDRA 23.0), all causalities*				
Blood and lymphatic system disorders	4 (15.4)	0	0	0
Cardiac disorders	1 (3.8)	0	0	0
Ear and labyrinth disorders	3 (11.5)	2 (22.2)	1 (33.3)	1 (16.7)
Eye disorders	5 (19.2)	0	0	0
Gastrointestinal disorders	9 (34.6)	4 (44.4)	1 (33.3)	3 (50.0)
General disorders and administration site conditions	13 (50.0)	5 (55.6)	2 (66.7)	3 (50.0)
Immune system disorders	1 (3.8)	0	0	0
Infections and infestations	7 (26.9)	4 (44.4)	2 (66.7)	2 (33.3)
Injury, poisoning and procedural complications	4 (15.4)	0	0	0
Investigations	7 (26.9)	5 (55.6)	2 (66.7)	3 (50.0)
Metabolism and nutrition disorders	5 (19.2)	2 (22.2)	0	2 (33.3)

	FAS N (%)	SP P1 All patients N (%)	SP P1 600mg (D1) N (%)	SP P1 800mg (D2) N (%)
Musculoskeletal and connective tissue disorders	1 (3.8)	0	0	0
Nervous system disorders	18 (69.2)	8 (88.9)	2 (66.7)	6 (100)
Psychiatric disorders	3 (11.5)	4 (44.4)	2 (66.7)	2 (33.3)
Renal and urinary disorders	1 (3.8)	1 (11.1)	0	1 (16.7)
Respiratory, thoracic and mediastinal disorders	1 (3.8)	1 (11.1)	1 (33.3)	0
Skin and subcutaneous tissue disorders	8 (30.8)	4 (44.4)	2 (66.7)	2 (33.3)
Vascular disorders	4 (15.4)	2 (22.2)	1 (33.3)	1 (16.7)
SAEs by System Organ Class (MedDRA 23.0), all causalities*				
Eye disorders	1 (3.8)	0	0	0
Infections and infestations	3 (11.5)	1 (11.1)	0	1 (16.7)
Nervous system disorders	1 (3.8)	0	0	0
Vascular disorders	1 (3.8)	0	0	0
SAEs by System Organ Class (MedDRA 23.0), related*				
No SAEs with a suspected relationship to the study treatment were reported.				
DLTs by System Organ Class (MedDRA 23.0)*				
No DLTs were reported.				
RLTs by System Organ Class (MedDRA 23.0)*				
No RLTs were reported.				

* The displayed number shows the amount of patients with one or more events in the specific system organ class. Each patient is counted only once per system organ class.

Other Safety Data

In the following presentation of other safety data only tests and examinations that were performed on or after date of first treatment of the respective patient are included.

For the Full Analysis Set, karnofsky index ranged from 70 to 100, mean KPI over all visits and patients was 86.2. Vital signs were unremarkable. Most recorded clinical laboratory values (>99%) were within normal ranges or not clinically significant. Most clinically significant values occurred for parameters creatinine clearance, white blood cell count, neutrophils and lymphocytes. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameters pH-value and nitrite. Most ECG results (>97%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 42 bpm to 82 bpm, mean: 62.0 bpm), PQ interval (range: 146 msec to 170 msec, mean: 158.0 msec), QRS interval (range: 45 msec to 100 msec, mean: 80.75 msec), QT interval (range: 360 msec to 470 msec, mean: 410.5 msec) and QTcF interval (range: 369 msec to 451 msec, mean: 410.075 msec).

For the Safety Population Phase I, karnofsky index ranged from 60 to 100, mean KPI over all visits and patients was 82.9. Vital signs were unremarkable. Most recorded clinical laboratory values (>99%) were within normal ranges or not clinically significant. Clinically significant values occurred for parameters ALT, lymphocytes, sodium and GGT. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameter nitrite. Most

ECG results (90%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 42 bpm to 52 bpm, mean: 47.0 bpm), PQ interval (range: 128 msec to 158 msec, mean: 136.4 msec), QRS interval (range: 61 msec to 98 msec, mean: 74.2 msec), QT interval (range: 420 msec to 470 msec, mean: 440.4 msec) and QTcF interval (range: 397 msec to 417.3 msec, mean: 404.66 msec).

CONCLUSION:

The data from Subtrial A (APG101) of the N^2M^2 trial show low efficacy for the primary endpoint (overall 15.4% patients without progression after 6 months). The subtrial was terminated due to futility compared to standard of care (H_0: p=23.1%).

The observed DLT-rate in patients receiving the starting dose (600mg) is 0% (0/3 patients) (95% two-sided Clopper-Pearson CI: [0, 0.708]). The observed RLT-rate in patients receiving the determined MTD 800mg is 0% (0/26 patients) (95% two-sided Clopper-Pearson CI: [0, 0.132]), thus tolerability of the MTD is confirmed.

Date of the report:

May 20th 2022

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol C

Idasanutlin plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma with p53 wildtype status, MDM2 amplification and/or MDM2 over-expression

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. This report covers the results of subtrial C (Idasanutlin). Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N²M²

Final Sub-Study Report according to §13(9) GCP-V

Version Number/ Date:	Final, December 16th 2021
Investigational Product:	Idasanutlin
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 4.0 September 10th 2021 / N2M2 Subtrial C: MDM2 idasanutlin, 1.5, October 21st 2020

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Subtrial C (idasanutlin): Initiation and Completion Dates:
First Patient in: November 20th 2018
Last Patient in: June 3rd 2020
Date of early termination: December 17th 2020
Last Patient Last Visit: December 17th 2020
Data base lock: December 13th 2021

Signatures

The present sub-study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	HD, 17 Dec 2021 Place, Date
Biostatistician	Lanz Lisa-Marie Lanz, M.Sc.	Weinheim, 17. 12. 2021 Place, Date

Synopsis

Name of Sponsor/Company:

Heidelberg University Hospital
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:

Idasanutlin

Name of Active Ingredient:

RO5503781/F17 (50 mg), RO5503781/F16 (200 mg), RO5503781/F13 (300 mg)

Title of Study:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol C: Idasanutlin plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma with p53 wildtype status, MDM2 amplification and/or MDM2 over-expression

Short Title/ Acronym:

N^2M^2 – Subtrial C (Idasanutlin)

Protocol versions:

Umbrella protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Final 2.0, December 10th 2020 (Substantial Amendment)

Final 3.0, July 6th 2021 (Substantial Amendment)

Final 4.0 September 10th 2021 (Substantial Amendment)

Subtrial C (Idasanutlin) protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Study centers and Principle Investigators of umbrella trial:

01 Prof. Wolfgang Wick/CI
Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg

02 Prof. Dr. med. Dietmar Krex
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden

03 Prof. Dr. Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin

04 Prof. Dr. med. Uwe Schlegel
Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum

05 Prof. Dr. med. Ulrich Herrlinger
Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn

06 Prof. Dr. med. Martin Glas
Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen

07 PD Dr. med. Michael Burger
Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt

08 Prof. Dr. Roland Goldbrunner
Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln

09 Prof. Dr. med. Florian Ringel
Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz

10 Prof. Dr. Michael Platten
Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim

11 Prof. Dr. med. Peter Hau
Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg

12 Prof. Dr. med. Ralf Ketter,
Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg

13 Prof. Dr. med. Ghazaleh Tabatabai,
Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen

14 OA Dr. med. Clemens Seidel
Universitätsklinikum Leipzig AöR, Klinik für Strahlentherapie und Radiologie, Stephanstraße 9a, 04103 Leipzig

Sites 01, 04, 07, 09 and 10 treated patients in subtrial C (Idasanutlin).

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N^2M^2)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N^2M^2) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2*. Journal of Clinical Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090

- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N²M² (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years) for subtrial C (idasanutlin):	**Phase of development**:
Date of first enrollment: November 20th 2018 Date of last enrollment: June 3rd 2020 Date of early trial termination: December 17th 2020 Date of last completed: December 17th 2020 Early termination after the treatment of 9 patients due to discontinuation of the development program of Idasanutlin by Roche.	Phase I/IIa

Objectives:

Phase I:

The *primary Objective* of the phase I part of the trial was the determination of safety and tolerability of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial.
- Progression-free survival at six months (PFS-6) according to RANO criteria (Wen et al. 2010; Okada et al. 2015)

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N²M² subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.

Please note

Subtrial C (Idasanutlin) did not reach the phase IIa part of the trial and thus only phase I objectives are analyzed.

Methodology:

The trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. The phase I part of the trial shall determine the MTD for the combination therapy Idasanutlin + RT with an accelerated rule based design. Patients treated at the final dose of phase I, can also be evaluated in the phase IIa part of the trial.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily
- Idasanutlin: Weeks 1, 5, 9, 13, 17, 21, 25
- AEs, Concomitant Medication: Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- DLTs: Week 1 – 6
- RLTs: Week 7 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab, Karnofsky Performance Index (KPI)): Weeks 4, 8, 12, 16, 20, 24
- EOS: Week 26

Number of patients (planned and analyzed):

Number of patients planned:	≤64 (40 of them planned to be analyzed for phase IIa)
Number of patients analyzed	9 (only phase I)

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials)
- p53 wildtype status and MDM2 amplification (>1.8 fold) or MDM2 overexpression (suitable for subtrial C only)

Investigational product, dose and mode of administration, batch number:

Drug Code: Idasanutlin

Pharmaceutical formulation: film coated tablets

Route of administration: orally

Storage conditions: ≤ 25°C

Manufacturer/Importer: Roche Pharma AG

Marketing Authorization number: not applicable

Dose: Eight dose levels were available for examination (bold dose levels were actually administered): D0 (50 mg), **D1 (100 mg)**, **D2 (150 mg)**, **D3 (200 mg)**, **D4 (250 mg)**, D5 (300 mg), D6 (350 mg), D7 (400 mg)

Batch numbers: 1153789, 1153881, 1161359, 1153789S01

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

Up to 6 months.

Criteria for evaluation:

Phase I:

Safety:

The *primary safety endpoint* was the determination of posterior probability of Dose Limiting Toxicity (DLT), defined as all adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA) ≥ Grade 3 according to the National Cancer Institute Common Terminology Criteria for AE (CTCAE) v5.0 that are definitely, probably or possibly related to the administration of Idasanutlin in combination with RT.

Secondary safety endpoint:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial for patients recruited for phase I.

Efficacy:

The *secondary efficacy endpoint* was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. See also the primary efficacy endpoint for phase IIa for more information.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without a PFS event at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events*
- Karnofsky Index (KPI)
- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory Parameters (hematology, chemistry, urinalysis), ECG

Please note:

- Subtrial C (Idasanutlin) did not reach the phase IIa part of the trial and thus only phase I endpoints are analyzed.

* This endpoint is analyzed for phase I although originally planned for phase IIa.

Statistical methods:

Statistical analysis:

Subtrial C (Idasanutlin) of the Umbrella-trial N^2M^2 was stopped prematurely when 9 patients were treated due to discontinuation of the development program of Idasanutlin by the manufacturer Roche Pharma AG. The subtrial did not reach the phase IIa part of the trial. For this reason, any confirmatory statistical analysis is inappropriate. The statistical analysis actually performed is therefore in a strictly exploratory and mainly descriptive manner. All data collected which have value towards assessing the safety, efficacy or other properties

of the drug are reported in either the summary presentations or listings or in both. If not stated differently, all patients receiving any amount of study treatment in this subtrial are included in the analyses.

Analysis of the safety endpoints:

- For the primary safety endpoint (DLTs), the different examined dose-levels are presented, together with the amount and type (Preferred Term (PT) and System Organ Class level) of DLTs, patients experienced at these dose levels. Determination of a MTD is unfeasible. Summary tables present the number of patients observed with a DLT, the corresponding percentage, and exact 95% two-sided Clopper-Pearson CI. Please note, that not all of the 8 dose-levels were examined. Starting dose was 100 mg. All patients who completed the combined treatment phase or who experienced a DLT are included.
- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs, the corresponding percentages, and exact 95% two-sided Clopper-Pearson CI. All patients who completed the combined treatment phase are included.
- Additionally, but originally unplanned, adverse events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs, the corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs.
  Please note: This endpoint was originally part of the phase IIa endpoints, but due to the early termination prior to start of phase IIa, this endpoint is analyzed with the patients in phase I.

Analysis of the efficacy endpoint:

- Progression-free survival at six months (PFS-6) according to RANO criteria as a binary endpoint is analyzed. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing.

Sub-Study population

A total of 9 patients were included in 5 trial centers and treated in the phase I part of the trial. Due to early trial termination, no final dose of phase I could be found and thus no patients are analyzed for phase IIa. All 9 patients are analyzed in the Safety Population Phase I. Administered dosages are D1 (100 mg) to D4 (250 mg). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		Idasanutlin N (%)
Status at the End of the Study	Defined end of study at week 26 is reached	3 (33.3)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	3 (33.3)

	Premature study termination	3 (33.3)
Reason(s) for premature study termination*	Undue toxicity	3 (100)
	Death	0
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	3 (33.3)
	(Premature) end of treatment reached prior to week 26	6 (66.7)
Reason(s) for premature end of treatment (for patients who prematurely discontinued only)*	Disease progression (lack of clinical benefit)	2 (33.3)
	Undue toxicity	4 (66.7)
	Investigator's opinion	1 (16.7)
	Death	0

* Multiple answers were possible.

Demographics:

	All Patients	**Male**	**Female**
Sex, n (%)			
Male	5 (55.6)	5 (100)	0
Female	4 (44.4)	0	4 (100)
Age continuous (years), Mean (SD)	57.2 (12.21)	58.6 (8.62)	55.5 (17.08)
BMI (kg/m²), Mean (SD)	28.2 (6.56)	28.7 (3.01)	27.5 (10.09)
Height (cm), Mean (SD)	171.4 (6.04)	175.0 (5.70)	167.0 (2.58)
Weight (kg), Mean (SD)	82.7 (18.42)	87.9 (10.19)	76.3 (25.82)
Age categorical (years), n (%)			
18-44	1 (11.1)	0	1 (25.0)
45-64	6 (66.7)	4 (80.0)	2 (50.0)
≥65	2 (22.2)	1 (20.0)	1 (25.0)
Ethnic Group, n(%)			
Caucasian/white	9 (100)	5 (100)	4 (100)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

This sub-study was performed in order to evaluate the safety, feasibility and preliminary efficacy of Idasanutlin for patients with p53 wildtype status and MDM2 amplification or overexpression. The secondary efficacy endpoint of the subtrial for phase I was the progression-free survival after 6 months.

The response-status (number of patients being free of progression or not) and the specific RANO-assessments per dose are shown in the following table for the Safety Population Phase I:

	All Patients	**100 mg (D1)**	**150 mg (D2)**	**200 mg (D3)**	**250 mg (D4)**
Response-Status*					
Missing	1	1	0	0	0
Yes	4 (50.0)	0	1 (50.0)	3 (60.0)	0
No	4 (50.0)	0	1 (50.0)	2 (40.0)	1 (100)
RANO-Assessment					

Missing	1	1	0	0	0
Stable Disease (SD)	4 (50.0)	0	1 (50.0)	3 (60.0)	0
Progressive Disease (PD)	4 (50.0)	0	1 (50.0)	2 (40.0)	1 (100)

*: Patients are assessed as responders if stable disease, partial response or complete response is present after 6 months

In the following table response-status and RANO-assessment are shown together with the best available source of information:

	All Patients	**Central RANO Assessment**	**No progression, but different anti-cancer therapy received****	**No information available**
Response-Status*				
Missing	1	0	0	1
Yes	4 (50.0)	4 (57.1)	0	0
No	4 (50.0)	3 (42.9)	1 (100)	0
RANO-Assessment				
Missing	1	0	0	1
Stable Disease (SD)	4 (50.0)	4 (57.1)	0	0
Progressive Disease (PD)	4 (50.0)	3 (42.9)	1 (100)	0

*: Patients are assessed as responders if stable disease, partial response or complete response is present after 6 months
**: Patients in this category are assumed to be treatment-failures and thus are counted as having PD

Overrall, 50% (4/8) of the patients with available information were assessed as responders (95%-Clopper-Pearson CI: [15.70%, 84.30%]). All of them were confirmed by central RANO Assessment. One patient received D2 (150 mg) and 3 patients received D3 (200 mg). The best (and only) identified response type was ‘stable disease’.

SAFETY RESULTS:

Overall all patients experienced at least one (all causality) AE (total number of AEs=111). AEs occuring several times were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Gastrointestinal disorders” and “General disorders and administration site conditions”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. All patients experienced at least one treatment related AE (total number of treatment-related AEs=70). 4 DLTs occurred in 2 patients (22.2%) patients. 12 RLTs were observed in 4 (44.4%) patients. DLTs included Neutropenia and Thrombocytopenia. RLTs included Leucopenia, Neutropenia, Thrombocytopenia and a decrease in platelet count, neutrophil count and white blood cells. 8 SAEs occurred in overall 4 patients and 11 AESIs in 5 patients. For more information (especially on dose levels of patients experiencing (S)AEs and system organ class of the AEs) see the following table:

	All patients	100 mg (D1)	150 mg (D2)	200 mg (D3)	250 mg (D4)
Overview all AEs					
Any AE	9 (100)	1 (100)	2 (100)	5 (100)	1 (100)
Any SAE	4 (44.4)	1 (100)	0	3 (60.0)	0
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	5 (55.6)	1 (100)	0	3 (60.0)	1 (100)
Any DLT	2 (22.2)	0	0	1 (20.0)	1 (100)
Any RLT	4 (44.4)	1 (100)	0	3 (60.0)	0
Any AESI*	5 (55.6)	1 (100)	0	3 (60.0)	1 (100)
Patients discontinued study drug due to AEs	4 (44.4)	1 (100)	0	2 (40.0)	1 (100)
Patients with dose of study drug reduced or temporary discontinuation due to AE	5 (55.6)	1 (100)	0	4 (80.0)	0
Patients with AE resulting in death	0	0	0	0	0
Overview related AEs**					
Any AE	9 (100)	1 (100)	2 (100)	5 (100)	1 (100)
Any SAE	4 (44.4)	1 (100)	0	3 (60.0)	0
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	5 (55.6)	1 (100)	0	3 (60.0)	1 (100)
Any DLT	2 (22.2)	0	0	1 (20.0)	1 (100)
Any RLT	4 (44.4)	1 (100)	0	3 (60.0)	0
Any AESI*	5 (55.6)	1 (100)	0	3 (60.0)	1 (100)
Patients discontinued study drug due to AEs	4 (44.4)	1 (100)	0	2 (40.0)	1 (100)
Patients with dose of study drug reduced or temporary discontinuation due to AE	5 (55.6)	1 (100)	0	4 (80.0)	0
Patients with AE resulting in death	0	0	0	0	0
AEs by System Organ Class (MedDRA 23.0), all causalities					
Blood and lymphatic system disorders	7 (77.8)	0	1 (50.0)	5 (100)	1 (100)
Ear labyrinth disorders	1 (11.1)	1 (100)	0	0	0
Eye disorders	2 (22.2)	0	0	2 (40.0)	0
Gastrointestinal disorders	9 (100)	1 (100)	2 (100)	5 (100)	1 (100)
General disorders and administration site conditions	9 (100)	1 (100)	2 (100)	5 (100)	1 (100)
Infections and infestations	2 (22.2)	0	2 (100)	0	0
Investigations	4 (44.4)	1 (100)	0	3 (60.0)	0
Metabolism and nutrition disorders	6 (66.7)	1 (100)	1 (50.0)	3 (60.0)	1 (100)
Musculoskeletal and connective tissue disorders	1 (11.1)	0	0	1 (20.0)	0
Nervous system disorders	8 (88.9)	1 (100)	2 (100)	4 (80.0)	1 (100)
Psychiatric disorders	1 (11.1)	0	0	1 (20.0)	0

Respiratory, thoracic and mediastinal disorders	1 (11.1)	0	1 (50.0)	0	0
Skin and subcutaneous tissue disorders	5 (55.6)	0	1 (50.0)	3 (60.0)	1 (100)
SAEs by System Organ Class (MedDRA 23.0), all causalities, related**					
Blood and lymphatic system disorders	3 (33.3)	0	0	3 (60.0)	0
Investigations	1 (11.1)	1 (100)	0	0	0
AESI by System Organ Class (MedDRA 23.0), related**					
Blood and lymphatic system disorders	4 (44.4)	0	0	3 (60.0)	1 (100)
Investigations	2 (22.2)	1 (100)	0	1 (20.0)	0

* For a definition of AESI, see the subprotocol for subtrial C

** (S)AEs and AESIs with certain, probable, possible or missing relationship with Idasanutlin were considered

CONCLUSION:

Due to the early sub-study termination prior to the start of phase II resulting in reduced sample size and correspondingly reduced power, any conclusions in regard to study objectives could not be demonstrated, especially dose-finding could not be finished and thus no optimal dose was found.

Date of the report:

December 16th 2021

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N^2M^2 (NOA-20)

Subtrial Protocol D

Atezolizumab plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) of the N^2M^2 project. This report covers the results of subtrial D (Atezolizumab). Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N^2M^2

Final Sub-Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.0 February 2nd 2024
Investigational Product:	Atezolizumab
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 5.0 April 5th 2022 / N2M2 Subtrial D: atezolizumab, 2.0, April 5th 2022

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Subtrial D (Atezolizumab): Initiation and Completion Dates:
First Patient in: July 4th 2018
Last Patient in: June 20th 2022
Last Patient Last Visit: February 22nd 2023
Data base lock: October 25th 2023

Signatures

The present sub-study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	HEIDELBERG, 5/2/24 Place, Date
Biostatistician	Lanz Lisa-Marie Lanz, M.Sc.	Weinheim, 06.02.24 Place, Date

List of abbreviations:

AE	Adverse Event
ALT	Alanine transaminase
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
DLT	Dose-limiting toxicity
ECG	Electrocardiography
EES	Efficacy Evaluable Set
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-glutamyltransferase
KPI	Karnofsky Performance Index
MGMT	O-6-methylguanine-DNA methyltransferase
MTD	Maximum tolerated dose
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
RANO	Response assessment in neuro-oncology criteria
REES	Regular Efficacy Evaluable Set
RLT	Regime-limiting toxicity
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SP P1	Safety Population Phase I

Synopsis

Name of Sponsor/Company:

Heidelberg University Hospital
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:

Atezolizumab

Name of Active Ingredient:

Atezolizumab

Title of Study:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol D: Atezolizumab plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma

Short Title/ Acronym:

N^2M^2 – Subtrial D (Atezolizumab)

Protocol versions:

Umbrella protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Final 2.0, December 10th 2020 (Substantial Amendment)

Final 3.0, July 6th 2021 (Substantial Amendment)

Final 4.0 September 10th 2021 (Substantial Amendment)

Final 5.0 April 5th 2022 (Substantial Amendment)

Subtrial D (Atezolizumab) protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Final 2.0, April 5th 2022 (Substantial Amendment)

Clinical trial sites and Principle Investigators of umbrella trial:

01 Prof. Wolfgang Wick/CI
Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg

02 Prof. Dr. med. Dietmar Krex
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden

03 Prof. Dr. Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin

04	Prof. Dr. med. Uwe Schlegel Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum
05	Prof. Dr. med. Ulrich Herrlinger Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn
06	Prof. Dr. med. Martin Glas Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen
07	PD Dr. med. Michael Burger Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt
08	Prof. Dr. Roland Goldbrunner Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln
09	Prof. Dr. med. Florian Ringel Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz
10	Prof. Dr. Michael Platten Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
11	Prof. Dr. med. Peter Hau Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg
12	Prof. Dr. med. Ralf Ketter, Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg
13	Prof. Dr. med. Ghazaleh Tabatabai, Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen

All sites except site 4 (Bochum) treated patients in subtrial D (Atezolizumab).

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N^2M^2)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N^2M^2) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2*. Journal of Clinical Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090

- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N^2M^2 (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years) for subtrial D (Atezolizumab):	**Phase of development**:
Date of first enrollment: July 5th 2018 Date of last enrollment: June 20th 2022 Date of last completed: February 22nd 2022	I/IIa

Objectives:

Phase I:

The *primary Objective* of the phase I part of the trial was the determination of safety and tolerability of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial.
- Progression-free survival at six months (PFS-6) according to RANO criteria (Wen et al. 2010; Okada et al. 2015)

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N^2M^2 subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.
  As stated in the protocol, this objective is not analyzed in this final trial report, but will be addressed in future manuscripts.

Methodology:

The trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N^2M^2 project. The phase I part of the subtrial shall determine the MTD for the combination therapy Atezolizumab + RT with an accelerated rule based design. Patients treated at the final dose of phase I, can also be evaluated in the phase IIa part of the trial.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily
- Atezolizumab: Weeks 1, 4, 7, 10, 13, 16, 19, 22, 25
- AEs: Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26

- Concomitant Medication: Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- DLTs (only phase I): Week 1 – 6
- RLTs (phase I): Week 7 – 26
- RLTs (phase IIa): Week 1 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab (chemistry), Karnofsky Performance Index (KPI)): Screening, Attribution, Weeks 4, 8, 12, 16, 20, 24
- Examinations (safety lab (hematology)): Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- EOS: Week 26

Number of patients (planned and analyzed in subtrial D):

Number of patients planned: 40

Number of patients analyzed: 42

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials; no further biomarker is defined for subtrial D (atezolizumab) as it is part of the non-match group)

Investigational product, dose and mode of administration, batch number:

Drug Code: Atezolizumab

ATC Code: L01FF05

Pharmaceutical formulation: Sterile concentrate for solution for infusion

Route of administration: i.v.

Storage conditions: 2-8°C

Manufacturer/Importer: Roche Pharma AG

Marketing Authorization number: EU/1/17/1220/001

Dose: One dose level was available for examination: D1 (1200mg)

Batch numbers: 1154634; 1162400; 1164852; 1169751; 1171774; 1171830

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

Up to 6 months.

Criteria for evaluation:

Phase I:

Safety:

The *primary safety endpoint* was the determination of posterior probability of Dose Limiting Toxicity (DLT), defined as all adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA) ≥ Grade 3 according to the National Cancer Institute Common Terminology Criteria for AE (CTCAE) v5.0 that are definitely, probably or possibly related to the administration of Atezolizumab in combination with RT.

Secondary safety endpoint:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial for patients recruited for phase I.

Efficacy:

The *secondary efficacy endpoint* was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. See also the primary efficacy endpoint for phase IIa for more information.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without an event relevant for PFS (progression or death) at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events
- Karnofsky Index (KPI)
- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory Parameters (hematology, chemistry, urinalysis), ECG

Statistical methods:

Statistical analysis:

Subtrial D (Atezolizumab) of the Umbrella-trial N^2M^2 passed the first and second interim analysis and recruited to the final analysis.

Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results may be presented in the umbrella report.

Phase I

Analysis of the safety endpoints:

- For the primary safety endpoint (DLTs), the different examined dose-levels are presented, together with the amount and type (Preferred Term (PT) and System Organ Class level) of DLTs, patients experienced at these dose levels. Summary tables present the number of patients observed with a DLT and the corresponding percentage. Exact 95% two-sided Clopper-Pearson CIs are presented. Starting dose was 75 mg.
- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CIs are presented. All patients who completed the combined treatment phase are included.

Analysis of the efficacy endpoint:

Progression-free survival at six months (PFS-6) according to RANO criteria as a binary endpoint is analyzed. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing.

Phase IIa

Analysis of the efficacy endpoints:

- The primary efficacy endpoint PFS-6 according to RANO criteria as a binary endpoint is analyzed with a one-sample one-sided Binomial test of the null hypothesis $H_0: p = 0.231$ Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing, but for the calculation of the p-value those patients are assumed to be non-responders. α-level for the primary analysis is 10%.
  Response assessment is determined by combining information from the clinical trial site (local RANO Assessment, a status page in the eCRF showing the information if the patient experienced progression during the 6 months after study entry and survival follow-up in case of premature EOS) and central RANO assessment performed by central neuroradiology in Heidelberg. If the clinical trial site stated a progression on the status page, the patient is assumed to be a non-responder, irrespective of other information. Central RANO assessment is the preferred type of assessment, but if not available (or differing to a stated progression on the status page) other sources of information are used to determine the response status/assessment.
- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first) minus 1 day. Patients without an event relevant for PFS* at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

* Please note, that patients with a death event in the survival follow-up (without a preceding progression event) are only considered as having an event relevant for PFS, if regular

information on disease assessment for that patient is available. Otherwise the patient is censored at the last date of disease assessment.

Analysis of the (secondary) safety endpoints:

- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CI are presented.
- Adverse Events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages.
- Karnofsky Index (KPI) is summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages).
- Vital Signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening), respiratory rate) are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented. This includes changes (differences) from the baseline assessment, except for body height.
- Clinical laboratory parameters (hematology, chemistry, urinalysis) and ECG are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented (for ECG: only for abnormal results). The number of patients with laboratory values that are below, within or above normal ranges are tabulated for each parameter. Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and of changes from baseline are presented for each parameter. The number and percentage of patients with normal and abnormal ECG results at baseline and follow-up are tabulated. ECG findings are tabulated by patient.

Sub-Study populations

A total of 44 patients were included in 12 clinical trial sites. 42 patients were treated. 9 of these patients were treated in phase I and are thus part of the Safety Population Phase I (SP P1), all patients received the final dose (1200 mg) and are thus also evaluable for phase IIa. All 42 patients received the final dose of phase I and are thus part of the Full Analysis Set (FAS) and 40 patients are available for the primary endpoint analysis and are thus part of the Efficacy Evaluable Set (EES). A total of 31 patients were treated at the final dose of phase I, had regular EOT (i.e. the patient had maximum treatment duration or premature EOT due to progression or death) and a central RANO assessment for PFS-6 is available (or the patient terminated treatment/study early due to death) and thus fulfill the criteria to be part of the Regular Efficacy Evaluable Set (REES). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		SP P1 **N (%)**	**FAS** **N (%)**	**EES** **N (%)**
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	3 (33.3)	21 (50.0)	21 (52.5)

		SP P1 N (%)	FAS N (%)	EES N (%)
	(Premature) end of treatment reached prior to week 26	6 (66.7)	21 (50.0)	19 (47.5)
Reason(s) for premature end of treatment *	Disease progression (lack of clinical benefit)	3 (50.0)	15 (71.4)	15 (78.9)
	Undue toxicity	1 (16.7)	4 (19.0)	4 (21.1)
	Withdrawal of informed consent (patients decision)	1 (16.7)	1 (4.8)	0
	Adverse event other than undue toxicity	1 (16.7)	1 (4.8)	0
	Other reason(s)	3 (50.0)	3 (14.3)	1 (5.3)
Other reasons include progression of disease, patient prefers early end of therapy and physician decision.				
Status at the End of the Study	Defined end of study at week 26 is reached	3 (33.3)	21 (50.0)	21 (52.5)
	Death	1 (11.1)	2 (4.8)	2 (5.0)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	2 (22.2)	2 (4.8)	2 (5.0)
	90 days safety follow-up is reached after premature EOT due to toxicity or progression	1 (11.1)	2 (4.8)	2 (5.0)
	90 days safety follow-up is reached after premature EOT due to progression	0	9 (21.4)	9 (22.5)
	Week 26 after premature EOT due to reason other than progression is reached	0	1 (2.4)	1 (2.5)
	Premature study termination (and no safety follow-up was performed)	2 (22.2)	5 (11.9)	3 (7.5)
Reason(s) for premature study termination*	Undue toxicity	0	2 (40.0)	2 (66.7)
	Adverse event other than undue toxicity	1 (50.0)	1 (20.0)	0
	Protocol violation	1 (50.0)	1 (20.0)	0
	Other Reason(s)	1 (50.0)	2 (40.0)	1 (33.3)
Other reasons include physician decision due to SAE and tumor progression.				

* Documentation of multiple reasons were possible.

Demographics FAS:

	All Patients	Male	Female
Sex, n (%)			
Male	28 (66.7)	28 (100)	0
Female	14 (33.3)	0	14 (100)
Age continuous (years), Mean (SD)	58.2 (10.17)	56.8 (9.78)	61.0 (10.70)
BMI (kg/m²), Mean (SD)*	26.8 (5.08)	27.6 (4.34)	25.3 (6.14)
Height (cm), Mean (SD)*	173.9 (8.76)	177.7 (7.33)	166.4 (6.08)
Weight (kg), Mean (SD)*	81.3 (17.67)	87.3 (14.76)	69.9 (17.65)
Age categorical (years), n (%)			
18-44	3 (7.1)	2 (7.1)	1 (7.1)
45-64	25 (59.5)	19 (67.9)	6 (42.9)
≥65	14 (33.3)	7 (25.0)	7 (50.0)
Ethnic Group, n(%)			
Caucasian/white	42 (100)	28 (100)	14 (100)

* For one patient neither weight nor height was documented.

Demographics Safety Population Phase I:

	All Patients	Male	Female
Sex, n (%)			
Male	7 (77.8)	7 (100)	0
Female	2 (22.2)	0	2 (100)
Age continuous (years), Mean (SD)	62.4 (8.75)	60.6 (9.13)	69.0 (1.41)
BMI (kg/m²), Mean (SD)	29.5 (6.24)	30.7 (6.12)	25.5 (6.72)
Height (cm), Mean (SD)	178.2 (7.36)	181.0 (5.57)	168.5 (2.12)
Weight (kg), Mean (SD)	94.2 (22.53)	100.5 (20.48)	72.2 (17.25)
Age categorical (years), n (%)			
45-64	4 (44.4)	4 (57.1)	0
≥65	5 (55.6)	3 (42.9)	2 (100)
Ethnic Group, n(%)			
Caucasian/white	9 (100)	7 (100)	2 (100)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The objective of Phase IIa part is the determination of efficacy of Atezolizumab in conjunction with radiotherapy for patients with newly diagnosed MGMT-non-hypermethylated glioblastoma.

Primary endpoint for phase IIa and secondary endpoint for phase I is the PFS-6 rate (corresponds to response rate), defined as the proportion of patients free of progression at 6 months after study entry. The tested null hypothesis (for phase IIa) is $H_0: p_0 = 23.1\%$.

Secondary endpoints for phase IIa include progression-free survival (PFS) and overall survival (OS).

Primary (Phase IIa)/secondary (Phase I) endpoint: PFS-6:

In the following 4 tables response-status and RANO-assessment are shown together with the best available source of information for the Full Analysis Set (FAS), the Efficacy Evaluable Set (EES), the Regular Efficacy Evaluable Set (REES) and the Safety

Population Phase I (SP P1). Please note, that for this trial, patients are assessed as responders if stable disease, partial response or complete response is present after 6 months.

FAS (N=42)	**All Patients**	**Central RANO Assess-ment**	**Local RANO Assess-ment**	**No progression, but different anti-cancer therapy received**	**No information available**
Response Status					
Missing	2	0	0	0	2
Yes	9 (22.5)	9 (28.1)	0	0	0
No	31 (77.5)	24 (72.7)	6 (100)	1 (100)	0
Response-Assessment					
Missing	2	0	0	0	2
Partial Response (PR)	1 (2.5)	1 (3.1)	0	0	0
Stable Disease (SD)	8 (20.0)	8 (25.0)	0	0	0
Progressive Disease (PD)	31 (77.5)	24 (72.7)	6 (100)	1 (100)	0

EES (N=40)	**All Patients**	**Central RANO Assessment**	**Local RANO Assessment**	**No progression, but different anti-cancer therapy received**
Response-Status				
Yes	9 (22.5)	9 (27.3)	0	0
No	31 (77.5)	24 (72.7)	6 (100)	1 (100)
Response-Assessment				
Partial Response (PR)	1 (2.5)	1 (3.0)	0	0
Stable Disease (SD)	8 (20.0)	8 (24.2)	0	0
Progressive Disease (PD)	31 (77.5)	24 (72.7)	6 (100)	1 (100)

REES (N=31)	All Patients	Central RANO Assessment	Local RANO Assessment**
Response-Status			
Yes	8 (25.8)	8 (26.7)	0
No	23 (74.2)	22 (73.3)	1 (100)
RANO-Assessment			
Stable Disease (SD)	8 (25.8)	8 (27.6)	0
Progressive Disease (PD)	23 (74.2)	22 (73.3)	1 (100)

SP P1 (N=9)	All Patients	Central RANO Assessment	No information available
Response Status			
Missing	2	0	2
Yes	1 (14.3)	1 (14.3)	0
No	6 (85.7)	6 (85.7)	
RANO-Assessment			
Missing	2	0	2
Stable Disease (SD)	1 (14.3)	1 (14.3)	0
Progressive Disease (PD)	6 (85.7)	6 (85.7)	0

For the primary analysis the FAS is used. Overall, 21.4% (9/42) of these patients were assessed as responders (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [10.3%, 36.8%]). All of them were confirmed by central RANO assessment. Best available assessment was “partial response”. The corresponding p-value of the one-sided binomial test is $p = 0.660$. CI and p-value using only patients with non-missing response-status match with the results for the EES below.

As a sensitivity analysis, the same calculations were performed on the EES and REES. In the EES 22.5% (9/40) of these patients were assessed as responders (95%-Clopper-Pearson CI: [10.84%, 38.45%]). The corresponding p-value of the one-sided binomial test is $p = 0.5970$. In the REES 25.81% (8/31) patients were assessed as responders (95%-Clopper-Pearson CI: [11.86%, 44.61%]). The corresponding p-value of the one-sided binomial test is $p = 0.4278$.

As secondary endpoint for Phase I, PFS-6 is analyzed using SP P1. 11.1% (1/9) of these patients were assessed as responder (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [0. 28%, 48.25%]) and confirmed by central RANO assessment. The corresponding p-value of the one-sided binomial test is $p = 0.9060$. Results using only patients with non-missing response-status are as follows: 14.29% (1/7) patients were assessed as responders (95%-Clopper-Pearson CI: [0.36%, 57.87%]). The p-value of the one-sided binomial test is $p = 0.8410$.

Secondary endpoint: PFS

The secondary endpoint PFS is analyzed using the FAS and EES. The number of patients with an event relevant for PFS is 31. Median progression-free survival is 4.2 months for FAS and EES. For more information see the following table:

	FAS	EES
Number of Patients (%)	42 (100)	40 (100)
Number of Patients with the Event (%)	31 (73.8)	31 (77.5)
25 Percent Point Estimate* (95% CI)	2.6 (2.6, 3.0)	2.6 (2.6, 3.0)
Median* (95% CI)	4.2 (2.8, 5.8)	4.2 (2.8, 5.8)
75 Percent Point Estimate* (95% CI)	6.0 (5.8, 7.7)	6.0 (5.8, 7.7)
6-month event free rate** (95% CI)	0.188 (0.065, 0.359)	0.188 (0.065, 0.359)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAS and EES. The number of patients with the event until database lock is 30 (FAS, 71.4%) and 29 (EES, 72.5%). Median overall survival is 11.7 months (FAS) and 11.7 months (EES). For more information see the following table:

	FAS	EES
Number of Patients (%)	42 (100)	40 (100)
Number of Patient with the Event (%)	30 (71.4)	29 (72.5)
25 Percent Point Estimate* (95% CI)	10.2 (8.2, 11.0)	10.2 (8.2, 10.8)
Median* (95% CI)	11.7 (10.4, 14.1)	11.7 (10.4, 12.8)
75 Percent Point Estimate* (95% CI)	14.7 (12.7, 23.4)	18.2 (12.5, 23.4)
6-month event free rate** (95% CI)	0.951 (0.819, 0.988)	0.950 (0.815, 0.987)
9-month event free rate** (95% CI)	0.823 (0.663, 0.911)	0.818 (0.655, 0.909)
12-month event free rate** (95% CI)	0.452 (0.279, 0.610)	0.435 (0.262, 0.596)
18-month event free rate** (95% CI)	0.249 (0.114, 0.409)	0.260 (0.121, 0.424)
24-month event free rate** (95% CI)	0.050 (0.004, 0.199)	0.052 (0.004, 0.206)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

SAFETY RESULTS:

For the Full Analysis Set the total drug exposure for all patients was 5143 days.

41/42 patients experienced at least one (all causality) AE (total number of AEs=256) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Nervous system disorders” and “Investigations”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. 34 (81.0%) patients experienced at least one treatment related AE (total number of treatment-related AEs=108). The most frequent treatment related AEs in terms of system organ class were “Nervous System Disorders” and “General disorders and administration site conditions”. 16

SAEs occurred in overall 13 (31.0%) patients. Most of these SAEs were reported in the system organ classes “General disorders and administration site conditions”, “Hepatobiliary disorders”, “Infections and infestations” and “Nervous system disorder”. 9 RLTs in 8 patients and 2 DLTs in 2 patients were reported.

For the Safety Population Phase I the total drug exposure for all patients was 847 days.

All patients experienced at least one (all causality) AE (total number of AEs=70) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Nervous system disorders”. 7 SAEs occurred in 5 (55.6%) patients.

2 DLTs in 2 patients were reported. No RLTs were observed.

For detailed information see the following table:

	FAS **N (%)**	**SP P1** **N (%)**
Overview all AEs		
Any AE	41 (97.6)	9 (100)
Any SAE	13 (31.0)	5 (55.6)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	19 (45.2)	6 (66.7)
Any DLT	2 (4.8)	2 (22.2)
Any RLT	8 (19.0)	0
Patients discontinued study drug due to AEs	8 (19.0)	3 (33.1)
Patients with dose of study drug reduced or temporary discontinuation due to AE	9 (21.4)	2 (22.2)
Patients with AE resulting in death	1 (2.4)	0
Overview related AEs		
Any AE	34 (81.0)	8 (88.9)
Any SAE	9 (21.4)	3 (33.3)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	10 (23.8)	2 (22.2)
Any DLT	2 (4.8)	2 (22.2)
Any RLT	8 (19.0)	0
Patients discontinued study drug due to AEs	7 (16.7)	3 (33.3)
Patients with dose of study drug reduced or temporary discontinuation due to AE	5 (11.9)	1 (11.1)
Patients with AE resulting in death	0	0
AEs by System Organ Class (MedDRA 23.0), all causalities*		
Blood and lymphatic system disorders	11 (26.2)	2 (22.2)
Cardiac disorders	2 (4.8)	0
Ear and labyrinth disorders	2 (4.8)	0
Endocrine disorders	2 (4.8)	0
Eye disorders	5 (11.9)	1 (11.1)

	FAS N (%)	SP P1 N (%)
Gastrointestinal disorders	15 (35.7)	3 (33.3)
General disorders and administration site conditions	24 (57.1)	7 (77.8)
Hepatobiliary disorders	4 (9.5)	1 (11.1)
Infections and infestations	15 (35.7)	5 (55.6)
Injury, poisoning and procedural complications	5 (11.9)	1 (11.1)
Investigations	16 (38.1)	5 (55.6)
Metabolism and nutrition disorders	9 (21.4)	5 (55.6)
Musculoskeletal and connective tissue disorders	10 (23.8)	2 (22.2)
Nervous system disorders	23 (54.8)	6 (66.7)
Psychiatric disorders	4 (9.5)	1 (11.1)
Renal and urinary disorders	2 (4.8)	0
Reproductive system and breast disorders	1 (2.4)	0
Respiratory, thoracic and mediastinal disorders	2 (4.8)	0
Skin and subcutaneous tissue disorders	18 (42.9)	4 (44.4)
Surgical and medical procedures	1 (2.4)	0
Vascular disorders	3 (7.1)	1 (11.1)
SAEs by System Organ Class (MedDRA 23.0), all causalities*		
Blood and lymphatic system disorders	1 (2.4)	1 (11.1)
General disorders and administration site conditions	3 (7.1)	1 (11.1)
Hepatobiliary disorders	3 (7.1)	1 (11.1)
Infections and infestations	3 (7.1)	2 (22.2)
Injury, poisoning and procedural complications	1 (2.4)	0
Investigations	1 (2.4)	1 (11.1)
Nervous system disorders	3 (7.1)	1 (11.1)
Psychiatric disorders	1 (2.4)	0
SAEs by System Organ Class (MedDRA 23.0), related*		
General disorders and administration site conditions	2 (4.8)	1 (11.1)
Hepatobiliary disorders	3 (7.1)	1 (11.1)
Investigations	1 (2.4)	1 (11.1)
Nervous system disorders	2 (4.8)	0
Psychiatric disorders	1 (2.4)	0
DLTs by System Organ Class (MedDRA 23.0)*		
Hepatobiliary disorders	1 (2.4)	1 (11.1)
Investigations	1 (2.4)	1 (11.1)
RLTs by System Organ Class (MedDRA 23.0)*		

	FAS N (%)	SP P1 N (%)
Blood and lymphatic system disorders	1 (2.4)	0
Hepatobiliary disorders	3 (7.1)	0
Investigations	2 (4.8)	0
Nervous system disorders	1 (2.4)	0
Psychiatric disorders	1 (2.4)	0

* The displayed number shows the amount of patients with one or more events in the specific system organ class. Each patient is counted only once per system organ class.

Other Safety Data

In the following presentation of other safety data only tests and examinations that were performed on or after date of first treatment of the respective patient are included.

For the Full Analysis Set where all treated patients are included, Karnofsky Index (KPI) ranged from 40 to 100, mean KPI over all visits and patients was 88.4. Vital signs were unremarkable. Most recorded clinical laboratory values (>98%) were within normal ranges or not clinically significant. Most clinically significant values occurred for parameters lymphocytes, total bilirubin, direct bilirubin and ALT. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameters leukocyte esterase, urobilinogen, nitrite and blood. Most ECG results (>96%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 47 bpm to 111 bpm, mean: 67.6 bpm), PQ interval (range: 134 msec to 244 msec, mean: 180.9 msec), QRS interval (range: 43 msec to 104 msec, mean: 88.4 msec), QT interval (range: 328 msec to 434 msec, mean: 397.1 msec) and QTcF interval (range: 394 msec to 425 msec, mean: 413.0 msec).

CONCLUSION:

The data from Subtrial D (Atezolizumab) of the N^2M^2 trial does not show significant efficacy for the primary endpoint (overall 21.4% patients without progression after 6 months with H_0: p_0=23.1%). The corresponding p-value is $p = 0.660$.

For the primary safety endpoint of phase I concerning DLTs, in 22.2% (2/9) of the patients DLTs were observed (95% two-sided Clopper-Pearson CI: [0.028, 0.600]).

Overall 23.8% (10/42) patients experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.121, 0.395]) thus the DLT/RLT rate is below the unacceptable rate of 30%, but tolerability cannot be confirmed with a confidence of 95% according to the confidence interval.

Substantial amendments / interruptions:

Substantial amendments: substantial amendments of the umbrella trial are listed

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Updated Informed Consent Forms (ICF) due to EU GDPR and updated IBs and SmPCs	25.05.2018
02	Change of deputy at site 13	13.07.2018
03	Change of deputy site 06, 07, 09, 10 change of investigator at site 07	21.01.2019, 28.01.2019, 29.01.2019, 06.03.2019
04	Change of deputy at site 12	28.10.2019

Amendment No.	Content	Approval Date
05	Protocol amendment (v1.4), updated IBs, ICF	29.12.2019
06	Protocol amendment (v1.5), updated IBs, ICF, new site Leipzig (no. 14), change of deputy at site 08 and 02	12.11.2020, 19.11.2020, 04.12.2020, 28.01.2021
07	Protocol amendment (v2.0), updated IBs, ICF	12.01.2021
08	New deputy at site 03, change of address at site 11	25.03.2021, 08.04.2021
09	Protocol amendment (v3.0), updated IBs, ICF	03.08.2021
10	Protocol amendment (v4.0), updated IBs, ICF	08.10.2021
11	New deputy at site 13	17.03.2022
12	Protocol amendment (v5.0), updated IBs, ICF	18.05.2022
13	New deputy at site 06	03.06.2022
14	Change of investigator and deputy at site 04	07.10.2022

Paul Ehrlich Institute (PEI)

Amendment No.	Content	Approval Date
01	Change requests from ec from initial submission, IMPD Atezolizumab, updated IBs and SmPCs	10.04.2018
02	IMPD Alectinib and Idasanutlin	29.06.2019
03	Protocol amendment (v1.4), updated IBs, manufacturing documents Vismodegib	20.12.2019
04	Protocol amendment (v1.5), updated IBs, labels Idasanutlin	25.11.2020
05	Protocol amendment (v2.0), updated IB Idasanutlin, IMPD APG101	06.01.2021
06	Protocol amendment (v3.0), updated IBs	05.08.2021
07	Protocol amendment (v4.0), updated SmPCs	06.10.2021
08	Protocol amendment (v5.0), updated IBs, ICF	13.05.2022

Interruptions:

There was no interruption.

Date of the report:

February 2nd 2024

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum Universitätsklinikum Heidelberg Thoraxklinik-Heidelberg Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N^2M^2 (NOA-20)

Subtrial Protocol F

Palbociclib plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma and activity of the CDK4 or CDK6 and CDKN2A/B co-deletion

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) of the N^2M^2 project. This report covers the results of subtrial F (Palbociclib). Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N^2M^2

Final Sub-Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1.1, September 21st 2023
Investigational Product:	CDK4 / CDK6 palbociclib
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 5.0 April 5th 2022 / N2M2 Subtrial F: CDK4 / CDK6 palbociclib, 2.1, April 5th 2022

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Subtrial F (Palbociclib): Initiation and Completion Dates:
First Patient in: May 18th 2018
Last Patient in: March 14th 2022
Last Patient Last Visit: September 26th 2022
Data base lock: August 7th 2023

Signatures

The present sub-study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	Heidelberg, 21/9/23 Place, Date
Biostatistician	Lanz Lisa-Marie Lanz, M.Sc.	Weinheim, 05/10/23 Place, Date

List of abbreviations:

AE	Adverse Event
ALT	Alanine transaminase
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
DLT	Dose-limiting toxicity
ECG	Electrocardiography
EES	Efficacy Evaluable Set
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-glutamyltransferase
KPI	Kanrofsky Performance Index
MGMT	O-6-methylguanine-DNA methyltransferase
MTD	Maximum tolerated dose
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Response
RANO	Response assessment in neuro-oncology criteria
REES	Regular Efficacy Evaluable Set
RLT	Regime-limiting toxicity
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation
SOC	Standard of Care
SP P1	Safety Population Phase I

Synopsis

Name of Sponsor/Company: Heidelberg University Hospital Im Neuenheimer Feld 672 69120 Heidelberg, Germany
Name of Finished Product: Palbociclib (IBRANCE®)
Name of Active Ingredient: Palbociclib
Title of Study: Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20) Subtrial Protocol F: Palbociclib plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma and activity of the CDK4 or CDK6 and CDKN2A/B co-deletion **Short Title/ Acronym:** N^2M^2 – Subtrial F (Palbociclib) **Protocol versions:** Umbrella protocol: Final 1.3, February 8th 2018 (First Authorization) Final 1.4, October 23rd 2019 (Substantial Amendment) Final 1.5, October 21st 2020 (Substantial Amendment) Final 2.0, December 10th 2020 (Substantial Amendment) Final 3.0, July 6th 2021 (Substantial Amendment) Final 4.0 September 10th 2021 (Substantial Amendment) Final 5.0 April 5th 2022 (Substantial Amendment) Subtrial F (Palbociclib) protocol: Final 1.3, February 8th 2018 (First Authorization) Final 1.4, October 23rd 2019 (Substantial Amendment) Final 1.5, October 21st 2020 (Substantial Amendment) Final 2.0, September 10th 2021 (Substantial Amendment) Final 2.1, April 5th 2022 (Substantial Amendment)
Clinical trial sites and Principle Investigators of umbrella trial: 01 Prof. Wolfgang Wick/CI Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg 02 Prof. Dr. med. Dietmar Krex Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden 03 Prof. Dr. Peter Vajkoczy

	Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin
04	Prof. Dr. med. Uwe Schlegel Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum
05	Prof. Dr. med. Ulrich Herrlinger Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn
06	Prof. Dr. med. Martin Glas Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen
07	PD Dr. med. Michael Burger Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt
08	Prof. Dr. Roland Goldbrunner Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln
09	Prof. Dr. med. Florian Ringel Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz
10	Prof. Dr. Michael Platten Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
11	Prof. Dr. med. Peter Hau Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg
12	Prof. Dr. med. Ralf Ketter, Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg
13	Prof. Dr. med. Ghazaleh Tabatabai, Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen

All sites treated patients in subtrial F (Palbociclib).

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N^2M^2)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N^2M^2) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2*. Journal of Clinical

Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090
- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N^2M^2 (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years) for subtrial F (Palbociclib):	**Phase of development**:
Date of first enrollment: May 18th 2018 Date of last enrollment: March 14th 2022 Date of last completed: September 26th 2022	I/IIa

Objectives:

Phase I:

The *primary Objective* of the phase I part of the trial was the determination of safety and tolerability of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial.
- Progression-free survival at six months (PFS-6) according to RANO criteria (Wen et al. 2010; Okada et al. 2015)

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N^2M^2 subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.
  As stated in the protocol, this objective is not analyzed in this final trial report, but will be addressed in future manuscripts.

Methodology:

The trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N^2M^2 project. The phase I part of the subtrial shall determine the MTD for the combination therapy Palbociclib + RT with an accelerated rule based design. Patients treated at the final dose of phase I, can also be evaluated in the phase IIa part of the trial.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily

- Palbociclib: Daily weeks 1-3, 5-7, 12-14, 16-18, 20-22, 24-26
- AEs: Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- Concomitant Medication: Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- DLTs (only phase I): Week 1 – 6
- RLTs (phase I): Week 7 – 26
- RLTs (phase IIa): Week 1 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab (chemistry), Karnofsky Performance Index (KPI)): Screening, Attribution, Weeks 4, 8, 12, 16, 20, 24
- Examinations (safety lab (hematology)): Screening, Attribution, Week 1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- EOS: Week 26

Number of patients (planned and analyzed in subtrial F):

Number of patients planned: ≤52 (40 of them planned to be analyzed for phase IIa)

Number of patients analyzed: 48

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials)
- CDK4 / CDK6 amplification or CDKN2A co-deletion (20%) (suitable for subtrial F)

Investigational product, dose and mode of administration, batch number:

Drug Code: ATC-Code: L01EF01

Pharmaceutical formulation: Hard Capsules (study start until Sept. 2021) and Smooth-coated tablet (from Oct. 2021 onwards)

Route of administration: oral

Storage conditions: <30°C

Manufacturer/Importer: Pfizer Pharma GmbH, Berlin

Marketing Authorization number:
Hard capsules: 75 mg: EU/1/16/1147/001, EU/1/16/1147/002; 100 mg: EU/1/16/1147/003, EU/1/16/1147/004; 125 mg: EU/1/16/1147/005, EU/1/16/1147/006
Smooth-coated tablet: 75 mg: EU/1/16/1147/010, EU/1/16/1147/011, EU/1/16/1147/016; 100 mg: EU/1/16/1147/012, EU/1/16/1147/013, EU/1/16/1147/017; 125 mg: EU/1/16/1147/014, EU/1/16/1147/015, EU/1/16/1147/018

Dose: Three dose levels were available for examination (all dose levels were administered at least once): D0 (75mg), D1 (100mg), D2 (125mg)

Batch numbers:

AD9471, AK6760, AK6763, AL6587, AL6600, AL6834, AP0670, AT3017, CD0873, CD7594, CF8486, CM3686, CM6848, CM9130, CN3686, CN3970, CY2037, CY3391, CY6848, CY7633, CY7669, DC7179, DJ6208, DJ7669, DK4064, DK4962, DN0350, DP8803, FF7981, FF8003, FH8748A, FK8574, FL4675, FM6851, FN2016, FN2916, FN2961, FR8463, FR8475, VO8967A, W13645A, W42744A, W57615, X28186, X29142, X70744, X84883

Reference therapy, dose and mode of administration, batch number:
Not applicable.

Duration of treatment:
Up to 6 months.

Criteria for evaluation:

Phase I:

Safety:

The *primary safety endpoint* was the determination of posterior probability of Dose Limiting Toxicity (DLT), defined as all adverse events (AEs) coded using Medical Dictionary for Regulatory Activities (MedDRA) ≥ Grade 3 according to the National Cancer Institute Common Terminology Criteria for AE (CTCAE) v5.0 that are definitely, probably or possibly related to the administration of Palbociclib in combination with RT.

Secondary safety endpoint:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I or during phase IIa of the trial for patients recruited for phase I.

Efficacy:

The *secondary efficacy endpoint* was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. See also the primary efficacy endpoint for phase IIa for more information.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without an event relevant for PFS (progression or death) at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events
- Karnofsky Index (KPI)

- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory Parameters (hematology, chemistry, urinalysis), ECG

Statistical methods:

Statistical analysis:

Subtrial F (Palbociclib) of the Umbrella-trial N²M² passed the first and second interim analysis and recruited to the final analysis.

Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results may be presented in the umbrella report.

Phase I

Analysis of the safety endpoints:

- For the primary safety endpoint (DLTs), the different examined dose-levels are presented, together with the amount and type (Preferred Term (PT) and System Organ Class level) of DLTs, patients experienced at these dose levels. Summary tables present the number of patients observed with a DLT and the corresponding percentage. Exact 95% two-sided Clopper-Pearson CIs are presented. Starting dose was 75 mg.
- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CIs are presented. All patients who completed the combined treatment phase are included.

Analysis of the efficacy endpoint:

Progression-free survival at six months (PFS-6) according to RANO criteria as a binary endpoint is analyzed. Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing.

Phase IIa

Analysis of the efficacy endpoints:

- The primary efficacy endpoint PFS-6 according to RANO criteria as a binary endpoint is analyzed with a one-sample one-sided Binomial test of the null hypothesis $H_0: p = 0.231$ Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing, but for the calculation of the p-value those patients are assumed to be non-responders. α-level for the primary analysis is 10%.
  Response assessment is determined by combining information from the clinical trial site (local RANO Assessment, a status page in the eCRF showing the information if the patient experienced progression during the 6 months after study entry and survival follow-up in case of premature EOS) and central RANO assessment performed by central neuroradiology in Heidelberg. If the clinical trial site stated a progression on the status page, the patient is assumed to be a non-responder, irrespective of other information. Central RANO assessment is the preferred type of assessment, but if not available (or differing to a stated progression on the status page) other sources of information are used to determine the response status/assessment.

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first) minus 1 day. Patients without an event relevant for PFS* at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

* Please note, that patients with a death event in the survival follow-up (without a preceding progression event) are only considered as having an event relevant for PFS, if regular information on disease assessment for that patient is available. Otherwise the patient is censored at the last date of disease assessment.

Analysis of the (secondary) safety endpoints:

- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs and the corresponding percentages. Exact 95% two-sided Clopper-Pearson CI are presented.
- Adverse Events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages.
- Karnofsky Index (KPI) is summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages).
- Vital Signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening), respiratory rate) are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented. This includes changes (differences) from the baseline assessment, except for body height.
- Clinical laboratory parameters (hematology, chemistry, urinalysis) and ECG are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented (for ECG: only for abnormal results). The number of patients with laboratory values that are below, within or above normal ranges are tabulated for each parameter. Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and of changes from baseline are presented for each parameter. The number and percentage of patients with normal and abnormal ECG results at baseline and follow-up are tabulated. ECG findings are tabulated by patient.

Sub-Study populations

A total of 50 patients were included in 13 clinical trial sites. 48 patients were treated. 13 of these patients were treated in phase I and are thus part of the Safety Population Phase I (SP P1), one patient received 75 mg (D0), 6 patients received 125 mg (D2) and the remaining 6 patients were treated at the final dose of phase I (100 mg, D1) and are thus also evaluable for phase IIa. Overall 41 patients received the final dose of phase I and thus part of the Full Analysis Set (FAS) and 40 patients are available for the primary endpoint analysis (and are thus part of the Efficacy Evaluable Set (EES)). A total of 32 patients were treated at the final dose of phase I, had regular EOT (i.e. the patient had maximum treatment

duration or premature EOT due to progression or death) and a central RANO assessment for PFS-6 is available (or the patient terminated treatment/study early due to death) and thus fulfill the criteria to be part of the Regular Efficacy Evaluable Set (REES). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		Palbociclib SP P1 N (%)	Palbociclib FAS N (%)	Palbociclib EES N (%)
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	6 (46.2)	22 (53.7)	22 (55.0)
	(Premature) end of treatment reached prior to week 26	7 (53.8)	19 (46.3)	18 (45.0)
Reason(s) for premature end of treatment *	Disease progression (lack of clinical benefit)	3 (42.9)	14 (73.7)	14 (77.8)
	Undue toxicity	3 (42.9)	1 (5.3)	0
	Death	0	2 (5.3)	2 (11.1)
	Withdrawal of informed consent (patients decision)	1 (14.3)	1 (5.3)	1 (5.6)
	Adverse event other than undue toxicity	0	2 (10.5)	2 (11.1)
	Investigator's opinion	0	1 (5.3)	1 (5.6)
	Other reason(s)	0	1 (5.3)	1 (5.6)
Other reasons include deterioration in general condition.				
Status at the End of the Study	Defined end of study at week 26 is reached	6 (46.2)	22 (53.7)	22 (55.0)
	Death	0	3 (7.3)	3 (7.5)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	4 (30.8)	3 (7.3)	3 (7.5)
	30 days safety follow-up is reached after premature EOT due to progression	0	6 (14.6)	6 (15.0)
	Week 26 after premature EOT due to reason other than progression is reached	0	1 (2.4)	1 (2.5)
	Premature study termination (and no safety follow-up was performed)	3 (23.1)	6 (14.6)	5 (12.5)
Reason(s) for premature study termination*	Undue toxicity	1 (33.3)	1 (16.7)	1 (20.0)
	Withdrawal of informed consent	1 (33.3)	1 (16.7)	0
	Other Reason(s)	1 (33.3)	4 (66.7)	4 (80.0)
Other reasons include disease progression and deterioration in general condition.				

* Documentation of multiple reasons were possible.

Demographics FAS:

	All Patients	Male	Female
Sex, n (%)			
Male	26 (63.4)	26 (100)	0
Female	15 (36.6)	0	15 (100)
Age continuous (years), Mean (SD)	58.0 (9.63)	57.8 (10.78)	58.2 (7.57)
BMI (kg/m²), Mean (SD)	25.8 (4.73)	27.2 (4.46)	23.3 (4.19)
Height (cm), Mean (SD)	172.9 (9.12)	177.8 (5.83)	164.4 (7.44)
Weight (kg), Mean (SD)	77.7 (18.30)	86.2 (15.33)	63.1 (13.21)
Age categorical (years), n (%)			
18-44	4 (9.8)	4 (15.4)	0
45-64	27 (65.9)	14 (53.8)	13 (86.7)
≥65	10 (24.4)	8 (30.8)	2 (13.3)
Ethnic Group, n(%)			
Caucasian/white	41 (100)	26 (100)	15 (100)

Demographics Safety Population Phase I:

	All Patients	Male	Female
Sex, n (%)			
Male	7 (53.8)	7 (100)	0
Female	6 (46.2)	0	6 (100)
	All Patients	**Male**	**Female**
Age continuous (years), Mean (SD)	59.7 (11.09)	58.4 (13.43)	61.2 (8.59)
BMI (kg/m²), Mean (SD)	26.8 (2.93)	26.5 (3.43)	27.1 (2.50)
Height (cm), Mean (SD)	173.3 (7.19)	177.6 (4.61)	168.3 (6.59)
Weight (kg), Mean (SD)	80.4 (9.93)	83.7 (11.32)	76.6 (7.16)
Age categorical (years), n (%)			
18-44	1 (7.7)	1 (14.3)	0
45-64	8 (61.5)	4 (57.1)	4 (66.7)
≥65	4 (30.8)	2 (28.6)	2 (33.3)
Ethnic Group, n(%)			
Caucasian/white	13 (100)	7 (100)	6 (100)

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The objective of Phase IIa part is the determination of efficacy of Palbociclib in conjunction with radiotherapy for patients with newly diagnosed MGMT-non-hypermethylated glioblastoma.

Primary endpoint for phase IIa and secondary endpoint for phase I is the PFS-6 rate (corresponds to response rate), defined as the proportion of patients free of progression at 6 months after study entry. The tested null hypothesis (for phase IIa) is $H_0: p_0 = 23.1\%$.

Secondary endpoints for phase IIa include progression-free survival (PFS) and overall survival (OS).

Primary (Phase IIa)/secondary (Phase I) endpoint: PFS-6:
In the following 4 tables response-status and RANO-assessment are shown together with the best available source of information for the Full Analysis Set (FAS), the Efficacy Evaluable Set (EES), the Regular Efficacy Evaluable Set (REES) and the Safety Population Phase I (SP P1):

FAS (N=41)	**All Patients**	**Central RANO Assess-ment**	**Local RANO Assess-ment**	**Progress-ion according to trial site, not diagnosed with MRI**	**Termina-ted early due to death**	**No infor-ma-tion avail-able**
Response-Status*						
Missing	1	0	0	0	0	1
Yes	10 (25.0)	9 (29.0)	1 (14.3)	0	0	0
No	30 (75.0)	22 (71.0)	6 (85.7)	1 (100)	1 (100)	0
Response-Assessment						
Missing	1	0	0	0	0	1
Stable Disease (SD)	10 (25.0)	9 (29.0)	1 (14.3)	0	0	0
Progressive Disease (PD)	29 (72.5)	22 (71.0)	6 (85.7)	1 (100)	0	0
Death	1 (2.5)	0	0	0	1 (100)	0

EES (N=40)	**All Patients**	**Central RANO Assess-ment**	**Local RANO Assess-ment**	**Progression according to trial site, not diagnosed with MRI**	**Terminated early due to death**
Response-Status*					
Yes	10 (25.0)	9 (29.0)	1 (14.3)	0	0
No	30 (75.0)	22 (71.0)	6 (85.7)	1 (100)	1 (100)
Response-Assessment					
Stable Disease (SD)	10 (25.0)	9 (29.0)	1 (14.3)	0	0
Progressive Disease (PD)	29 (72.5)	22 (71.0)	6 (85.7)	1 (100)	0
Death	1 (2.5)	0	0	0	1 (100)

REES (N=32)	**All Patients**	**Central RANO Assessment**	**Local RANO Assessment****	**Terminated early due to death**
Response-Status*				

Yes	8 (25.0)	8 (27.6)	0	0
No	24 (75.0)	21 (72.4)	2 (100)	1 (100)
REES (N=32)	**All Patients**	**Central RANO Assessment**	**Local RANO Assessment****	**Terminated early due to death**
RANO-Assessment				
Stable Disease (SD)	8 (25.0)	8 (27.6)	0	0
Progressive Disease (PD)	23 (71.9)	21 (72.4)	2 (100)	0
Death	1 (3.1)	0	0	1 (100)

SP P1 (N=13)	**All Patients**	**Local RANO Assess-ment**	**Central RANO Assess-ment**	**No Progression, but different anti-cancer therapy received**	**No information availabe**
Response-Status*					
Missing	2	0	0	0	2
Yes	4 (36.4)	0	4 (44.4)	0	0
No	7 (63.6)	1 (100.0)	5 (55.6)	1 (100)	0
Response-Assessment					
Missing	2	0	0	0	2
Stable Disease (SD)	4 (36.4)	0	4 (44.4)	0	0
Progressive Disease (PD)	7 (63.6)	1 (100.0)	5 (55.6)	1 (100)	0

*: Patients are assessed as responders if stable disease, partial response or complete response is present after 6 months
**: These patients, in addition to the locally assessed progression, terminated study early due to death

For the primary analysis the FAS is used. Overall, 24.4% (10/41) of these patients were assessed as responders (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [12.4%, 40.3%]). Nine of them were confirmed by central RANO assessment. Best available assessment was “stable disease”. The corresponding p-value of the one-sided binomial test is $p = 0.4823$. CI and p-value using only patients with non-missing response-status match with the results for the EES below.

As a sensitivity analysis, the same calculations were performed on the EES and REES. In the EES 25.0% (10/40) of these patients were assessed as responders (95%-Clopper-Pearson CI: [12.69%, 41.20%]). The corresponding p-value of the one-sided binomial test is $p = 0.4479$. In the REES 8/32 (25.0) patients were assessed as responders (95%-Clopper-Pearson CI: [11.46%, 43.40%]). The corresponding p-value of the one-sided binomial test is $p = 0.4668$.

As secondary endpoint for Phase I, PFS-6 is analyzed using SP P1. 30.8% (4/13) of these patients were assessed as responder (95%-Clopper-Pearson CI of all patients including patients with missing response-status: [9.10%, 61.43%]) and confirmed by central RANO assessment. The corresponding p-value of the one-sided binomial test is $p = 0.3522$. Results using only patients with non-missing response-status are as follows: 36.4% (4/11) patients were assessed as responders (95%-Clopper-Pearson CI: [10.93%, 69.21%]). The p-value of the one-sided binomial test is $p = 0.2359$.

Secondary endpoint: PFS
The secondary endpoint PFS is analyzed using the FAS and EES. The number of patients with an event relevant for PFS is 31. Median progression-free survival is 4.0 months for FAS and EES. For more information see the following table:

	FAS	**EES**
Number of Patients (%)	41 (100)	40 (100)
Number of Patients with the Event (%)	31 (75.6)	31 (77.5)
25 Percent Point Estimate* (95% CI)	2.6 (2.6, 2.9)	2.6 (2.6, 2.9)
Median* (95% CI)	4.0 (2.7, 6.0)	4.0 (2.7, 6.0)
75 Percent Point Estimate* (95% CI)	6.2 (5.8, 7.2)	6.2 (5.8, 7.2)
6-month event free rate** (95% CI)	0.368 (0.212, 0.524)	0.368 (0.212, 0.524)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAS and EES. The number of patients with the event until database lock is 34 (FAS, 82.9%) and 33 (EES, 82.5%). Median overall survival is 12.6 months (FAS) and 12.7 months (EES). For more information see the following table:

	FAS	**EES**
Number of Patients (%)	41 (100)	40
Number of Patient with the Event (%)	34 (82.9)	33 (82.5)
25 Percent Point Estimate* (95% CI)	9.6 (6.1, 11.1)	9.2 (6.1, 11.1)
Median* (95% CI)	12.6 (10.8, 14.2)	12.7 (10.8, 14.2)
75 Percent Point Estimate* (95% CI)	17.0 (13.9, 21.9)	17.0 (13.9, 21.9)
6-month event free rate** (95% CI)	0.902 (0.861, 0.962)	0.900 (0.755, 0.961)
9-month event free rate** (95% CI)	0.779 (0.618, 0.878)	0.773 (0.610, 0.875)
12-month event free rate** (95% CI)	0.551 (0.385, 0.689)	0.565 (0.396, 0.703)
18-month event free rate** (95% CI)	0.200 (0.084, 0.351)	0.205 (0.086, 0.359)
24-month event free rate** (95% CI)	0.067 (0.012, 0.190)	0.068 (0.012, 0.194)
30-month event free rate** (95% CI)	0.067 (0.012, 0.190)	0.068 (0.012, 0.194)
36-month event free rate** (95% CI)	0.033 (0.003, 0.144)	0.034 (0.003, 0.148)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

SAFETY RESULTS:

For the Full Analysis Set the total drug exposure for all patients was 6004 days.

All patients experienced at least one (all causality) AE (total number of AEs=328) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Nervous system disorders” and “General disorder and administration site conditions”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. 36 (87.8%) patients experienced at least one treatment related AE (total number of treatment-related AEs=106). The most frequent treatment related AEs in terms of system organ class were “Blood and lymphatic system disorders” and “Investigations”. 16 SAEs occurred in overall 9 (22.0%) patients. Most of these SAEs were reported in the system organ class “Infections and infestations”. 16 RLTs in 10 patients and 1 DLT were reported.

For the Safety Population Phase I the total drug exposure for all patients was 1630 days.

All 13 patients experienced at least one (all causality) AE (total number of AEs=99, total number of AEs for patients with dosage 75 mg=15, total number of AEs for patients with dosage 125 mg=36, total number of AEs for patients with MTD dosage 100 mg=48) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class for patients receiving a dose of 75 mg as well as for patients receiving 100 mg were “Nervous system disorders”. For patients receiving 125 mg the most frequent AEs in terms of system organ class were “Investigations”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. 12 (92.3%) patients experienced at least one treatment related AE (total number of treatment-related AEs=45, total number of treatment-related AEs for patients with dosage 75 mg: 4, total number of treatment-related AEs for patients with MTD dosage 100 mg: 18, total number of treatment-related AEs for patients with dosage 125 mg: 23). The most frequent treatment-related AEs in terms of system organ class for patients receiving 75 mg and 125 mg “Investigations”. For patients receiving 100 mg the most frequent treatment-related AEs in terms of system organ class were “Blood and lymphatic disorders”. 2 SAEs occurred in 2 (15.4%) patients receiving 125 mg.

5 RLTs and 4 DLTs were reported (none of them for patients receiving 75 mg, 1 DLT for a patient receiving 100 mg and 3 DLTs and 5 RLTs in patients receiving 125 mg).

For detailed information see the following table:

	FAS N (%)	**SP P1 All patients N (%)**	**SP P1 75 mg (D0) N (%)**	**SP P1 100 mg (D1) N (%)**	**SP P1 125 mg (D2) N (%)**
Overview all AEs					
Any AE	41 (100)	13 (100)	1 (100)	6 (100)	6 (100)
Any SAE	9 (22.0)	2 (15.4)	0	0	2 (33.3)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	18 (43.9)	9 (69.2)	1 (100)	2 (33.3)	6 (100)
Any DLT	1 (2.4)	4 (30.8)	0	1 (16.7)	3 (50.0)
Any RLT	10 (24.3)	5 (38.5)	0	0	5 (83.3)
Patients discontinued study drug due to AEs	3 (7.3)	3 (23.1)	0	1 (16.7)	2 (33.3)

	FAS N (%)	SP P1 All patients N (%)	SP P1 75 mg (D0) N (%)	SP P1 100 mg (D1) N (%)	SP P1 125 mg (D2) N (%)
Patients with dose of study drug reduced or temporary discontinuation due to AE	14 (34.1)	7 (53.8)	1 (100)	2 (33.3)	4 (66.7)
Patients with AE resulting in death	2 (4.9)	0	0	0	0
Overview related AEs					
Any AE	36 (87.8)	12 (92.3)	1 (100)	5 (83.3)	6 (100)
Any SAE	6 (14.6)	1 (7.7)	0	0	1 (16.7)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	11 (26.8)	6 (46.2)	0	1 (16.7)	5 (83.3)
Any DLT	1 (2.4)	4 (30.8)	0	1 (16.7)	3 (50.0)
Any RLT	10 (24.3)	5 (38.5)	0	0	5 (83.3)
Patients discontinued study drug due to AEs	2 (4.9)	3 (23.1)	0	1 (16.7)	2 (33.3)
Patients with dose of study drug reduced or temporary discontinuation due to AE	9 (22.0)	6 (46.2)	1 (100)	1 (16.7)	4 (66.7)
Patients with AE resulting in death	1 (2.4)	0	0	0	0
AEs by System Organ Class (MedDRA 23.0), all causalities*					
Blood and lymphatic system disorders	20 (48.8)	8 (61.5)	1 (100)	3 (50.0)	4 (66.7)
Cardiac disorders	2 (4.9)	0	0	0	0
Ear and labyrinth disorders	7 (17.1)	3 (23.1)	0	3 (50.0)	0
Endocrine disorders	1 (2.4)	0	0	0	0
Eye disorders	9 (22.0)	2 (15.4)	0	2 (33.3)	0
Gastrointestinal disorders	18 (43.9)	6 (46.2)	1 (100)	2 (33.3)	3 (50.0)
General disorders and administration site conditions	25 (61.0)	7 (53.8)	1 (100)	3 (50.0)	3 (50.0)
Immune system disorders	0	1 (7.7)	0	0	1 (16.7)
Infections and infestations	19 (46.3)	5 (38.5)	1 (100)	2 (33.3)	2 (33.3)
Injury, poisoning and procedural complications	9 (22.0)	1 (7.7)	0	1 (16.7)	0
Investigations	20 (48.8)	8 (61.5)	1 (100)	3 (50.0)	4 (66.7)
Metabolism and nutrition disorders	8 (19.5)	2 (15.4)	1 (100)	0	1 (16.7)
Musculoskeletal and connective tissue disorders	7 (17.1)	2 (15.4)	0	0	2 (33.3)
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	2 (4.9)	0	0	0	0
Nervous system disorders	29 (70.7)	9 (69.2)	1 (100)	5 (83.3)	3 (50.0)
Psychiatric disorders	9 (22.0)	2 (15.4)	0	2 (33.3)	0
Renal and urinary disorders	4 (9.8)	0	0	0	0

	FAS N (%)	SP P1 All patients N (%)	SP P1 75 mg (D0) N (%)	SP P1 100 mg (D1) N (%)	SP P1 125 mg (D2) N (%)
Respiratory, thoracic and mediastinal disorders	7 (17.1)	2 (15.4)	0	1 (16.7)	1 (16.7)
Skin and subcutaneous tissue disorders	25 (61.0)	8 (61.5)	1 (100)	4 (66.7)	3 (50.0)
Surgical and medical procedures	1 (2.4)	0	0	0	0
Vascular disorders	3 (7.3)	1 (7.7)	0	0	1 (16.7)
SAEs by System Organ Class (MedDRA 23.0), all causalities*					
Blood and lymphatic system disorders	2 (4.9)	0	0	0	0
Cardiac disorders	1 (2.4)	0	0	0	0
General disorders and administration site conditions	1 (3.8)	1 (7.7)	0	0	1 (16.7)
Infections and infestations	6 (14.6)	0	0	0	0
Neoplasm benign, malignant and unspecified (incl. cysts and polyps)	2 (4.9)	0	0	0	0
Nervous system disorders	1 (2.4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (4.9)	1 (7.7)	0	0	1 (16.7)
SAEs by System Organ Class (MedDRA 23.0), related*					
Blood and lymphatic system disorders	2 (4.9)	0	0	0	0
Infections and infestations	3 (7.3)	0	0	0	0
Nervous system disorders	1 (2.4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.4)	1 (7.7)	0	0	1 (16.7)
DLTs by System Organ Class (MedDRA 23.0)*					
Blood and lymphatic system disorders	1 (2.4)	4 (30.8)	0	1 (16.7)	3 (50.0)
RLTs by System Organ Class (MedDRA 23.0)*					
Blood and lymphatic system disorders	7 (14.6)	2 (15.4)	0	0	2 (33.3)
Infections and infestations	2 (4.2)	0	0	0	0
Investigations	4 (8.3)	2 (15.4)	0	0	2 (33.3)
Nervous system disorders	1 (2.1)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.1)	1 (7.7)	0	0	1 (16.7)

* The displayed number shows the amount of patients with one or more events in the specific system organ class. Each patient is counted only once per system organ class.

Other Safety Data

In the following presentation of other safety data only tests and examinations that were performed on or after date of first treatment of the respective patient are included.

For the Full Analysis Set, Karnofsky Index (KPI) ranged from 50 to 100, mean KPI over all visits and patients was 87.2. Vital signs were unremarkable. Most recorded clinical laboratory values (>98%) were within normal ranges or not clinically significant. Most clinically significant values occurred for parameters White Blood Cell Count, Lymphocytes, Neutrophils (abs) and Platelets. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameters Leukocyte esterase, Nitrite, Blood and Glucose. Most ECG results (>84%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 50 bpm to 142 bpm, mean: 75.0 bpm), PQ interval (range: 106 msec to 210 msec, mean: 162.9 msec), QRS interval (range: 39 msec to 184 msec, mean: 96.3 msec), QT interval (range: 284 msec to 486 msec, mean: 405.1 msec) and QTcF interval (range: 381 msec to 565 msec, mean: 438.2 msec).

For the Safety Population Phase I, karnofsky index ranged from 60 to 100, mean KPI over all visits and patients was 89.2. Vital signs were unremarkable. Most recorded clinical laboratory values (>98%) were within normal ranges or not clinically significant. Most clinically significant values occurred for parameters White Blood Cell Count, Neutrophils (abs), Lymphocytes and Platelets. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameter Leukocyte esterase and Nitrite. Most ECG results (84%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 50 bpm to 63 bpm, mean: 56.0 bpm), PQ interval (range: 164 msec to 210 msec, mean: 176.8 msec), QRS interval (range: 80 msec to 92 msec, mean: 87.6 msec), QT interval (range: 388 msec to 416 msec, mean: 402.0 msec) and QTcF interval (range: 379.7 msec to 422 msec, mean: 391.9 msec).

CONCLUSION:

The data from Subtrial F (Palbociclib) of the N^2M^2 trial does not show significant efficacy for the primary endpoint (overall 24.4% patients without progression after 6 months with H_0: p_0=23.1%). The corresponding p-value is $p = 0.4823$.

For the primary safety endpoint of phase I concerning DLTs, in 50.0% (3/6) of the patients receiving 125 mg DLTs were observed (95% two-sided Clopper-Pearson CI: [0.118, 0.882]) and 16.7% (1/6) of the patients receiving the determined MTD experienced a DLT (95% two-sided Clopper-Pearson CI: [0.004, 0.641]).

Overall 83.3% (5/6) patients receiving a dose of 125 mg experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.359, 0.996]) thus the probability is high that the tolerability is unacceptable. For the dose of 75 mg neither DLTs nor RLTs were observed (0/1 patients) (95% two-sided Clopper-Pearson CI: [0, 0.95]). For the determined MTD of 100 mg, overall 26.8% (11/41) of the patients experienced either DLT or RLT (95% two-sided Clopper-Pearson CI: [0.142, 0.429]), thus the DLT rate is below the unacceptable rate of 30%, but tolerability of the MTD cannot be confirmed with a confidence of 95% according to the confidence interval.

Substantial amendments / interruptions:

Substantial amendments: substantial amendments of the umbrella trial are listed

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Updated Informed Consent Forms (ICF) due to EU GDPR and updated IBs and SmPCs	25.05.2018
02	Change of deputy at site 13	13.07.2018

Amendment No.	Content	Approval Date
03	Change of deputy site 06, 07, 09, 10 change of investigator at site 07	21.01.2019, 28.01.2019, 29.01.2019, 06.03.2019
04	Change of deputy at site 12	28.10.2019
05	Protocol amendment (v1.4), updated IBs, ICF	29.12.2019
06	Protocol amendment (v1.5), updated IBs, ICF, new site Leipzig (no. 14), change of deputy at site 08 and 02	12.11.2020, 19.11.2020, 04.12.2020, 28.01.2021
07	Protocol amendment (v2.0), updated IBs, ICF	12.01.2021
08	New deputy at site 03, change of address at site 11	25.03.2021, 08.04.2021
09	Protocol amendment (v3.0), updated IBs, ICF	03.08.2021
10	Protocol amendment (v4.0), updated IBs, ICF	08.10.2021
11	New deputy at site 13	17.03.2022
12	Protocol amendment (v5.0), updated IBs, ICF	18.05.2022
13	New deputy at site 06	03.06.2022
14	Change of investigator and deputy at site 04	07.10.2022

Paul Ehrlich Institute (PEI)

Amendment No.	Content	Approval Date
01	Change requests from ec from initial submission, IMPD Atezolizumab, updated IBs and SmPCs	10.04.2018
02	IMPD Alectinib and Idasanutlin	29.06.2019
03	Protocol amendment (v1.4), updated IBs, manufacturing documents Vismodegib	20.12.2019
04	Protocol amendment (v1.5), updated IBs, labels Idasanutlin	25.11.2020
05	Protocol amendment (v2.0), updated IB Idasanutlin, IMPD APG101	06.01.2021
06	Protocol amendment (v3.0), updated IBs	05.08.2021
07	Protocol amendment (v4.0), updated SmPCs	06.10.2021
08	Protocol amendment (v5.0), updated IBs, ICF	13.05.2022

Interruptions:

There was an interruption of subtrial F Palbociclib from October 28th 2020 until October 8th 2021. Recruitment was stopped in 2020 because the first interim analysis of the effectiveness showed a response rate below the limit of the futility stopping rules specified in the protocol at that time (first null hypothesis). After adjustment of the null hypothesis to the actually observed response rate of patients on standard treatment (Protocol amendment (v3.0)), there was a second efficacy analysis and the results allowed recruitment to be continued.

Date of the report:

September 21st 2023

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG
getragen von: Deutsches Krebsforschungszentrum, Universitätsklinikum Heidelberg, Thoraxklinik-Heidelberg, Deutsche Krebshilfe

Study Title:

Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol G

Temsirolimus plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma with phosphorylation of mTOR^{Ser2448}

The trial is designed as an open-label, multicenter, seamless phase I/IIa trial evaluating toxicity and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. This report covers the results of subtrial G (temsirolimus). Patients are observed 6 months to evaluate the phase IIa primary endpoint PFS-6.

Short Title/ Acronym: N²M²

Final Sub-Study Report according to §42b AMG and §13(9) GCP-V

Version Number/ Date:	Final 1, March 14th 2022
Investigational Product:	p-mTOR^{Ser2448} Temsirolimus
EudraCT Number:	2015-002752-27
Protocol-Number:	NCT-2014-0235 / N2M2 Umbrella Protocol Version 4.0 September 10th 2021 / N2M2 Subtrial G: p-mTOR^{Ser2448} Temsirolimus, 1.5, October 21st 2020

Sponsor:
Heidelberg University Hospital
represented in law by its Commercial Director
Katrin Erk
Im Neuenheimer Feld 672
69120 Heidelberg, Germany
Phone +49 (0)6221 56 7000
Fax: +49 (0)6221 56 4888
E-mail: Kaufmaennische-Direktion@med.uni-heidelberg.de

Coordinating Investigator:
Prof. Wolfgang Wick, MD
Heidelberg University Hospital
Department of Neurology
Im Neuenheimer Feld 400
69120 Heidelberg, Germany
Phone: +49 (0)6221 56 7075
Fax: +49 (0)6221 56 7554
E-mail: wolfgang.wick@med.uni-heidelberg.de

Author of Subtrial Report:
Lisa-Marie Lanz, M.Sc.
NCT Trial Center
Im Neuenheimer Feld 130/3
69120 Heidelberg
Phone: +49 6221/56-6085
Fax: +49 6221/56-5863
lisa-marie.lanz@nct-heidelberg.de

Subtrial G (temsirolimus): Initiation and Completion Dates:
First Patient in: May 17th 2018
Last Patient in: August 28th 2020
Last Patient Last Visit: March 22nd 2021
Data base lock: March 7th 2022

Signatures

The present sub-study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

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

Coordinating Investigator/ Designated Representative of Sponsor	Prof. Wolfgang Wick	HEIDELBERG 15 MAR 22 Place, Date
Biostatistician	Lanz Lisa-Marie Lanz, M.Sc.	Weinheim, 15.03.2022 Place, Date

List of abbreviations:

AE	Adverse Event
CI	Confidence interval
CR	Complete response
CRP	C-reactive protein
ECG	Electrocardiography
EES	Efficacy Evaluable Set
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-glutamyltransferase
KPI	Kanrofsky Performance Index
MGMT	O-6-methylguanine-DNA methyltransferase
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
p-mTOR^{Ser2448}	Phosphorylation of mTOR at serine 2448
PR	Partial Response
RANO	Response assessment in neuro-oncology criteria
REES	Regular Efficacy Evaluable Set
RLT	Regime-limiting toxicity
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
SD	Standard Deviation

Synopsis

Name of Sponsor/Company:
Heidelberg University Hospital
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:
Temsirolimus (Torisel®)

Name of Active Ingredient:
Temsirolimus

Title of Study:
Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promoter methylation: NCT Neuro Master Match - N²M² (NOA-20)

Subtrial Protocol G: Temsirolimus plus radiotherapy for patients with newly diagnosed MGMT-unmethylated glioblastoma with phosphorylation of mTORSer2448

Short Title/ Acronym:

N^2M^2 – Subtrial G (Temsirolimus)

Protocol versions:

Umbrella protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Final 2.0, December 10th 2020 (Substantial Amendment)

Final 3.0, July 6th 2021 (Substantial Amendment)

Final 4.0 September 10th 2021 (Substantial Amendment)

Subtrial G (Temsirolimus) protocol:

Final 1.3, February 8th 2018 (First Authorization)

Final 1.4, October 23rd 2019 (Substantial Amendment)

Final 1.5, October 21st 2020 (Substantial Amendment)

Clinical trial sites and Principle Investigators of umbrella trial:

01 Prof. Wolfgang Wick/CI
Universitätsklinikum Heidelberg, Neurologische Klinik, Im Neuenheimer Feld 400, 69120 Heidelberg

02 Prof. Dr. med. Dietmar Krex
Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik für Neurochirurgie, Fetscherstr. 74, 01307 Dresden

03 Prof. Dr. Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Klinik für Neurochirurgie, Charitéplatz 1, 10117 Berlin

04 Prof. Dr. med. Uwe Schlegel

	Knappschaftskrankenhaus Bochum GmbH, In der Schornau 23-25, 44892 Bochum
05	Prof. Dr. med. Ulrich Herrlinger Universitätsklinikum Bonn, Klinik für Neurologie, Venusberg Campus 1, 53127 Bonn
06	Prof. Dr. med. Martin Glas Universitätsklinikum Essen (AöR), Abteilung Klinische Neuroonkologie, Hufelandstr. 55, 45147 Essen
07	PD Dr. med. Michael Burger Universitätsklinikum Frankfurt, Dr. Senckenbergisches Institut für Neuroonkolgie, Schleusenweg 2-16, 60528 Frankfurt
08	Prof. Dr. Roland Goldbrunner Universitätsklinikum Köln, Zentrum für Neurochirurgie, Kerpener Str. 62, 50937 Köln
09	Prof. Dr. med. Florian Ringel Johannes Gutenberg-Universität Mainz, Neurochirurgische Klinik und Poliklinik, Langenbeckstr. 1, 55131 Mainz
10	Prof. Dr. Michael Platten Universitätsmedizin Mannheim, Neurologische Klinik, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim
11	Prof. Dr. med. Peter Hau Universitätsklinikum Regensburg, Klinik und Polyklinik für Neurologie, Franz-Josef-Strauß-Allee 11, 93053 Regensburg
12	Prof. Dr. med. Ralf Ketter, Universitätsklinikum des Saarlandes, Klinik für Neurochirurgie, Kirrberger Straße, 66421 Homburg
13	Prof. Dr. med. Ghazaleh Tabatabai, Universitätsklinikum Tübingen, Zentrum für Neurologie und Klinik für Neurochirurgie, Hoppe Seyler Str. 3, 72076 Tübingen
14	OA Dr. med. Clemens Seidel Universitätsklinikum Leipzig AöR, Klinik für Strahlentherapie und Radiologie, Stephanstraße 9a, 04103 Leipzig
All sites except 09 and 14 treated patients in subtrial G (Temsirolimus).	

Publication (reference) of Umbrella trial:

- Hertenstein A, Jones D, Sahm F, Pfaff E, Hutter B, Karapanagiotou-Schenkel I, et al. *Umbrella protocol for phase I/IIa trials of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed glioblastoma without MGMT promotor methylation Neuro Master Match (N²M²)*. Journal of Clinical Oncology. 2016 May 20; 34, no. 15_suppl. DOI: 10.1200/JCO.2016.34.15_suppl.TPS2084
- Pfaff E, Kessler T, Balasubramanian GP, Berberich A, Schrimpf D, Wick A, et al. *Feasibility of real-time molecular profiling for patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation-the NCT Neuro Master Match (N²M²) pilot study*. Neuro Oncology. 2018 May 18;20(6):826-837. DOI: 10.1093/neuonc/nox216
- Kessler T, Sahm F, Balasubramanian GP, Pfaff E, Jones DTW, Wick A, et al. *Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N²M²*. Journal of Clinical

Oncology. 2018 June 01;36, no. 15_suppl. DOI: 10.1200/JCO.2018.36.15_suppl.12090
- Wick W, Dettmer S, Berberich A, Kessler T, Karapanagiotou-Schenkel I, Wick A, et al. *N²M² (NOA20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma*. Neuro Oncology. 2019 Jan 1;21(1):95-105. DOI: 10.1093/neuonc/noy161

Studied period (years) for subtrial G (temsirolimus):	**Phase of development**:
Date of first enrollment: May 17th 2018 Date of last enrollment: August 28th 2020 Date of last completed: March 22nd 2021	Umbrella: Phase I/IIa Subtrial: Phase IIa

Objectives:

Phase I:

No phase I was planned for this subtrial and thus no phase I objectives are defined.

Phase IIa:

The *primary Objective* of the phase IIa part of the trial was the determination of efficacy of the systemic molecularly defined therapy in conjunction with radiotherapy.

Secondary Objectives:

The determination of:

- Safety and tolerability (in particular RLTs, SAEs and AEs) of the systemic molecularly defined therapy,
- Progression-free survival (PFS),
- Overall survival (OS),
- Biomarker development, i.e. association of markers discovered in other preclinical or clinical studies with the outcome data of an N²M² subtrial; develop hypotheses on new prognostic or predictive markers from the molecular information obtained.
  As stated in the protocol, this objective is not analyzed in this final trial report, but will be addressed in future manuscripts.

Methodology:

The umbrella-trial was designed as an open-label, multicenter, seamless phase I/IIa trial evaluating safety and efficacy separately in each target-treatment cohort (subtrial) of the N²M² project. For subtrial G, no phase I was planned and thus all patients were recruited for phase IIa.

Visit schedule:

- Screening: Day -42 to -14
- Molecular Assessment/ Tumor Board
- Attribution: Day -13 to 0
- RT: Week 1 – 6, daily
- Temsirolimus: Weeks -1 to 26
- AEs: Attribution, Week -1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- Concomitant Medication: Attribution, Week -1 – 6, weekly, Weeks 8, 12, 16, 20, 24, 26
- RLTs: Week -1 – 26
- Examinations (physical examination, vital signs, urinalysis, safety lab, Karnofsky Performance Index (KPI)): Attribution, Weeks 4, 8, 12, 16, 20, 24
- EOS: Week 26

Number of patients (planned and analyzed in subtrial G):

Number of patients planned: 40

Number of patients analyzed: 46

Diagnosis and main criteria for inclusion:

- Histologically confirmed, newly diagnosed glioblastoma (astrocytoma WHO grade IV) with unmethylated *MGMT* promoter determined by one of the accepted methods (qPCR, pyrosequencing, methylation array) and without mutation of the isocitrate dehydrogenase genes (suitable for all subtrials)
- Phosphorylation of mTOR at serine 2448 (p-mTOR^{Ser2448}) as determined by immunohistochemistry (suitable for subtrial G)

Investigational product, dose and mode of administration, batch number:

Drug Code: ATC-Code: L01X E09

Pharmaceutical formulation: Concentrate and solvent for solution for infusion

Route of administration: i.v.

Storage conditions: 2 – 8°C

Manufacturer/Importer: Pfizer Pharma GmbH

Marketing Authorization number: EU/1/07/424/001

Dose: 25 mg once per week

Batch numbers: AKT3/59, AKT3/5Q, AKT3/68, AKT3/92, ALEG/6A, ALEG/6U, ALEG/9A, ALEG/9K, AM7T/1N

Reference therapy, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

Up to 6 months.

Criteria for evaluation:

Phase I:

For this subtrial no phase I was planned and thus no phase I endpoints are defined.

Phase IIa:

Efficacy:

The primary efficacy endpoint was the progression-free survival at six months (PFS-6) according to RANO criteria as binary endpoint. Response is defined as the proportion of patients without progression at six months after study entry. Basis for the baseline assessment of the disease progression were MRI scans that were done ≤ 2 weeks before start of therapy (for RT planning).

Secondary efficacy endpoints:

- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first). Patients without an event relevant for PFS (progression or death) at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

Safety:

Secondary safety endpoints:

- Regimen-limiting toxicity (RLT), defined as any toxicity that meets the criteria of a DLT, but is observed after the end of the combination therapy in phase I (for patients recruited at the final dose of phase I) or during phase IIa of the trial
- Type, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0), seriousness and relatedness of adverse events
- Karnofsky Index (KPI)
- Vital signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening))
- Clinical laboratory Parameters (hematology, chemistry, urinalysis), ECG

Statistical methods:

Statistical analysis:

Subtrial G (temsirolimus) of the Umbrella-trial N²M² passed first and second interim analyses successfully and recruitment was continued to the final analysis.

If not otherwise mentioned, all patients receiving any dose of study treatment in this subtrial are included in the analyses.

Data for time-to-event endpoints is further collected after EOS in the survival follow-up. Survival follow-up information is collected until overall EOS of the umbrella trial, thus updated results may be presented in the umbrella report.

Analysis of the efficacy endpoints:

- The primary efficacy endpoint PFS-6 according to RANO criteria as a binary endpoint is analyzed with a one-sample one-sided Binomial test of the null hypothesis $H_0: p = 0.231$ Number of responses, defined as patients being definitely free of progression after 6 months (confirmed by MRI scans), are presented in descriptive tables together with corresponding percentages, and exact 95% two-sided Clopper-Pearson CIs. Patients with missing information on PFS-6 are tabulated as missing, but for the calculation of the p-value those patients are assumed to be non-responders. α-level for the primary analysis is 10%.
  Response assessment is determined by combining information from the clinical trial site (local RANO Assessment, a status page in the eCRF showing the information if the patient experienced progression during the 6 months after study entry and survival follow-up in case of premature EOS) and central RANO assessment performed by central neuroradiology in Heidelberg. If the clinical trial site stated a progression on the status page, the patient is assumed to be a non-responder, irrespective of other information. Central RANO assessment is the preferred type of assessment, but if not available (or differing to a stated progression on the status page) other sources of information is used to determine the response status/assessment.
- PFS, defined as time from study entry (day of attribution=baseline) until the day of first documentation of clinical or radiographic tumor progression or death of any cause (whichever occurs first) minus 1 day. Patients without an event relevant for PFS* at the time of analysis are censored at the last disease assessment showing no progression or at baseline if the patient has no post-baseline disease assessments.
- OS, defined as the time from study entry (day of attribution) until death due to any cause. Patients still alive or lost to follow-up at the time of the analysis are censored at the last date they were known to be alive.

* Please note, that patients with a death event (without a preceding progression event) are only considered as having an event relevant for PFS, if regular information on disease assessment for that patient is available. Otherwise the patient is censored.

Analysis of the (secondary) safety endpoints:

- For the secondary safety endpoint (RLT), the amount and type of Regimen-limiting toxicities (RLTs) are tabulated. Summary tables present the number of patients observed with RLTs, the corresponding percentages, and exact 95% two-sided Clopper-Pearson CI.
- Adverse Events are analyzed. Frequencies of patients experiencing at least one AE are displayed. Detailed information collected for each AE include: A description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Summaries of incidence rates (frequencies and percentages) of AEs by MedDRA (version 23.0) System Organ Class (SOC) and Preferred Term (PT) are prepared. Such summaries are displayed for all AEs, AEs by intensity and AEs by relationship to study drug. Summary tables present the number of patients observed with AEs and the corresponding percentages.
- Karnofsky Index (KPI) is summarized descriptively for each visit by presenting the absolute and relative frequencies (percentages).
- Vital Signs (blood pressure (BP), heart rate (HR), temperature, body weight, body height (only at screening), respiratory rate) are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented. This includes changes (differences) from the baseline assessment, except for body height.
- Clinical laboratory parameters (hematology, chemistry, urinalysis) and ECG are summarized descriptively by visit. Number of observations (n, nmiss), mean, standard deviation, median, minimum and maximum are presented (for ECG: only for abnormal results). The number of patients with laboratory values that are below, within or above normal ranges are tabulated for each parameter. Descriptive summaries (mean, SD, median, minimum and maximum) of actual values and of changes from baseline are presented for each parameter. The number and percentage of patients with normal and abnormal ECG results at baseline and follow-up are tabulated. ECG findings are tabulated by patient.

Sub-Study population

A total of 49 patients were included in 12 clinical trial sites. 46 patients were treated (and are thus part of the Full Analysis Set (FAS)) and all 46 patients are available for the primary endpoint analysis (and are thus part of the Efficacy Evaluable Set (EES)). A total of 33 patients had regular EOT (i.e. the patient had maximum treatment duration or premature EOT due to progression or death) and a central RANO assessment for PFS-6 is available and thus fulfills the criteria to be part of the Regular Efficacy Evaluable Set (REES). For details on discontinuations and demographics of patients, see the following tables:

Discontinuations from Sub-Study:

		Temsirolimus FAS/EES N (%)
Status at End of Treatment	Maximum treatment duration (26 weeks) is reached	26 (56.5)
	Premature end of treatment reached prior to week 26	20 (43.5)

Reason(s) for premature end of treatment *	Disease progression (lack of clinical benefit)	12 (60.0)
	Undue toxicity	1 (5.0)
	Death	2 (10.0)
	Withdrawal of informed consent (patients decision)	1 (5.0)
	Adverse event other than undue toxicity	4 (20.0)
	Non-compliance	1 (5.0)
	Investigator's opinion	1 (5.0)
	Other reason(s)	1 (5.0)
Status at the End of the Study	Defined end of study at week 26 is reached	26 (56.5)
	Death	2 (4.3)
	30 days safety follow-up is reached after premature EOT due to toxicity or progression	12 (26.1)
	Premature EOT due to reasons other than progression is reached, but remained in study until week 26	1 (2.2)
	Premature study termination (and no safety follow-up was performed)	5 (10.9)
Reason(s) for premature study termination*	Adverse event other than undue toxicity	3 (60.0)
	Withdrawal of informed consent	1 (20.0)
	Non-compliance	1 (20.0)

* Documentation of multiple reasons were possible.

Demographics:

	All Patients	**Male**	**Female**
Sex, n (%)			
Male	27 (58.7)	27 (100)	0
Female	19 (41.3)	0	19 (100)
Age continuous (years), Mean (SD)	59.4 (10.15)	58.5 (9.94)	60.6 (10.59)
BMI (kg/m²), Mean (SD)	26.7 (4.15)	26.7 (3.91)	26.7 (4.57)
Height (cm), Mean (SD)	173.5 (9.18)	179.1 (7.63)	165.9 (4.45)
Weight (kg), Mean (SD)	80.6 (15.09)	85.7 (14.71)	73.6 (12.93)
Age categorical (years), n (%)			
18-44	4 (8.7)	1 (3.7)	3 (15.8)
45-64	25 (54.3)	18 (66.7)	7 (36.8)
≥65	17 (37.0)	8 (29.6)	9 (47.4)
Ethnic Group, n(%)			
Caucasian/white	45 (97.8)	26 (96.3)	19 (100)
Oriental	1 (2.2)	1 (3.7)	0

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The objective of Phase IIa part is the determination of efficacy of temsirolimus in conjunction with radiotherapy for patients with phosphorylation of mTOR at serine 2448.

Primary endpoint is the PFS-6 rate (corresponds to response rate), defined as the proportion of patients free of progression at 6 months after study entry. The tested null hypothesis is $H_0: p_0 = 23.1\%$.
Secondary endpoints include progression-free survival (PFS) and overall survival (OS).

Primary endpoint: PFS-6:
In the following 2 tables response-status and RANO-assessment are shown together with the best available source of information for the Full Analysis Set (FAS)/Efficacy Evaluable Set (EES) and the Regular Efficacy Evaluable Set (REES):

FAS/EES (N=46)	**All Patients**	**Central RANO Assess-ment**	**Local RANO Assess-ment**	**No progression, but different anti-cancer therapy received****	**Survival Follow-Up (until week 26 after premature EOS)**	**Progression according to trial site, not diagnosed with MRI**
Response-Status*						
Yes	18 (39.1)	18 (50.0)	0	0	0	0
No	28 (60.9)	18 (50.0)	6 (100)	1 (100)	1 (100)	2 (100)
Response-Assessment						
Stable Disease (SD)	18 (39.1)	18 (50.0)	0	0	0	0
Progressive Disease (PD)	27 (58.7)	18 (50.0)	6 (100)	1 (100)	0	2 (100)
Death***	1 (2.2)	0	0	0	1 (100)	0

REES (N=33)	**All Patients**	**Central RANO Assessment**
Response-Status*		
Yes	16 (48.5)	16 (48.5)
No	17 (51.5)	17 (51.5)
RANO-Assessment		
Stable Disease (SD)	16 (48.5)	16 (48.5)
Progressive Disease (PD)	17 (51.5)	17 (51.5)

*: Patients are assessed as responders if stable disease, partial response or complete response is present after 6 months
**: Patients in this category are assumed to be treatment-failures and thus are counted as having PD
***: Please note, that the two patients with EOT/EOS (see table “Discontinuations from Sub-Study") due to death were assessed as being progressive prior to death by central RANO assessment and thus are counted as “PD” and not “death”.

For the primary analysis the FAS is used (in this case identical to the EES). Overall, 39.1% (18/46) of these patients were assessed as responders (95%-Clopper-Pearson CI: [25.09%, 54.63%]). All of them were confirmed by central RANO Assessment. Best available assessment was “stable disease”. The corresponding p-value of the one-sided binomial test is $p = 0.0109$.
As a sensitivity analysis, the same calculations were performed on the REES. 48.5% (16/33) of these patients were assessed as responders (95%-Clopper-Pearson CI: [30.80%, 66.46%]). The corresponding p-value of the one-sided binomial test is $p = 0.0012$.

Secondary endpoint: PFS
The secondary endpoint PFS is analyzed using the FAS/EES. The number of patients with an event relevant for PFS until database lock is 29/46 (63.0%). Median progression-free survival is 5.8 months. For more information see the following table:

Number of Patients (%)	46 (100)
Number of Patients with the Event (%)	29 (63.0)
25 Percent Point Estimate* (95% CI)	2.8 (2.8, 4.5)
Median* (95% CI)	5.8 (3.1, 7.7)
75 Percent Point Estimate* (95% CI)	7.7 (6.1,)
6-month event free rate** (95% CI)	0.448 (0.300, 0.586)
9-month event free rate** (95% CI)	0.123 (0.010, 0.386)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

Secondary endpoint: OS
The secondary endpoint OS is analyzed using the FAS/EES. The number of patients with the event until database lock is 41/46 (89.1%). Median overall survival is 15.4 months. For more information see the following table:

Number of Patients (%)	46 (100)
Number of Patient with the Event (%)	41 (89.1)
25 Percent Point Estimate* (95% CI)	10.8 (7.2, 11.9)
Median* (95% CI)	15.4 (11.7, 18.0)
75 Percent Point Estimate* (95% CI)	19.6 (17.4, 22.4)
6-month event free rate** (95% CI)	0.890 (0.755, 0.953)
9-month event free rate** (95% CI)	0.801 (0.652, 0.891)
12-month event free rate** (95% CI)	0.601 (0.443, 0.726)
18-month event free rate** (95% CI)	0.362 (0.222, 0.503)
24-month event free rate** (95% CI)	0.078 (0.020, 0.187)
30-month event free rate** (95% CI)	0.039 (0.004, 0.151)

*corresponding to time to progression in months
**Kaplan-Meier estimates for the respective time points are displayed

SAFETY RESULTS:

The total drug exposure for all patients were 6836 days.

Overall 43 (93.5%) patients experienced at least one (all causality) AE (total number of AEs=457) that occurred after first treatment and prior to EOS/ safety follow-up. AEs occurring more than once were only counted once per patient if they were assigned to the same preferred term. The most frequent AEs in terms of system organ class were “Nervous system disorders”, “Skin and subcutaneous tissue disorders” and “Infections and infestations”. AEs with causality assessed as certainly, probably, possibly related or with missing information on relatedness were considered as treatment related. 40 (87.0%) patients experienced at least one treatment related AE (total number of treatment-related

AEs=196). The most frequent treatment related AEs in terms of system organ class were “Skin and subcutaneous tissue disorders”, “Gastrointestinal disorders” and “General disorders and administration site conditions”. 24 RLTs were observed in 16 (34.8%) patients. 28 SAEs occurred in overall 16 (34.8%) patients, one fatal SAE assessed as unrelated to study treatment occurred (cerebral haemorrhage). Most of these RLTs and SAEs were reported in the system organ class “Infections and infestations”. For detailed information see the following table:

	N (%)
Overview all AEs	
Any AE	43 (93.5)
Any SAE	16 (34.8)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	24 (52.2)
Any RLT	16 (34.8)
Patients discontinued study drug due to AEs	4 (8.7)
Patients with dose of study drug reduced or temporary discontinuation due to AE	24 (52.2)
Patients with AE resulting in death	1 (2.2)
Overview related AEs	
Any AE	40 (87.0)
Any SAE	10 (21.7)
Any Severe Adverse Event (CTCAE v5.0 grade 3 or 4)	16 (34.8)
Any RLT	16 (34.8)
Patients discontinued study drug due to AEs	4 (8.7)
Patients with dose of study drug reduced or temporary discontinuation due to AE	19 (41.3)
Patients with AE resulting in death	0
AEs by System Organ Class (MedDRA 23.0), all causalities*	
Blood and lymphatic system disorders	21 (45.7)
Cardiac disorders	1 (2.2)
Ear labyrinth disorders	8 (17.4)
Eye disorders	5 (10.9)
Gastrointestinal disorders	27 (58.7)
General disorders and administration site conditions	27 (58.7)
Hepatobiliary disorders	2 (4.3)
Immune system disorders	2 (4.3)
Infections and infestations	32 (69.6)
Injury, poisoning and procedural complications	9 (19.6)
Investigations	22 (47.8)
Metabolism and nutrition disorders	16 (34.8)
Musculoskeletal and connective tissue disorders	6 (13.0)
Nervous system disorders	29 (63.0)
Psychiatric disorders	11 (23.9)
Renal and urinary disorders	2 (4.3)
Reproductive system and breast disorders	1 (2.2)
Respiratory, thoracic and mediastinal disorders	13 (28.3)
Skin and subcutaneous tissue disorders	32 (69.6)

Surgical and medical procedures	1 (2.2)
Vascular disorders	11 (23.9)
SAEs by System Organ Class (MedDRA 23.0), all causalities*	
Blood and lymphatic system disorders	1 (2.2)
Eye disorders	1 (2.2)
Gastrointestinal disorders	1 (2.2)
General disorders and administration site conditions	3 (6.5)
Infections and infestations	11 (23.9)
Nervous system disorders	3 (6.5)
Respiratory, thoracic and mediastinal disorders	2 (4.3)
Vascular disorders	1 (2.2)
SAEs by System Organ Class (MedDRA 23.0), related*	
Gastrointestinal disorders	1 (2.2)
General disorders and administration site conditions	3 (6.5)
Infections and infestations	6 (13.0)
Nervous system disorders	1 (2.2)
Respiratory, thoracic and mediastinal disorders	2 (4.3)
RLTs by System Organ Class (MedDRA 23.0)*	
Blood and lymphatic system disorders	3 (6.5)
Gastrointestinal disorders	3 (6.5)
General disorders and administration site conditions	2 (4.3)
Hepatobiliary disorders	1 (2.2)
Infections and infestations	8 (17.4)
Investigations	1 (2.2)
Metabolism and nutrition disorders	2 (4.3)
Nervous system disorders	1 (2.2)

* The displayed number shows the amount of patients with one or more events in the specific system organ class. Each patient is counted only once per system organ class.

Other Safety Data

In the following presentation of other safety data only tests and examinations that were performed on or after date of first treatment of the respective patient are included.

Karnofsky index ranged from 50 to 100, mean KPI over all visits and patients was 87.3. Vital signs were unremarkable. Most recorded clinical laboratory values (>98%) were within normal ranges or not clinically significant. Most clinically significant values occurred for parameters lymphocytes, CRP, GGT, hemoglobin and white blood cell count. Most documented urinalysis values (>99%) were assessed as within normal ranges or not clinically significant. Clinically significant values were documented for parameters glucose, protein, leukocyte esterase and nitrite. Most ECG results (>96%) were documented as normal. Quantitative values of patients with abnormal ECG results include heart rate (range: 53 bpm to 92 bpm, mean: 73.3 bpm), PQ interval (range: 138 msec to 366 msec, mean: 202.4 msec), QRS interval (range: 78 msec to 142 msec, mean: 98.7 msec), QT interval (range: 356 msec to 424 msec, mean: 386.9 msec) and QTcF interval (range: 378 msec to 465 msec, mean: 415.75 msec).

CONCLUSION:

The data from Subtrial G (Temsirolimus) of the N²M² trial show efficacy for the primary endpoint (overall 39.1% patients without progression after 6 months) with a highly significant p-value of 0.0109 (α-level of this trial is 10%). This shows benefit compared to the assumed PFS-6 rate in standard of care ($p_0 = 23.1\%$).

The observed RLT-rate is 34.8% (95% Clopper-Pearson CI: [0.214, 0.502]), which is slightly above the predefined unacceptable rate for RLTs of 30%, thus, using the confidence interval, an acceptable safety profile can neither be confirmed nor denied. Most RLTs had severity grade 3, one RLT had severity grade 4. No RLTs resulted in death.

Substantial amendments / interruptions:

Substantial amendments: substantial amendments of the umbrella trial are listed

IEC Independent Ethics Committee(s)

Amendment No.	Content	Approval Date
01	Updated Informed Consent Forms (ICF) due to EU GDPR and updated IBs and SmPCs	May 25th 2018
02	Change of deputy at site 13	July 13th 2018
03	Change of deputy site 06, 07, 09, 10 change of investigator at site 07	January 21st 2019, January 28th 2019, January 29th, March 6th 2019
04	Change of deputy at site 12	October 28th 2019
05	Protocol amendment (v1.4), updated IBs, ICF	December 29th 2019
06	Protocol amendment (v1.5), updated IBs, ICF, new site Leipzig (no. 14), change of deputy at site 08 and 02	November 12th 2020, November 19th 2020, December 4th 2020, January 28th 2021
07	Protocol amendment (v2.0), updated IBs, ICF	January 12th 2021
08	New deputy at site 03, change of address at site 11	March 25th 2021, April 8th 2021
09	Protocol amendment (v3.0), updated IBs, ICF	August 3rd 2021
10	Protocol amendment (v4.0), updated IBs, ICF	October 8th 2021

Paul Ehrlich Institute (PEI)

Amendment No.	Content	Approval Date
01	Change requests from ec from initial submission, IMPD Atezolizumab, updated IBs and SmPCs	April 10th 2018
02	IMPD Alectinib and Idasanutlin	June 29th 2019
03	Protocol amendment (v1.4), updated IBs, manufacturing documents Vismodegib	December 20th 2019
04	Protocol amendment (v1.5), updated IBs, labels Idasanutlin	November 25th 2020
05	Protocol amendment (v2.0), updated IB Idasanutlin, IMPD APG101	January 6th 2021

06	Protocol amendment (v3.0), updated IBs	August 5th 2021
07	Protocol amendment (v4.0), updated SmPCs	October 6th 2021

Interruptions:
There were no interruptions of subtrial G Temsirolimus and the subtrial was continued to the final analysis as planned.

Date of the report:
March 14th 2022