Case Report

Case Report WIN-MTB-2024001 – WIN International Molecular Tumor Board: A 55-year-old male with glioblastoma exhibiting amplifications in MDM2 and EGFR

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ABSTRACT

The WIN Consortium International Molecular Tumor Board brings together precision oncology experts from 18 organizations in 13 countries across four continents and provides discussion for patients with cancer across the world. This case report details the medical journey of a 55-year-old man diagnosed with high-grade glioblastoma (GBM), characterized by amplifications of *MDM2* and *EGFR*, alongside other critical genomic alterations, including a *CDKN2A* frameshift mutation. Despite the aggressive nature of GBM, the patient was in remission following a combination of radiotherapy and chemotherapy, surgery and participation in a phase II clinical trial (PI3K/mTOR inhibitor) combined with ketogenic diet and metformin. However, the patient was also considering personalized neoantigen vaccine therapy targeting tumor-specific mutated peptides as part of his treatment strategy.

This case underscores the immense complexity of treating GBM. Next generation sequencing showed *MDM2* amplification, which hinders the tumor-suppressive functions of p53, and *EGFR* amplification, which promotes oncogenic signaling. The experts highlighted various therapeutic options discussed in the event of relapse: *EGFR* inhibitors, various *MDM2* inhibitors, and personalized combination therapies targeting both *EGFR* and *CDK4/6*. Additionally, the Molecular Tumor Board discussed the reported risk of resistance or hyper-progression with immune checkpoint blockade in the presence of *EGFR* and *MDM2* alterations. Innovative approaches such as combining *MDM2* and *EGFR* inhibitors with immunotherapy, as well as the use of teserpaturev, a genetically engineered herpes simplex virus were addressed. This case emphasizes the importance of personalized treatment strategies for GBM and the need for ongoing clinical research to explore novel therapeutic options.

INTRODUCTION

Glioblastoma (GBM) remains one of the most aggressive and lethal primary brain tumors in adults [1–3]. In the current WHO classification, glioblastoma is defined as a diffuse astrocytic glioma, IDH-wildtype, CNS WHO grade IV [4]. Characterized by rapid tumor growth and diffuse infiltration, GBM presents significant challenges in terms of treatment and prognosis [3, 5–8]. Although there have been advancements in multimodal treatments including surgical resection, radiotherapy, and chemotherapy, the median survival for GBM patients remains approximately 15 months and the five-year survival rate is around 5–10% [9, 10].

The molecular heterogeneity of GBM contributes to its resistance to therapy and underscores the importance of studying specific genetic alterations that drive tumor progression [11, 12]. *MDM2*, frequently amplified in high-grade gliomas, acts as a negative regulator of p53, a key tumor suppressor that controls the cell cycle [13]. By binding to p53 and promoting its degradation, *MDM2* impairs p53's tumor-suppressive functions, driving tumorigenesis, uncontrolled cell proliferation, resistance to apoptosis, and enhanced survival of glioma cells [14, 15]. Elevated *MDM2* expression correlates with tumor grade and poor prognosis [16]. Given its pivotal role in suppressing p53, *MDM2* has emerged as a therapeutic target in high-grade gliomas. Inhibiting *MDM2* is being explored as a strategy to reactivate p53, restoring its potent tumor-suppressive functions and potentially reversing tumor progression [15]. Also, *MDM2* overexpression is associated with chemoresistance, particularly to drugs that rely on p53-mediated apoptosis [17]. This is especially problematic in GBM, which is commonly treated with chemotherapy agents like temozolomide. Therefore, *MDM2* inhibition has been proposed as a potential strategy to sensitize glioma cells to chemotherapy by reactivating p53 and enhancing the response to agents like temozolomide. Although preclinical models have shown encouraging results with *MDM2* inhibitors, clinical applications are still under investigation [18].

Beyond its regulation of p53, *MDM2* is also involved in other pathways critical to glioma progression, including cell cycle regulation, DNA repair, and cell survival [14]. The *MDM2*-p53 pathway interacts with multiple other pathways in gliomas, and alterations in these regulatory proteins collectively contribute to tumor progression and resistance to therapy [19]. *MDM2* interacts with various proteins, including retinoblastoma (RB) and alternate reading frame (p14ARF), and is influenced by cellular signaling pathways such as epidermal growth factor receptor (EGFR) signaling, which is often dysregulated in GBM [14, 20–23]. Amplification of *EGFR* drives oncogenic signaling pathways that promote proliferation, invasion, angiogenesis, and resistance to therapy [20]. Both *MDM2* and *EGFR* alterations are associated with aggressive tumor behavior and worse clinical outcomes [14, 21, 24]. Studies have shown that *MDM2* amplification occurs in approximately 10–14% of GBMs, while *EGFR* amplification is observed in approximately 50% of cases [25–27].

CDKN2A is another important tumor suppressor gene that regulates the cell cycle, preventing uncontrolled cell proliferation by producing two different tumor-suppressor proteins – (i) p16INKa, which blocks CDK4/6 and helps to keep the RB pathway off and prevent cells from entering the S-phase too easily, and (ii) p14ARF which restrains MDM2 and helps keep p53 active when the cell is stressed/damaged [28–30]. Molecular alterations in *CDKN2A*, including loss of heterozygosity and deletions, are commonly observed in GBM, where they drive tumor progression and correlate with poor prognosis [31, 32].

This paper presents a case of a 55-year-old male patient diagnosed with high-grade GBM, exhibiting amplifications of both *MDM2* and *EGFR*, along with other molecular aberrations such as *CDKN2A* frameshift mutation and loss of heterozygosity. We provide detailed account of the patient's clinical history, molecular profiling and treatment course.

An international Molecular Tumor Board (MTB), composed of expert physicians and scientists specializing in personalized cancer medicine from 18 centers across 13 countries as shown in Figure 1, convened by the Worldwide Innovative Network (WIN) Association - WIN Consortium, discussed the case. While the patient was in remission at the time of the discussion, the MTB considered potential therapeutic options should the disease progress. This report builds on prior published WIN Consortium's International MTB case reporting [33].

CASE REPORT DESCRIPTION

The patient, a 55-year-old man, was diagnosed with high-grade GBM in June 2023. He was generally healthy with a medical history of hypertension and hyperlipidemia. He had a 10-pack year tobacco history but had quit 20 years ago.

The patient's medical journey began in February 2023, when he experienced dizziness while driving and presented to the emergency room, where he subsequently had a generalized tonic-colonic (GTC) seizure. Following this episode, he suffered from impaired speech. MRI and CT scans of the brain revealed a small mass in the left temporal area, as shown in Figure 2A. However, no immediate action was necessary at that time, and he was discharged with a 10-day course of anti-epileptic medication.

By June 2023, the patient had another episode of GTC seizure, this time with a loss of consciousness. A follow-up MRI revealed that the left temporal lobe mass had grown, as shown in Figure 2B, 2C. The patient

underwent neurosurgical procedure consisting of anterior temporal lobectomy and amygdalohippocampectomy, as outlined in Figure 3. The MRI scan post-surgery is shown in Figure 2D.

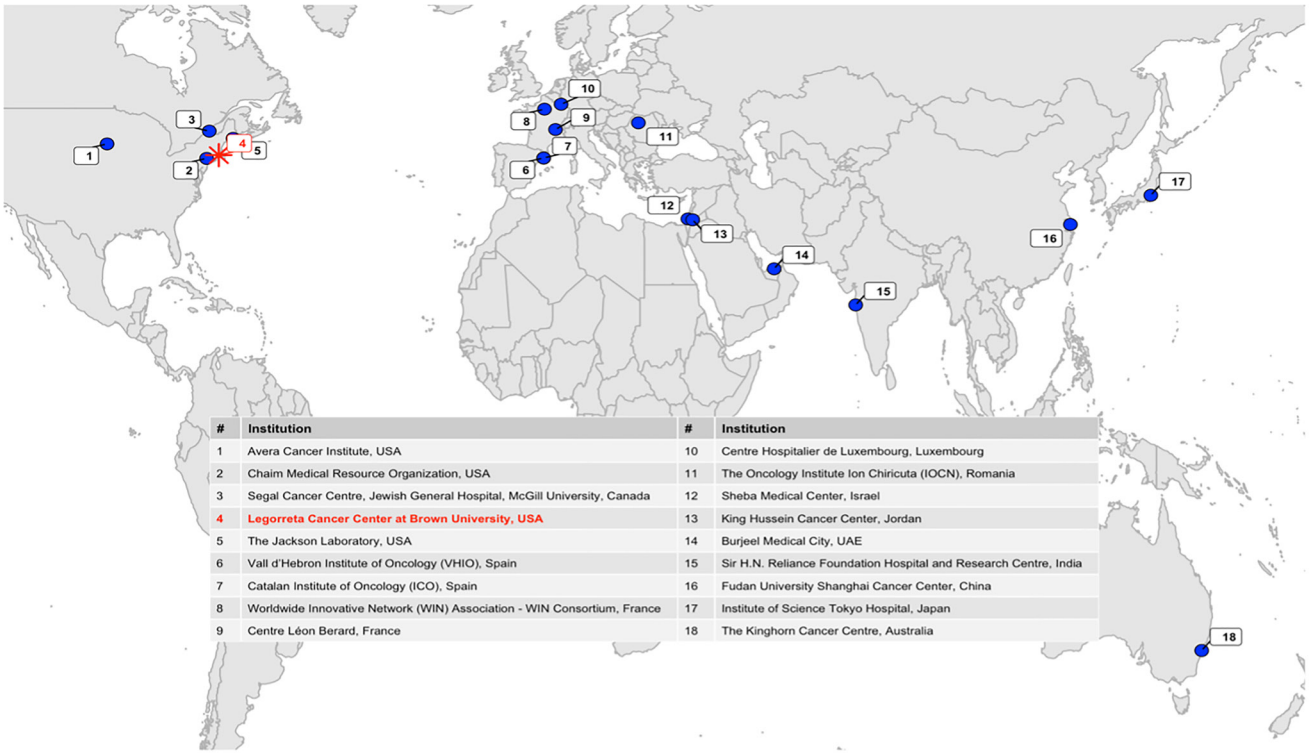
Histological analysis of the brain tissue revealed high-grade diffuse astrocytoma with epithelial component, which was histologically consistent with GBM.

The patient underwent multiple molecular profiling assessments, as outlined in Table 1. The pathology report performed by the treating institution included immunohistochemistry (IHC) results that were positive for ATRX, GFAP, CD34 and synaptophysin. No evidence of *BRAF-V600E* and *H3-K27M* mutations were found. The methylation profile indicated an *IDH*-wild type tumor, matching the GBM diagnosis [4], and consistent with the retained ATRX positive finding. Also, the tissue was unmethylated for *MGMT* promoter. Results of fluorescence *in situ* hybridization (FISH) test revealed *EGFR* amplification and heterozygous deletion of *CDKN2A*. Since *CDKN2A* and *MTAP* are located adjacent to each other on chromosome 9p21 and are frequently co-deleted, *MTAP* loss could not be excluded based on the available molecular findings [34]; however, *MTAP* expression was not assessed by IHC in this case.

A formalin-fixed paraffin-embedded (FFPE) tissue sample was tested by the Oncomine Comprehensive Next-Generation Sequencing (NGS) assay (80% neoplastic content), confirming *EGFR* amplification. New findings from the Oncomine test included *CDKN2A* frameshift deletion and amplification of *MDM2* and *PTCH1*.

A fresh frozen brain tissue sample was also analyzed by BostonGene (57% neoplastic content), showing a low tumor mutational burden (TMB) and microsatellite stability (MSS). Consistent with previous results, the BostonGene test confirmed unmethylated *MGMT* promoter, *EGFR* amplification, *CDKN2A* loss, and *MDM2* amplification. New discoveries included *EGFR* loss of heterozygosity and *HMGA2* amplification. The tumor microenvironment (TME) showed moderate PD-L1 expression and significant immune infiltration with a high number of CD4 T-cells, CD8 T-cells and T-regs, while angiogenesis and extracellular matrix gene signatures were low.

Additionally, the New York Genome Center conducted another molecular profiling assessment, which involved whole-genome sequencing of DNA from FFPE brain tissue and matched blood, as well as RNA transcriptome sequencing of FFPE brain tissue. The TMB was low, consistent with previous tests, but the assessment indicated microsatellite instability (MSI), in contrast to the MSS result from the BostonGene test. This discordance was not resolved by orthogonal testing, as IHC for mismatch repair proteins or another validated MSI/MMR assay was not performed. The *CDKN2A* frameshift mutation was also detected here, along with a new missense mutation in *KMT2C*. Notably, the variant allele frequency (VAF) for *KMT2C* was 10%, below the assay's



#	Institution	#	Institution
1	Avera Cancer Institute, USA	10	Centre Hospitalier de Luxembourg, Luxembourg
2	Chaim Medical Resource Organization, USA	11	The Oncology Institute Ion Chiricuta (IOCN), Romania
3	Segal Cancer Centre, Jewish General Hospital, McGill University, Canada	12	Sheba Medical Center, Israel
4	Legorreta Cancer Center at Brown University, USA	13	King Hussein Cancer Center, Jordan
5	The Jackson Laboratory, USA	14	Burjeel Medical City, UAE
6	Vall d'Hebron Institute of Oncology (VHIO), Spain	15	Sir H.N. Reliance Foundation Hospital and Research Centre, India
7	Catalan Institute of Oncology (ICO), Spain	16	Fudan University Shanghai Cancer Center, China
8	Worldwide Innovative Network (WIN) Association - WIN Consortium, France	17	Institute of Science Tokyo Hospital, Japan
9	Centre Léon Berard, France	18	The Kinghorn Cancer Centre, Australia

Figure 1: WIN Consortium International Molecular Tumor Board participants. The figure highlights 18 institutions participating from 13 countries worldwide (blue dots), with the patient discussed in the MTB originating from USA (red Asterisk).

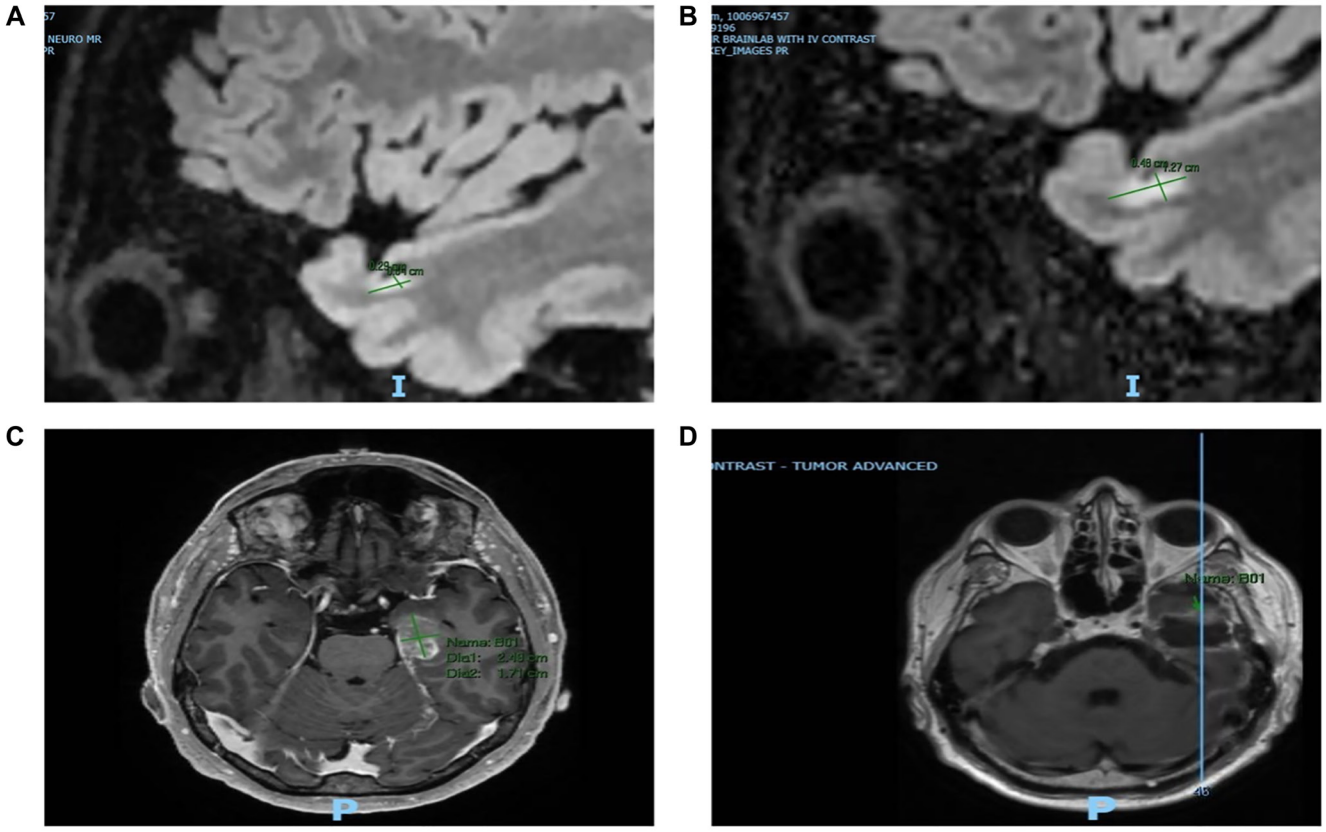


Figure 2: MRI brain scan images. (**A**) February 2023 - A mass measuring 0.29 × 0.04 cm in the left temporal lobe. (**B**) June 2023 - The mass has enlarged to 1.27 × 0.48 cm in the left temporal lobe. (**C**) June 2023 – A hyperintense mass in the left medial temporal lobe, measuring 2.49 × 1.71 cm, infiltrating the hippocampus, amygdala, and anterior temporal lobe. (**D**) June 2023, post-surgery – Nodular enhancement on the resection site, with a small residual mass not excluded.

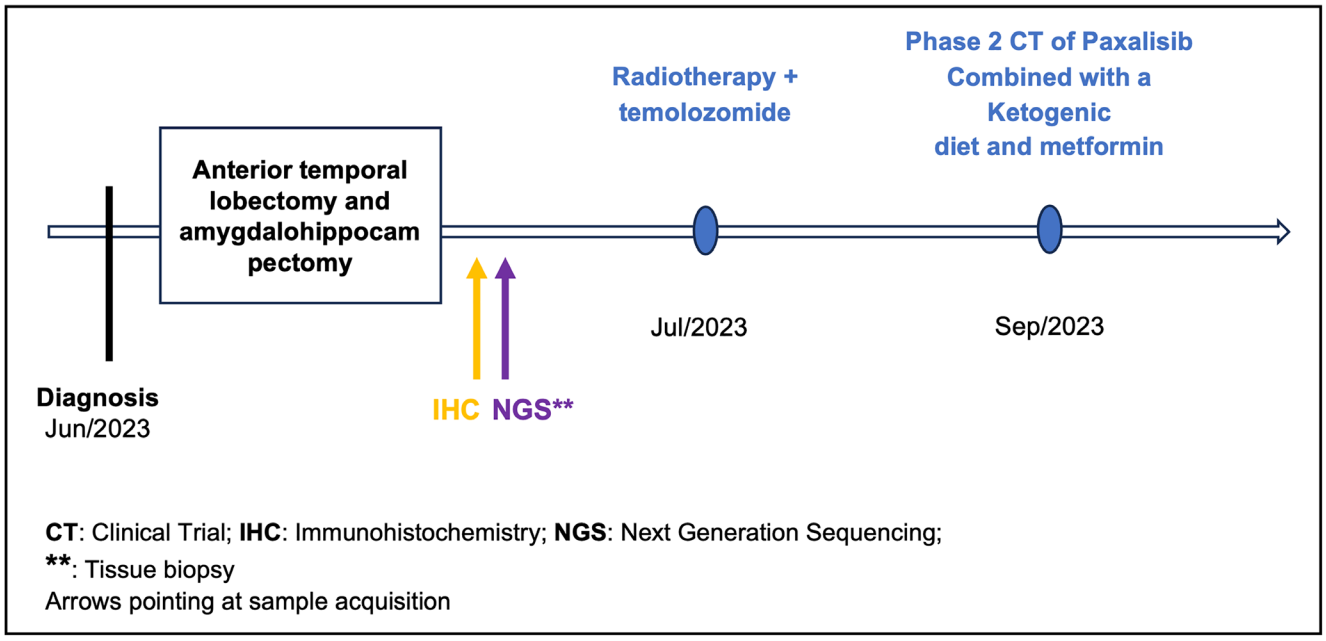


Figure 3: Treatments and molecular tests timeline. The figure outlines the treatments and molecular tests the patient has undergone throughout his medical history.

Table 1: Molecular alterations

Date of testing		June/2023	June/2023	June/2023	June/2023
Sample		Tissue	Tissue	Tissue	Tissue + Blood
Laboratory		On-Site	Oncomine Comprehensive	BostonGene	New York Genome Center
TMB (mutations/mb)				1.57 (low)	1.23 (low)
Microsatellite Status				Stable	Unstable
Mutations (MAF)	CDKN2A c.114delC,p. Asn39fs		+ Frameshift deletion 53.8%		+ Frameshift deletion 49%
	EGFR		N/A		
	KMT2C c.5053G>T,p. Ala1685Ser				+ Missense mutation 10%
Amplifications (CN)	EGFR	+	+ 116.28	+ >6	
	MDM2		+ 73.61	+ >6	
	PTCH1		+ 7.4		
	HMGA2			+ >6	
IHC tests	ATRX	+			
	GFAP	+			
	CD34 and synaptophysin	+			
	BRAF-V600E	−			
	H3-K27M	−			
Other findings	MGMT Promoter Methylation	Unmethylated		Unmethylated	
	Methylation Profile	IDH-WT			
	Heterozygous deletion	CDKN2A			
	Tumor microenvironment			• Medium PDL1. • High CD4 and CD8 T-cells. • High T-regs. • Low ECM gene signature.	

Data is provided where available. Only pathogenic alterations are included, and variants of unknown significance (VUS) are not included. Abbreviations: CN: copy number; ECM: extracellular matrix; IHC: immunohistochemistry; TMB: tumor mutations burden; VAF: variant allele frequency; WT: wild-type.

detection limit of 15%, so the mutation was confirmed by RNA sequencing. Additional genomic alterations are listed in Supplementary Tables 1 and 2.

In July 2023, the patient reported a slight decrease in sensation in his right leg compared to the left. At that point, he began chemotherapy treatment with temozolomide (75 mg/m^2) and radiotherapy to the tumor bed for six weeks, during which no progression was detected. However, given the post-surgical treatment setting, response to temozolomide could not be definitively assessed separately from the effects of surgery and radiotherapy. Although temozolomide is part of standard first-line therapy for GBM, the patient's unmethylated MGMT promoter status suggested a reduced likelihood of benefit from temozolomide compared with MGMT-methylated disease. In September 2023, the patient enrolled in a phase II clinical trial for newly diagnosed and recurrent GBM, receiving paxalisib (PI3K/mTOR inhibitor) combined with ketogenic diet and metformin. Trial enrollment was pursued as an investigational post-chemoradiotherapy strategy in the context of high-risk MGMT unmethylated GBM and the need for additional therapeutic approaches beyond standard treatment. The rationale for the paxalisib treatment was based on the frequent *PTEN* alterations in brain tumors and the common aberrations in the PI3K pathway in such tumors.

At the time of the MTB discussion, the patient was in remission while undergoing treatment with paxalisib, the ketogenic diet, and metformin, and he was considering a personalized neoantigen vaccine therapy in Germany (https://classic.clinicaltrials.gov/ct2/show/NCT05356312).

DISCUSSION

The WIN Consortium International MTB discussed potential therapy options in the event of disease progression, acknowledging that relapse is likely to occur at some point. The MTB considered the patient's comprehensive molecular profiling while also taking into account that the patient is also considering pursuing a vaccine therapy.

One limitation of the molecular interpretation was the discordant microsatellite status reported by two assays, with the BostonGene test indicating MSS and the New York Genome Center assessment indicating MSI. This discordance may reflect differences in assay methodology, tumor sampling, or intratumoral heterogeneity, as GBM can show substantial spatial molecular features [35]. Because MSI/MMR status may have therapeutic implications, particularly when considering immune checkpoint blockade (ICB), this result should be interpreted with caution. Orthogonal confirmation by IHC for mismatch repair proteins or another validated MSI/MMR assay would be required before using MSI status to guide treatment decisions.

The amplification of both *MDM2* and *EGFR* poses challenges for the patient when considering immune checkpoint inhibitor options, as these alterations are associated with resistance and hyperprogression [36]. While *EGFR* is less strongly linked to ICB related hyperprogression than *MDM2*, its alteration is still closely associated with resistance [37].

ERAS-801, an *EGFR* inhibitor with high central nervous system penetration being investigated in the THUNDERBBOLT-1 phase I study for recurrent GBM, recently received FDA fast-tracked status, and could have been a potential option if it was still open for enrollment [38, 39]. Alternatively, any available clinical trials offering *EGFR* inhibitors for this indication could be considered.

MDM2 amplification has been linked to suppression of the cytotoxic immune response to tumors, with studies showing its role in hyperprogression following ICB [37, 40, 41]. This amplification is also recognized as a poor prognostic factor across multiple cancer types [42], including GBM. *MDM2* is likely a driver in this patient's tumor and may pose challenges for the immune system's ability to fight the tumor, including in the context of potential vaccines, which are often given together with anti-PD-1 agents. Residual tumor cells with *MDM2* amplification could evade immune detection and become resistant to immune cell attack. In a pan-cancer analysis of ICB, both *MDM2* and *MDM4* amplifications were associated with poor outcomes in TP53-wildtype breast cancer. However, among ICB-treated non-small cell lung cancer (NSCLC) patients, *MDM4* amplification was associated with reduced survival [42]. A preclinical study demonstrated that an *MDM2* inhibitor (AMG-232) can enhance T-cell mediated killing and provide additional benefits when combined with immune checkpoint inhibitors like pembrolizumab, further boosting T-cell activity [40, 43]. Moreover, *MDM2* and *MDM4* amplification has been observed in brain cancers as well as in metastases to the brain from other primary cancers [44, 45]. In this context, *MDM2* inhibition may represent a biologically relevant therapeutic strategy; however, no *MDM2* inhibitor is currently approved for GBM, and access would generally require enrollment in a clinical trial. Therefore, *MDM2* inhibitors such as navtemadlin, idasanutlin, milademetan, or other agents should be considered investigational in this setting. Clinical trials evaluating MDM2 inhibition in GBM or in molecularly selected MDM2-amplified solid tumors may provide potential route for access, although trial availability, eligibility criteria, CNS activity, and the ability to combine with other matched therapies would need to be assessed at the time of relapse. Examples of clinical trials evaluating MDM2-pathway inhibition in GBM or molecularly selected tumors are summarized in Supplementary Table 3.

Tailored drug combinations could also be considered at the time of relapse to target both *EGFR* amplification and *CDKN2A* loss, which are commonly observed in GBM patients. The presence of *CDKN2A* loss raises the possibility of concurrent *MTAP* loss because of their proximity on chromosome 9p21 [34]. Therefore, orthogonal assessment of *MTAP* expression by IHC could be considered in the future, as confirmation of *MTAP* loss may support consideration of clinical trials evaluating PRMT5 inhibitors or other *MTAP*-directed synthetic-lethality approaches [46–48].

This strategy of personalized combination therapies builds upon the I-PREDICT and WINTHER trials [49–53] and is further supported by reports of exceptional responders in high-grade gliomas, highlighting the promise of biomarker-matched targeted therapy and the need for prospective evaluation [54]. For patients with *EGFR* amplification, therapy could include a small molecule inhibitor, such as osimertinib or lapatinib, combined with an antibody such as cetuximab, as this approach has shown synergistic effect both preclinically and clinically [55, 56]. Although the use of antibodies and some small molecule targeted therapies in GBM may be questioned due to concerns about their ability to cross the blood-brain barrier, many GBM patients already have a disrupted barrier [57, 58], which may actually facilitate intratumoral exposure to both antibodies and targeted agents with otherwise limited central nervous system penetration. The combination of osimertinb or lapatinib with cetuximab should be paired with abemaciclib (*CDK4* and *CDK6* inhibitor), which is known to cross the blood-brain barrier [59]. The rationale for this combination lies in the fact that *CDKN2A* loss results in dysregulation of the p16-CDK4/6-RB pathway and increased *CDK4/6* activity [60, 61]. When considering this novel combination, initial doses of the three agents

should be reduced by about half to ensure the patient's tolerance. In addition, the patient should initially be monitored weekly through clinic visits and laboratory tests, including complete blood count with differential, platelet count and metabolic profile, to assess toxicity and determine whether dose adjustments are necessary.

A theoretical combination involving an *MDM2* inhibitor, an *EGFR* inhibitor, and ICB was also discussed, primarily in reference *to PD-1*/*PD-L1* inhibition rather than *CTLA-4* blockade or other forms of immunotherapy. Because *MDM2* inhibitors are investigational and are not currently approved for GBM, such a strategy would only be feasible if an *MDM2* inhibitor were available through a clinical trial that permitted combination therapy, through expanded access, or through another appropriate regulatory pathway. This combination raises an important question: should *PD-1*/*PD-L1* blockade be administered simultaneously with both *EGFR* and *MDM2* inhibitors, and could this approach possibly overcome the resistance or accelerated progression that can occur with ICB in the presence of *EGFR* or *MDM2* alterations? *MDM2* is known to inhibit, or at least reduce, T-cell-mediated tumor cell killing, independent of ICB [40, 41]. Thus, combining *MDM2* inhibitor with immunotherapy could also enhance T-cell activity in tumors with *MDM2* amplifications. Notably, hyperprogression related to *MDM2* and *EGFR* alterations has been specifically observed with anti-*PD-1* agents as immunotherapy [37]. This raises the question of whether resistance and hyperprogression associated with *MDM2* and *EGFR* alterations, which have been mainly described in the context of *PD-1*/*PD-L1* ICB, would also extend to *CTLA-4* or other immunotherapeutic approaches. The mechanism responsible for immunotherapy related resistance or hyperprogression in the presence of *EGFR* or *MDM2* alterations remains unknown.

An alternative treatment option, teserpaturev (Delytact), which is currently only available in Japan, may be considered if the patient was willing to travel. This is a genetically engineered herpes simplex virus type I (strain F) in which the α47 gene and both copies of the γ34.5 gene have been deleted, and the infected cell protein 6 (ICP6) gene has been inactivated by the insertion of the lacZ gene from Escherichia coli. Teserpaturev injection, when intratumorally administered to patients with malignant glioma, is expected to produce two main effects: (1) the mutant virus selectively replicates in tumor cells, causing destruction of the infected cells through the replication process, exerting a cytocidal effect, and (2) the treatment stimulates the induction of tumor-responsive T cells, which activates antitumor immunity and thus prolongs the survival of patients with malignant glioma [62]. The BostonGene TME profile may provide additional context for this strategy. The report suggested a T-cell-infiltrated TME, with increased CD4+ and CD8+ T-cell infiltration, intermediate PD-L1 expression, and relatively low angiogenesis and extracellular matrix signature, suggesting a microenvironment that may be relatively permissive to immune-cell infiltration. These features could support the biological rationale of an immune-activating local therapy such as teserpaturev, whose proposed mechanism includes induction of tumor-responsive T cells. However, the concomitant abundance of regulatory T cells suggests a counter-regulated immunosuppressive component that could limit effective antitumor immunity. Therefore, the TME profile provides biologic context supporting cautious consideration of immune-modulating approaches, but should not be interpreted as sufficient evidence to establish expected clinical benefit from teserpaturev. There was also discussion about using circulating tumor DNA (ctDNA) to monitor the patient's recurrence. However, some studies suggest that blood-derived ctDNA in GMB patients almost entirely reflects clonal hematopoiesis of indeterminate potential (CHIP) rather than tumor derived DNA) [63]. These findings underscore the challenges associated with using ctDNA to predict relapse in brain tumor patients.

Overall, the MTB prioritized clinical trial enrollment at relapse, particularly trials evaluating *EGFR*-targeted therapy, *MDM2*-pathway inhibition, immune-modulating strategies, or rational biomarker-matched combinations. In the absence of a suitable trial, the leading personalized therapeutic considerations included *EGFR*-directed therapy combined with *CDK4/6* inhibition to address *EGFR* amplification and *CDKN2A* loss, while *MDM2*-directed approaches remained investigational and dependent on clinical trial or other regulated access. This case highlights how international MTBs can integrate clinical context, genomic alterations, and TME features to identify novel matched therapeutic options for patients with GBM.

AUTHOR CONTRIBUTIONS

W.S.E-D. contributed with investigation, data curation and resources. W.S.E-D. and R.K. contributed with conceptualization and ensured supervision; F.W. and S.M. contributed to visualization; W.S.E-D., R.K., F.W., C.B., and S.M. wrote the original draft of the manuscript; C.B. contributed to the project management; and all co-authors contributed to discussion, writing-review and editing.

CONFLICTS OF INTEREST

W.S.E-D. is Chair of the Worldwide Innovative Network (WIN) Association – WIN Consortium and the Scientific Founder of Oncoceutics, Inc. (acquired by Chimerix, Inc.), SMURF-Therapeutics, and p53-Therapeutics. He was also a founder and shareholder of Resurrect Therapeutics. He receives or has received recent funding from NIH/NCI, American Cancer Society, The Warren Alpert Foundation, AACR-Novocure, D&D Pharmatech, Chimerix, AstraZeneca, and Actuate

Therapeutics. W.S.E-D. serves as a co-chair and on the Executive Committee of the Caris Life Sciences Precision Oncology Alliance. He serves on the Scientific Advisory Board (uncompensated) of Ocean Biomedicals and American Cancer Society BrightEdge, hold stocks in Jazz Pharmaceuticals and RVMD, and holds equity in Global Cancer Technology. He also serves as co-Editor-in-Chief of Oncotarget, the journal that invited this manuscript in a Collection of articles on Precision Oncology. W.S.E-D. was not involved in the peer review of this manuscript or the decision to accept it.

C.B. and F.W. are full-time employees of Worldwide Innovative Network (WIN) Association – WIN Consortium.

S.M. receives consultancy from Worldwide Innovative Network (WIN) Association – WIN Consortium.

R.K. is Chief Medical Officer of the Worldwide Innovative Network (WIN) Association – WIN Consortium and has received research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, Medimmune, Merck Serono, OmniSeq, Pfizer, Sequenom, Sysmex, Takeda, and TopAlliance and from the NCI; as well as consultant and/or speaker fees and/or advisory board/consultant for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Inc., Biological Dynamics, Caris, Daiichi, Datar Cancer Genetics, EISAI, EMD Serono, EOM Pharmaceuticals, Iylon, Jackson Laboratories, LabCorp, Lanauria Therapeutics, Merck, NeoGenomics, Neomed, Pfizer, Precirix, Prosperdtx, Quanta Therapeutics, Recordati, Regeneron, Roche, TD2/Volastra, Turning Point Therapeutics, X-Biotech; has an equity interest in CureMatch Inc.; serves on the Board of CureMatch and CureMetrix and XZOM, and is a co-founder of CureMatch.

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ETHICAL STATEMENT AND CONSENT

Investigation has been conducted in accordance with the ethical standards and according to the Declaration of Helsinki and according to national and international guidelines. Informed consent was obtained from the patient to review his clinical data during the WIN Consortium International MTB and to re-use his data for educational and publication purposes as well as future cancer research.

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Case Report WIN-MTB-2024001 – WIN International Molecular Tumor Board: A 55-year-old male with glioblastoma exhibiting amplifications in MDM2 and EGFR

SUPPLEMENTARY MATERIALS

Supplementary Table 1: Genomic alterations detected by New York Genome Center

Chromosome	Start base position	End base position	Size (bp)	Genes	Type
4p16.3q12	68,596	52,936,603	52,868,008	RHOH, PHOX2B, FGFR3, SLC34A2, TEC, WHSC1, N4BP2	Loss
4q12	52,936,604	57,122,400	4,185,797	PDGFRA, FIP1L1, CHIC2, KDR, KIT	Gain
4q12q22.1	57,122,401	88,601,696	31,479,296	PTPN13, AFF1	Loss
4q22.1q28.3	91,280,241	136,837,039	45,556,799	IL2, RAP1GDS1, TET2, FAT4, LEF1	Loss
4q31.23q31.3	150,984,070	153,524,445	2,540,376	FBXW7	Loss
4q32.1q35.2	158,853,972	191,044,164	32,190,193	CASP3, DUX4L1, FAT1	Loss
6p25.3p25.1	147,786	6,591,695	6,443,910	IRF4	Loss
6p11.1q27	58,779,884	171,049,448	112,269,565	SGK1, PRDM1, GOPC, RSPO3, BCLAF1, TNFAIP3, EZR, FGFR1OP, EPHA7, CCNC, FOXO3, ROS1, PTPRK, MYB, ECT2L, ESR1, QKI, MLLT4, ARID1B	Loss
7p22.3q36.3	10,005	159,128,563	159,118,559	HNRNPA2B1, HOXA9, HOXA11, HOXA13, SFRP4, CARD11, PMS2, RAC1, ETV1, JAZF1, FKBP9, IKZF1, EGFR, FAM131B, MNX1, ZNF479, ELN, GRM3, EZH2, SBDS, HIP1, AKAP9, POT1, SND1, SMO, CREB3L2, TRIM24, KIAA1549, TRRAP, CUX1, MET, BRAF, CNTNAP2, KMT2C, CDK6	Gain
7p11.2	54,768,637	55,519,865	751,229	EGFR	Gain
8p23.3p12	31,278	31,984,310	31,953,003	LEPROTL1, ARHGEF10, WRN, PCM1	Loss
8p12q24.3	35,266,842	146,303,880	111,037,039	WHSC1L1, IKBKB, FGFR1, ANK1, HOOK3, PLAG1, CHCHD7, HEY1, COX6C, MYC, RECQL4, TCEA1, RUNX1T1, PABPC1, EIF3E, RAD21, NDRG1, PREX2, NCOA2, NBN, CDH17, UBR5, EXT1, FAM135B, CNBD1, CSMD3, RSPO2	Loss
9p24.3p21.1	10,000	32,847,640	32,837,641	CD274, PDCD1LG2, PSIP1, CDKN2A, JAK2, NFIB, MLLT3, PTPRD	Loss
9p13.3q13	33,584,061	66,454,673	32,870,613	FANCG, PAX5	Loss
9q21.2	79,308,312	80,414,238	1,105,927	GANQ	Gain
10p15.3q26.3	63,446	135,242,577	135,179,132	KLF6, NCOA4, PRF1, NUTM2B, NUTM2A, NFKB2, GATA3, KIF5B, RET, A1CF, BMPR1A, FAS, CYP2C8, LARP4B, ABI1, ZEB1, CCDC6, TET1, KAT6B, PTEN, CPEB3, TLX1, SUFU, TCF7L2, KIAA1598, FGFR2, MGMT, MLLT10, NT5C2, VTI1A	Loss
11q13.1	64,752,262	65,479,660	727,399	MALAT1	Gain
12q14.2q14.3	64,868,628	67,656,829	2,788,202	WIF1, HMGA2	Gain
12q15	68,769,939	69,753,356	983,418	MDM2	Gain
12q15	70,736,230	71,019,838	283,609	PTPRB	Gain
14q11.2q13.1	20,424,466	34,946,863	14,522,398	CCNB1IP1, ARHGAP5	Loss
14q21.1q21.3	38,036,685	49,817,055	11,780,371	FOXA1	Loss
14q23.1q24.2	58,157,154	73,053,178	14,896,025	SIX1, HIF1A, MAX, RAD51B, GPHN	Loss
15q11.1q26.3	20,000,005	102,521,290	82,521,286	NUTM1, FES, KNSTRN, CASC5, B2M, USP8, POLG, IDH2, BUB1B, MYO5A, TCF12, MAP2K1, SMAD3, PML, NTRK3, CRTC3, BLM, CHD2	Loss
22q13.1	38,776,969	40,523,778	1,746,810	APOBEC3B, PDGFB	Loss

Supplementary Table 2: Somatic variants of uncertain clinical significance detected by New York Genome Center

Gene	Ensemble ID	Chr :Position	Variant	Type	VAF
ATG2B	ENST00000359933	chr14:96777947	c.3922C>T,pArg1308Cys	NON_SYNONYMOUS_CODING	39%
C9orf171	ENST00000343036	chr9:135374822	c.467A>T,p.Tyr156Phe	NON_SYNONYMOUS_CODING	57%
CADPS2	ENST00000449022	chr7:122303397	c.679delA,p.Ser227fs	FRAME_SHIFT	21%
CASKIN2	ENST00000321617	chr17:73500047	c.1468-4G>A,NA	SPLICE_SITE_REGOIN+INTRON	43%
CNNM1	ENST00000356713	chr10:101090267	c.1123C>A,p.Pro375Thr	NON_SYNONYMOUS_CODING	16%
CTD-2162K18.4	ENST00000590750	chr19:37266387	c.233T>C,p.Val78AIa	NON_SYNONYMOUS_CODING	50%
CYP2A7	ENST00000301146	chr19:41386153	c.494-4G>A,NA	SPLICE_SITE_REGOIN+INTRON	45%
DKKL1	ENST00000221498	chr19:49878137	c.581G>A,p.Arg194Gin	NON_SYNONYMOUS_CODING	31%
FAT3	ENST00000298047	chr11:92531590	c.5411A>T,p.Asp1804Val	NON_SYNONYMOUS_CODING	51%
GRIA2	ENST00000323661	chr4:158142482	c.-266A>T,NA	START_GAINED+UTR_5_PRIME	32%
HEPH	ENST00000519389	chrX:65478715	c.3092G>T,p.Gly1031Val	NON_SYNONYMOUS_CODING	18%
HSPG2	ENST00000374695	chr1:22155546	c.12019C>T,p.Pro4007Ser	NON_SYNONYMOUS_CODING	47%
JMJD4	ENST00000366758	chr1:227921714	c. 586G>A,p.Val196lle	NON_SYNONYMOUS_CODING	49%
KIAA0947	ENST00000296564	chr5:5464339	c.4892C>G,p.Pro1631Arg	NON_SYNONYMOUS_CODING	29%
MAST4	ENST00000404260	chr5:66430465	c.2350G>A,p.Val784Met	NON_SYNONYMOUS_CODING	19%
MROH2A	ENST00000389758	chr2:234737654	c. 4382G>A,p.Arg1461Gln	NON_SYNONYMOUS_CODING	45%
MS4A6E	ENST00000300182	chr11:60105244	c.178A>G,p.Ser60Gly	NON_SYNONYMOUS_CODING	54%
NLRP3	ENST00000336119	chr1:247588075	c.1330G>A,p.Val444lle	NON_SYNONYMOUS CODING	36%
NRF1	ENST00000311967	chr7:129330253	c.473A>G,p.Lys158Arg	NON_SYNONYMOUS_CODING	21%
OR2G3	ENST00000320002	chr1:247769291	c.404T>C.p.lle135Thr	NON_SYNONYMOUS_CODING	49%
OR5P2	ENST00000329434	chr11:7817666	c.824C>T,p.Thr275lle	NON_SYNONYMOUS CODING	50%
OR7G2	ENST00000305456	chr19:9213600	c.383T>C,p.Phe128Ser	NON_SYNONYMOUS_CODING	44%
PCDH20	ENST00000409186	chr13:61986988	c.1244C>A.p Ser415Tyr	NON_SYNONYMOUS_CODING	50%
PDZD8	ENST00000334464	chr10:119044515	c.1729C>G.p.Gln577Glu	NON_SYNONYMOUS_CODING	18%
PKHD1	ENST00000371117	chr6:51914979	c.2255C>T,p.Thr752Met	NON_SYNONYMOUS_CODING	54%
QKI	ENST00000361752	chr6:163983094	c.628_634dupAAATCAC,NA	SPLICE_SITE_DONOR+INTRON	44%
RAB39A	ENST00000320578	chr11:107799343	c.49T>A.p.Ser17Thr	NON_SYNONYMOUS_CODING	38%
RAPGEF2	ENST00000264431	chr4:160252975	c.1286G>C.p.Arg429Pro	NON_SYNONYMOUS_CODING	45%
ROGDI	ENST00000586504	chr16:4847751	c.514C>T,p.Arg172Cys	NON_SYNONYMOUS_CODING	58%
RSAD1	ENST00000258955	chr17:48557021	c.167G>A,p.Cys56Tyr	NON_SYNONYMOUS_ CODING	46%
SAMD4B	ENST00000314471	chr19:39871325	c.1748T>G,p.Leu583Arg	NON_SYNONYMOUS_CODING	16%
SCYL1	ENST00000270176	chr11:65302732	c.1265C>T,p.Ala422Val	NON_SYNONYMOUS_CODING	22%
STX2	ENST00000392373	chr12:131293256	c.281-7T>C,NA	SPLICE_SITE_REGION+INTRON	18%
SUCLA2	ENST00000378654	chr13:48547466	c.596C>A,p.Ser199Tyr	NON_SYNONYMOUS_CODING	52%
SV2B	ENST00000330276	chr15:91795210	c.613C>T,p.Arg205*	STOP_GAINED	76%
TMEM132C	ENST00000435159	chr12:128899621	c.430C>T,p.Arg144 Trp	NON_SYNONYMOUS_CODING	35%
TTN	ENST00000589042	chr2:179428474	c.82385C>T,p.Thr27462Met	NON_SYNONYMOUS CODING	18%
XDH	ENST00000379416	chr2:31606023	c.887-5C>T,NA	SPLICE_SITE_REGION+INTRON	59%

Abbreviation: VAF: variant allele frequency.

Supplementary Table 3: Examples of clinical trials evaluating MDM2-pathway inhibition relevant to GBM or MDM2-amplified tumors

Trial	Agent	Target	Population	Phase	Relevance
NCT03107780	Navtemadlin/ KRT-232/ AMG-232	MDM2 inhibitor	Newly diagnosed or recurrent GBM	Phase 0/I	GBM-specific trial evaluating MDM2 inhibition, including tumor penetration/pharmacodynamic activity
NCT03654716	ALRN-6924/ sulanemadlin	Dual MDM2/ MDMX inhibitor	Pediatric relapsed/refractory solid tumors, brain tumors, lymphoma, or leukemia	Phase I	Includes brain tumors; relevant to MDM2/MDMX pathway inhibition but not adult GBM-specific
NCT05012397	Milademetan	MDM2 inhibitor	Advanced or metastatic solid tumors refractory or intolerant to standard-of-care therapy, with wild-type *TP53*and *MDM2* copy number ≥8 by prespecified biomarker criteria	Phase II basket	Molecularly selected MDM2-amplified tumors; relevant to MDM2 amplification but not GBM-specific
NCT03449381	Brigimadlin/ BI 907828	MDM2 inhibitor	Advanced solid tumors	Phase Ia/Ib	Relevant as an investigational MDM2 inhibitor in solid tumors, but not GBM-specific; trial eligibility, CNS activity, and feasibility for GBM would require case-specific assessment