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Dr. Richard Roe
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Name	Doe, Jane (*TT.MM.JJJJ)
Sex	Female
Patient-ID	#####
ICD-10	C71.9
Report date	TT.MM.JJJJ
Report-ID	R####

Treatment Recommendation – Doe, Jane (*TT.MM.JJJJ)

Indication **Astrocytoma, WHO-Grade II (ID 09/2017)**

Therapeutic History

Date	Type	Details
09/2017	Surgery	**Tumor Resection** of primary in brain (left frontal)
10/2017 -12/2017	Therapy	**Temozolomide** + **Radiotherapy of brain**
01/2018 -07/2019	Therapy	**Temozolomide**
07/2018 -03/2021	Therapy	**Optune**
11/2019	Staging	**PD** (brain)
since 12/2019	Therapy	**Temozolomide**
01/2020	Staging	**PR** (MRI of brain)
01/2020 -01/2020	Therapy	**Radiotherapy of brain**
04/2020-02/2023	Staging	**SD** (MRI of brain).
04/2023	Staging	**PD** (MRI of brain)

CR: complete response, **PR**: partial response, **SD**: stable disease, **PD**: progressive disease
Information in table above makes no claim to completeness. Stated staging results do not comply with RECIST or RANO rules as applied in clinical studies but aim to generally describe the course of the patient's disease.

Tumor Profiling

Tumor Profiling Next Generation Sequencing

Gene	Functional category	Variant	NAF	Effect on protein function
IDH1	missense	c.395G>A; p.Arg132His	0.36	function changed
ATRX	stop_gained	c.1375A>T; p.Lys459*	0.62	inactivating
MYCN	amplification	complete gene, non focal (≥5 copies)	N/A	activating
SETD2	frameshift	c.2756_2757delAG; p.Glu919Val*fs**15	0.05	inactivating
TP53	missense	c.742C>T; p.Arg248Trp	0.71	function changed

NAF: *Novel allele frequency*, the frequency with which the mutated allele occurs in the sequencing data (1 is 100%). The observed frequencies are influenced by the tumor content as well as copy number alterations and do not directly correlate with the variant's frequency in the tumor. The somatic alterations were classified with respect to their functional effect on protein levels in the following categories: inactivating/activating/function altered, likely inactivating/activating/function altered, unknown and benign (details in the methods section of the sequencing report).
Remark: The results shown in this table are based on the patient's sequenced sample. For full details please refer to the corresponding sequencing report from CeGaT listed below in section *Additional Information*.

Tumor Profiling NGS Signatures/Scores

Biomarker	Result	Interpretation
TMB	>5 mut/mb	low
HRD	13	negative
MSI	0.17	negative

TMB: Tumor mutational load, **HRD**: Homologous recombination deficiency, **MSI**: Microsatellite instability
Remark: The results shown in this table are based on the patient's sequenced sample. For full details please refer to the corresponding sequencing report from CeGaT listed below in section *Additional Information*.

Tumor Profiling Immunohistochemistry Analysis / Other Biomarkers

Biomarker	Result	Interpretation	Comment	Analysed at *(material)*
p53 *(IHC)*	-	positive	Mutation present	xx.xx.xxxx *(FFPE-ID)*
IDH1 *R132H (IHC)*	-	**positive**	**IDH1 mutation present**	xx.xx.xxxx *(FFPE-ID)*
ATRX *(IHC)*	-	negative	ATRX loss	xx.xx.xxxx *(FFPE-ID)*
Ki-67/Mib-1	10%	-	-	xx.xx.xxxx *(FFPE-ID)*
MGMT *promoter methylation*	31%	**positive**	**Methylated MGMT-promoter**	xx.xx.xxxx *(FFPE-ID)*

Possible Treatment Options

Please note that the therapeutic options listed below refer to molecular genetic data only. **The clinical situation and/or comorbidities of the patient are not taken into account. Therefore, in case of multiple treatment options, these have not been prioritized. The decision to carry out one of the listed therapies is at the discretion of the treating oncologist, who will take all factors into account**. It is also possible that standard therapies are still open, which have not been addressed here. We therefore recommend that the listed therapeutic options be presented in a tumor board in which the treating oncologist is present. Results of clinical trials and/or case reports used to generate evidence for the listed off label treatment options are listed in the Appendix.

Possible / Perspective Clinical Trials

This section lists possible clinical studies that could be relevant for your patient. The search is limited to study centers located in the countries indicated on the submission form or corresponding to the patient's country of residence. Please note that we cannot guarantee detailed screening of all inclusion and exclusion criteria. If trial screening is desired, please contact the trial coordinator listed under the NCT number on www.clinicaltrials.gov.

Interdisciplinary discussed at XXXX, XX.XX.XXXX

Option	Biomarker	Study-ID (study name)	Drug	Phase	Localisation
1	***IDH1*** *c.395G>A, p.R132H, NAF 36%*	NCT04056910	Ivosidenib + Nivolumab	2	USA: Pennsylvania, Pittsburgh
2	***IDH1*** *c.395G>A, p.R132H, NAF 36%*	NCT05484622	Vorasidenib + Pembrolizumab	1	USA: California: LA, San Francisco; Florida: Miami; Illinois: Chicago; Massachusetts: Boston; New York; North Carolina: Durham; Texas: Huston
3	***IDH1*** *c.395G>A, p.R132H, NAF 36%* ***ATRX*** c.1375A>T; p.Lys459*, NAF: 62% **ATRX (IHC)** negative	NCT03212274	Olaparib	2	USA: California: Costa Mesa, Orange; Connecticut: New Haven; Florida: Coral Gables, Deerfield Beach, Miami, Plantation; Kansas: Fairway, Kansas City, Overland Park, Westwood; Maryland: Baltimore; Massachusetts: Boston; Missouri: Creve Coeur, Kansas City, Lee's Summit, North Kansas City, Saint Louis; New Hampshire: Lebanon; New York; Ohio: Columbus; Oklahoma; Pennsylvania: Pittsburgh; Tennessee: Nashville; Texas: Houston; Wisconsin: Madison
4	***IDH1*** *c.395G>A, p.R132H, NAF 36%*	NCT05345002	Retifanlimab + All-trans retinoic acid	2	USA: Pennsylvania

Information in table above makes no claim to completeness. The search for suitable clinical trials is limited exclusively to a query of the publicly accessible clinicaltrials.gov database. Please note that the trial search on clinicaltrials.gov was focused on trials which might be suitable based on biomarkers detected in the tumor of the patient.

Perspective in Label / Off Label Therapies

Interdisciplinary discussed at XXXX, XX.XX.XXXX

Option	Biomarker	Drug Class	Drug	Availability
5	***IDH1*** *c.395G>A, p.R132H, NAF 36%*	IDH1 Inhibitor	Ivosidenib or Olutasidenib	Off Label

If several drugs of the same option are listed, this is understood to be a combination therapy.

Please do not hesitate to contact us if you have any questions.

Report written by: Dr. rer. nat. Forename Surname

With kind regards,

Dr. med. Dr. rer. nat. Saskia Biskup

Consultant for Human Genetics

Additional Information

Sequenced sample	DNA isolation from tumor in FFPE (FFPE-ID: xxxxxxx) after microdissection; sampled at xx.xx.xxxxx Estimated tumor content xx% (HE staining), diagnostically estimated tumor content xx%
Sequencing report	Report-ID: Rxxxxx Pxxxxx(Tumor) somatic analysis to Pxxxxx (Normal) from xx.xx.xxxx

Communication, dissemination and usage of this report for scientific purposes is only permitted in accordance with the German Genetic Diagnostics Legislation.

Appendix - Literature Evidence

Please note that the references provided may not match the patient's current situation or diagnosis. Results from clinical study data or case reports from patients with other tumor entities whose tumors have the same or similar biomarkers as your patient are also listed below. In addition, the results of clinical studies or case reports can also be listed that have not been stratified by biomarkers, but which could be a therapeutic approach for your patient according the molecular profile of the patient's tumor. Please note that it may here have been limited to the most important sources of literature and that there is no claim to completeness.

Literature Evidence 1/6	
Tumor type	**glioma**
Study ID/Name	NCT03684811 Phase 1b/2
Setting	- cohort: IDH1R132X-mutated glioma that relapsed or progressed on or following standard therapy and had measurable disease - staging: 58% WHO III, WHO IV: 27% - pretreatment: on or following standard therapy; 42% receiving ≥3 prior regimens - drug dosage: olutasidenib, 150 mg orally twice daily (BID) in continuous 28-day cycles - MRI: 88% contrast-enhancing, 12% contrast non-enhancing - cohort size: n=26 - endpoints: The primary endpoints were dose-limiting toxicities (DLTs) (cycle 1) and safety in phase I and objective response rate using the Modified Response Assessment in Neuro-Oncology criteria in phase II.
Biomarker	***IDH1*** (function changed)
Drug Class/Name	IDH1 inhibitor: **olutasidenib**
Outcome	ORR: 8% PR 8% (2/25) (both enhancing at baseline GBM) SD: 40% (10/25) SD >4 months: 32% (8/25) DCR: 48% CBR: 48% mPFS: 1.9 months mPFS low grade glioma: 16.9 months (n=4) 12-month PFS rate: 20.8% mOS: 17.2 months 12-month survival rate: 67.9% **genetic profile Patients with PR:** IDH1 R132H, TP53m, (1x ATRXm)
Publication	I de la Fuente et al., 2023, PMID: 35639513

Literature Evidence 2/6	
Tumor type	**glioma**
Study ID/Name	NCT02073994 Phase 1
Setting	- cohort: advanced gliomas with IDH1-mutation - histology: 34.8% oligodendroglioma, 28.8% astrocytoma, 18.2% oligoastrocytoma, 18.2% GBM - tumor characterization: 1p/19q co.deletion: 33.3%; ATRX mutation: 92.0% - tumor grade (WHO): 48.5% grade II, 27.3% grade III, 18.2% grade IV - pretreatment: 74.2% prior radiotherapy, 75.8% prior systemic therapy - drug dosage: 500 mg once per day was selected for the expansion cohort - cohort size: n=66
Biomarker	***IDH1*** (function changed)
Drug Class/Name	IDH1 inhibitor: **ivosidenib**
Outcome	**Non-enhancing (n=35)** ORR: 2.9% PR: 2.9% (1/35) SD: 85.7% (30/35) tumor volume reduction: 66.7% (22/33) mPFS: 13.6 months **Enhancing (n=31)** ORR: 0% SD: 45.2% (14/31) tumor volume reduction: 33.3% (9/27) mPFS: 1.4 months
Publication	Mellinghoff et al., 2020, PMID: 32530764

Literature Evidence 3/6	
Tumor type	**glioma**
Study ID/Name	NCT03343197 Phase 1
Setting	- cohort: recurrent, nonenhancing WHO 2016 Grade 2 or 3 mIDH1-R132H oligodendroglioma or astrocytoma - drug dosage: undergoing craniotomy were randomized 2:2:1 to Ivosidenib (IVO; AG-120) 500 mg QD, Vorasidenib (VOR; AG-881) 50 mg QD, or no treatment (control) for 4 wk preoperatively in Cohort 1. ostoperatively, pts continued to receive IVO or VOR, and control pts were randomized 1:1 to IVO or VOR. - cohort size: n=16
Biomarker	***IDH1*** (function changed)
Drug Class/Name	IDH1 inhibitor: **ivosidenib** IDH1/IDH2 inhibitor: **vorasidenib**
Outcome	In Cohort 1 of this phase 1 perioperative study, IVO and VOR were CNS penetrant and lowered tumor 2-HG levels compared with untreated samples
Publication	Mellinghoff et al., 2019, https://doi.org/10.1093/neuonc/noz126.004

Literature Evidence 4/6	
Tumor type	**glioblastoma**
Study ID/Name	Case report NCT02073994 Phase 1
Setting	recurrent, pretreated negative for 1p19q codeletion, MGMT promotor negative
Biomarker	***IDH1*** (function changed)
Drug Class/Name	IDH1 inhibitor: **ivosidenib**
Outcome	improved seizure control and radiographic stable disease for more than 4 years
Publication	Tejera et al., 2020, PMID: 32716208

Literature Evidence 5/6	
Tumor type	**glioma**
Study ID/Name	NCT02481154 Phase 1
Setting	- cohort: recurrent, relapse glioma - pretreatment: standard therapy - drug dosage: orally, once daily, in 28-day cycles until progression or unacceptable toxicity - cohort size: n =52
Biomarker	***IDH1, IDH2*** (function changed)
Drug Class/Name	IDH1/IDH2 inhibitor: **vorasidenib**
Outcome	**Low grade non-enhancing (n=22):** ORR: 18.2% (4/22) PR: 4.5% (1/22) Minor response: 13.6% (3/22) SD: 72.7% (16/22) mPFS: 36.8 months **Enhancing (n=30):** ORR: 0 SD: 56.7% (17/30) mPFS: 3.6 months
Publication	Mellinghoff et al., 2021, PMID: 34078652

Literature Evidence 6/6	
Tumor type	**glioma**
Study ID/Name	NCT04164901 *INDIGO* Phase 3
Setting	- cohort: residual or recurrent grade 2 glioma with an *IDH1* or IDH2 mutation - preatreatment: least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year (-1 month) and not more than 5 years (+3 months) before the date of randomization, and no other prior anticancer therapy, including chemotherapy and radiotherapy and not be in need of immediate chemotherapy or radiotherapy in the opinion of the Investigator. - drug dosage: andomized 1:1 to receive vorasidenib (VOR) 40 mg daily or placebo (PBO) daily in 28-day cycles - histological subtype: oligodendroglioma: 172 and astrocytoma: 159 - cohort size: n=331, 168 to VOR and 163 to PBO
Biomarker	***IDH1*** (function changed)
Drug Class/Name	IDH1 inhibitor: **vorasidenib**
Outcome	**Vorasidenib (n=168):** mPFS: 27.7 months **Placebo (n=163):** mPFS: 11.1 months HR, 0.26, p. significant
Publication	Mellinghoff et al., 2023; DOI: 10.1200/JCO.2023.41.17_suppl.LBA1