molecular tumor board

Durable Near-Complete Response to Olaparib Plus Temozolomide and Radiation in a Patient With *ATM*-Mutated Glioblastoma and *MSH6*-Deficient Lynch Syndrome

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INTRODUCTION

Glioblastoma (GBM) remains a life-limiting disease with a median overall survival of 14.6 months.[1] Prognosis is improved in patients who undergo gross total resection and those whose tumors demonstrate O6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation and isocitrate dehydrogenase (*IDH*) mutations.[2-4]

Given that GBM commonly recurs within 2 years, there is a clear rationale for improving upfront therapy. Poly (ADP-ribose) polymerase inhibitors (PARPi) represent one approach, as investigated in previous studies using olaparib.[5-7]

We describe a patient with an unresectable *MGMT* unmethylated, *IDH* wild-type GBM. Tumor genomic profiling and germline results provided rationale for the addition of olaparib to standard therapy. The patient had a remarkable response, with an ongoing near-total absence of radiographic disease 2 years beyond diagnosis. Her consent was obtained for publication of this article.

CASE

A 52-year-old female with suspected Lynch syndrome on the basis of family history and a personal history of endometrial cancer as well as premalignant breast and colon lesions presented with neurologic complaints. Magnetic resonance imaging revealed a 2.7 × 1.9-cm T2 hyperintense cortically based mass in the inferomedial right frontal lobe, which was determined to be unresectable because of bihemispheric involvement. *MGMT* promoter was unmethylated, and no *IDH* mutations were detected. The patient was enrolled in an observational clinical study (sponsored by Strata Oncology, Ann Arbor, MI), through which whole-exome and RNA sequencing on formalin-fixed paraffin-embedded tumor tissue revealed loss-of-function mutations in *ATM* and tumor protein 53 (*TP53*). The tumor was classified as tumor mutational burden (TMB) high, programmed death-ligand 1 (PD-L1) low, and microsatellite stable (MSS; Table 1). After completion of therapy, additional review of the patient's records revealed a germline *MSH6* loss-of-function mutation, which confirmed Lynch syndrome.

The genomic findings and high likelihood of Lynch syndrome, along with early-phase data suggesting safety and brain penetration, provided rationale for the treating oncologist to initiate olaparib with standard chemoradiation. Olaparib was dosed at 150 mg daily for 3 consecutive days each week during chemoradiation. After chemoradiation, the patient received 6 cycles of maintenance temozolomide. She was also treated with alternating tumor-treating fields (Optune; Novocure, St Helier, Jersey), an externally applied, low-intensity electromagnetic field treatment shown to improve survival by 4.9 months over maintenance temozolomide alone when used 18 hours per day.[8] Device compliance was limited, and treatment was discontinued after 1 month. She has received no additional therapy.

Treatment was well tolerated. Interval imaging showed continued tumor shrinkage (Fig 1). Two years since diagnosis, further reduction in size was observed, compatible with ongoing partial response by RECIST. The patient remains fully functional.

MOLECULAR TUMOR BOARD DISCUSSION

Given the excellent response in the setting of germline and somatic mutations in DNA repair genes, this patient was discussed at the institutional multidisciplinary molecular tumor board (MTB). The objective was to broaden the understanding of the impact of the mutations individually and collectively with respect to susceptibility to chemotherapy, radiation, and PARPi.

Germline *MSH6* p.F1088Sfs*2 Mutation; MSS

Pathogenic; loss of function (exon 5).

The presence of this mutation was not known at the time of treatment because it was not reported on the tumor sequencing report. Outside hospital records included this finding on germline testing performed by Ambry Genetics (Aliso Viejo, CA).

MSH6 is involved in DNA mismatch repair (Appendix Table A1). A deleterious mutation constitutes Lynch

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Sequencing Results

Mutation Type	Mutations Identified	Predicted Consequence	Pertinent Negatives	Sequencing Platform
Germline	*MSH6* p.F1088Sfs*2	Loss of function	*ATM*, *BRCA1*, *BRCA2*, *TP53*	NGS or Sanger sequencing by Ambry Genetics
Somatic	*ATM* p.G1016X (VAF 45%)	Loss of function	*MSH6*[a]	NGS by Strata Oncology
	TP53 p.R181H (VAF 39%)	Reduced function		
	TP53 p.R248Q (VAF 45%)	Loss of function		
	PD-L1 low (RNA expression score 7)			NGS (PD-L1 expression reported as an RNA expression score, predictive of TPS)
	MSS			NGS (on the basis of length variant allele counts at multiple microsatellite loci)
	TMB high (69 mutations/MB)			NGS (on the basis of noncoding and coding, synonymous and nonsynonymous, and single-nucleotide and multinucleotide variants present at > 10% VAF)

Abbreviations: MB, megabase; MSS, microsatellite stable; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; TPS, tumor proportion score; VAF, variant allele frequency.

[a]On initial report.

syndrome and results in high susceptibility to mutations in tumor suppressor and proto-oncogenes, which lead to a fourfold increased risk of primary brain tumors.[9,10] Germline *MSH6* mutations are rare in GBM. Most mutations are somatic, found almost exclusively after temozolomide therapy.[11] In this setting, they are associated with resistance to alkylating agents, hypothesized to be the dominant mechanism of acquired temozolomide resistance after therapy, likely because of failure of temozolomide-induced DNA damage to result in apoptosis in mismatch repair–deficient (dMMR) cells.[12-24] When *MSH6* mutations are present in treatment-naïve patients with *MGMT* methylated, otherwise chemosensitive tumors, treatment response is markedly attenuated.[13] Beyond treatment resistance, ongoing temozolomide exposure after *MSH6* inactivation leads to a hypermutator phenotype and tumor progression.[14-16] PARPi restore sensitivity to temozolomide in dMMR cells.[25] dMMR cells may also have increased resistance to radiotherapy.[26-28]

Lynch syndrome was not identified by somatic testing. Often, Lynch syndrome is discovered after a tumor is found to be microsatellite instability high (MSI-h) or dMMR on immunohistochemistry. *MSH6*-mutated brain tumors, however, are often not MSI-h by standard polymerase chain reaction testing, and immunohistochemistry is not standardly performed.[29] In this case, MSS status was determined from next-generation sequencing (NGS) on the basis of length variant allele counts at multiple microsatellite loci. While alternate NGS methods have demonstrated sensitivity and specificity in brain tumors, the performance of this specific methodology in GBM is unknown.[30,31] While deficient *MSH6* immunohistochemical staining would confirm a pathogenic mutation, intact staining would not rule out dMMR because some mutations result in intact expression of dysfunctional protein.[32-35]

The *MSH6* mutation was not reported by somatic testing because of its presence in a stretch of repeating cytosines, known as a homopolymer region. Determination of nucleotide calls in homopolymer regions is a common source of sequencing errors in NGS, regardless of the platform used. Most laboratories do not report findings from homopolymer regions because of the uncertainty in base calling that occurs when repeating identical bases incorporate during the same synthesis cycle.[27] After the germline *MSH6* mutation was discovered, Strata Oncology was able to detect the mutation in the tumor sample with 94% allele frequency.

ATM p.G1016X Mutation

Likely pathogenic; nonsense (premature stop codon in exon 20/63).

There were no reports of this mutation in the queried databases; however, it is a predicted loss-of-function mutation that is based on other pathogenic mutations in a similar gene region. *ATM* is mutated in < 5% of glioblastomas.[36]

ATM is involved in DNA damage response (DDR; Appendix Table 1). Unlike dMMR, which prevents damaged cells from undergoing apoptosis, decreasing treatment efficacy, *ATM* mutations increase cell vulnerability to cytotoxic therapy.[37] They are associated with increased platinum sensitivity and superior survival.[37,38] Tumors with loss-of-function *ATM* mutations have increased radiosensitivity.[39] ATM suppression in the setting of p53 deficiency sensitizes tumors to DNA-damaging chemotherapy and radiotherapy, whereas ATM suppression with intact p53 leads to a worse response.[40,41]

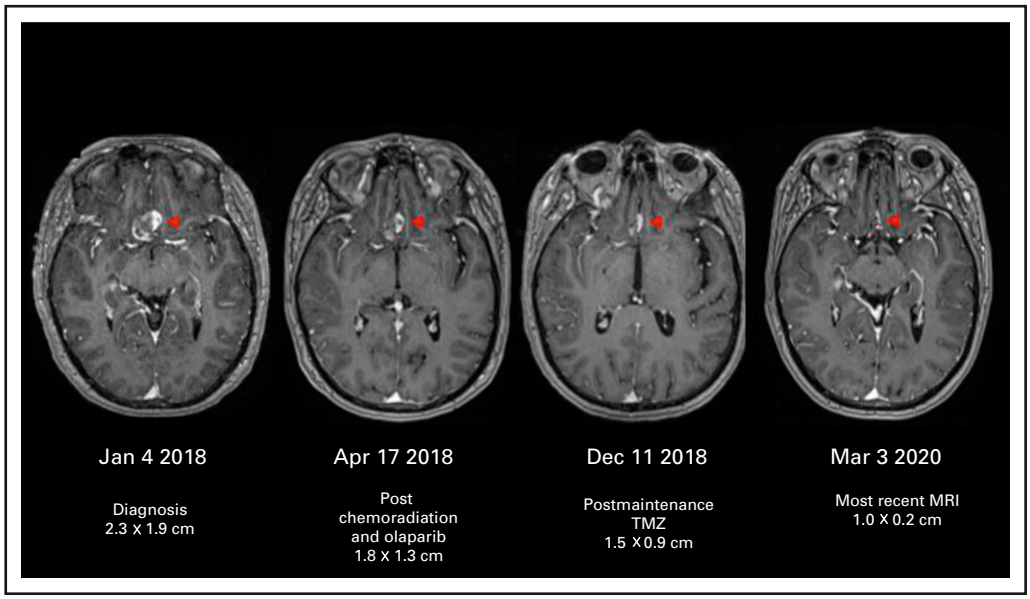

FIG 1. Magnetic resonance imaging (MRI) of glioblastoma at the time of diagnosis (left). Glioblastoma was noted to be smaller after initial treatment with chemoradiation and olaparib and was further reduced in size after maintenance temozolomide. On the most recent MRI (right), obtained > 14 months after completion of therapy, the tumor demonstrated further regression, compatible with a durable, near-complete treatment response. TMZ, temozolomide.

Inactivating mutations in *ATM* result in DDR-deficient tumors that are susceptible to synthetic lethality with DNA-damaging agents and PARPi.[42,43] In the absence of data, it may be predicted that a tumor both dMMR and DDR deficient is exceptionally unstable and susceptible to synthetic lethality, although the complexity of the roles of *MSH6* and *ATM* in DNA repair and apoptosis make this uncertain.

TP53 p.R181H and p.R248Q

Potential clinical significance; missense.

TP53 encodes the p53 tumor suppressor protein and is mutated in > 30% of GBMs[36,44] (Appendix Table A1). *TP53* p.R181H disrupts protein function but may allow partial residual protein activity.[45] *TP53* p.R248Q is reported in > 380 CNS tumors associated with protein loss of function.[45] As previously mentioned, p53-deficent cells may be particularly vulnerable to DNA-damaging treatment when an *ATM* mutation is present. Conversely, the combination of dMMR and p53-deficient cells worsens response because of failed phosphorylation of p53 and, thus, failed cell arrest after treatment-induced DNA damage.[46] In general, cancers with mutant p53 have reduced sensitivity to chemotherapy and radiation; however, there are many instances where mutant p53 has no effect or even enhances treatment effect.[47]

TMB High

TMB was determined from NGS and included noncoding and coding, synonymous and nonsynonymous, and single- nucleotide and multinucleotide variants present at > 10% variant allele frequency. The high TMB is likely secondary to the *MSH6* mutation and resultant tumor genome hypermutation.[14,48-50] In treated patients, hypermutation can result from exposure to alkylating agents.[51] The therapeutic implications of high TMB are not fully understood. Cancers with high TMB as a result of prior alkylator exposure are resistant to alkylators, but it is not clear whether tumors with high TMB from alternate etiologies share this resistance.[51]

PD-L1 Low

PD-L1 expression is used to predict response to immunotherapy. While frequently performed through immunohistochemistry, classification was based on sequencing results in this patient, using a score derived from the percent of maximum PD-L1 expression across tested tumor samples. This method is validated in a lung cancer cohort, but accuracy in GBM is less certain. PD-L1 is expressed on the surface of most glioma cells, with increased frequency in high-grade gliomas such as GBM, and variable detection is based on technique.[52-54] Of note, several studies demonstrated high PD-L1 association with worse survival in GBM.[55]

There are no currently approved drugs that target PD-L1 in GBM, although several trials are ongoing. Given the efficacy of programmed death 1 (PD-1)/PD-L1 blockade in dMMR tumors, immunotherapy could be considered.[56] The PD-1 inhibitor pembrolizumab is approved for all MSI-h tumors, making it a treatment option for patients with Lynch syndrome–associated cancers, which are typically MSI-h.

Rationale for Olaparib

PARP is involved in single-strand DNA break and base excision repair. PARP-1 nuclear staining supports its

expression in GBM.[57] Olaparib is a PARPi that impairs the DDR, increasing treatment-induced chromosomal instability, cell cycle arrest, and apoptosis.[58] In patients with germline *BRCA1/2* mutations that impair double-strand DNA break repair by homologous recombination, PARPi cause synthetic lethality with significant clinical benefit.[59-62] PARPi also have efficacy in tumors with mutations in DDR genes, including *ATM*, and in patients with neither a germline *BRCA* mutation nor other homologous recombination deficiency.[63,64]

PARPi have been used as monotherapy and in combination with radiation and chemotherapy to prevent the repair of treatment-induced DNA breaks, thereby promoting tumor cell death. PARPi increase sensitivity to temozolomide in cell and xenograft models of GBM.[65-67] This effect persists in *MGMT* unmethylated tumors.[68] PARPi also restore sensitivity to temozolomide in dMMR cells.[25,69] In addition, exposure to temozolomide before or concurrently with a PARPi increases the magnitude of DNA damage and led to complete regression of GBM cells in one study.[70] This treatment-sensitizing effect is not present in patients with temozolomide resistance, which suggests optimal incorporation in newly diagnosed GBM.[71]

There have been 3 phase I trials of olaparib with temozolomide and/or radiation in GBM. The OPARATIC trial confirmed tumor penetration and dosing schedule, with promising early results.[5,7] PARADIGM-2 investigated olaparib plus radiotherapy with or without temozolomide.[6,72] These studies support the addition of olaparib to temozolomide and radiation as safe, well tolerated, and potentially radiosensitizing.[5]

DISCUSSION

This patient had an excellent, durable response despite many factors that predict a poor prognosis. Incomplete resection, an unmethylated *MGMT* promotor, and wild-type *IDH* are associated with exceptionally poor outcomes. In addition, somatic *MSH6* loss-of-function mutations contribute to temozolomide resistance, glioma recurrence, and tumor progression, with similar effects expected from a deleterious germline mutation. While *ATM* mutations improve treatment sensitivity, particularly with concurrent TP53 mutations, it is unlikely that this would result in a sustained, near-complete response with standard chemoradiation alone. It is also unlikely that tumor-treating fields improved clinical outcome given short duration of use.

In addition to the general chemo- and radiosensitizing properties of PARPi, the ability for PARPi to restore sensitivity to temozolomide in dMMR and *MGMT* unmethylated tumors, as well as efficacy of PARPi in DDR-deficient tumors, strongly suggests that olaparib was an essential component of the treatment regimen. The likelihood of olaparib-induced synthetic lethality is high, through impairment of single-stranded DNA break repairs in a tumor already deficient in base-base substitution, single-base insertion, and single-base deletion mismatch repair as well as double-stranded DNA break repair.

Genomic sequencing allows identification of patients with targetable mutations who may benefit from currently available treatments, which are increasing rapidly.[73] This is particularly important for patients predicted to have poor outcomes with standard treatment and limited access to clinical trials.

Novel treatment approaches in the first-line setting are needed. MTB discussions broaden the understanding of the interplay among complex genomic alterations and serve as a forum to share cases of successful molecular targeting to inform the care of future patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Normal Gene Function

Gene	Function
MSH6	One of 4 major proteins in the DNA mismatch repair system Involved in the repair of base-base substitutions and single-base insertion or deletion mismatches Results in high susceptibility to mutations in tumor suppressor and proto-oncogenes, resulting in increased risk of many malignancies
ATM	Expressed in most tissues Key regulator of DNA damage response Serves as a tumor suppressor by initiating DNA damage checkpoint signaling after accumulation of double-stranded DNA breaks and initiating repair by homologous recombination
TP53	The most commonly mutated gene in human cancer A transcription factor that induces antitumor responses, including DNA repair and apoptosis, to cellular stress