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Metastatic Thymoma Harboring a Deleterious *BRCA2* Mutation Derives Durable Clinical Benefit from Olaparib

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Thymomas comprise a group of rare epithelial neoplasms of the anterior mediastinum. Whereas localized disease carries a favorable prognosis, the majority of patients with metastatic thymomas experience progression or recurrence over a 10-year period. Although targeted therapies have become standard of care in many malignancies, no clinically actionable mutations have consistently been identified in metastatic thymomas. Here, we describe a patient with an aggressive thymoma complicated by extensive pleural metastases. Over a 16-year period, she progressed on multiple treatment regimens. To identify additional treatment options, tissue from a pleural metastasis was sent for next-generation sequencing, revealing mutations in *BRCA2*, tyrosine kinase 2, and SET domain containing 2. Based on supporting evidence for poly (ADP-ribose) polymerase (PARP) inhibition in other BRCA-mutated tumors, the patient was started on the PARP inhibitor olaparib. She derived significant clinical benefit from treatment, with imaging showing overall stabilization of her disease. Here, we review the genotyping results of her tumor and discuss the functional and clinical significance of the mutations in her cancer as well as implications for managing patients with advanced BRCA-mutant thymomas. ***The Oncologist*** 2020;25:301–305

Key Points

- Targeted therapy has yet to enter the standard clinical management of metastatic thymomas.
- Patients with *BRCA2*-mutant thymomas may benefit from poly (ADP-ribose) polymerase inhibition.

Patient Story

A 60-year-old woman with a history of autoimmune hepatitis was diagnosed with both thymoma (World Health Organization type B) and papillary thyroid cancer in September 2003. At this time, she underwent resection of the thymoma as well as thyroidectomy followed by iodine-131 therapy for her thyroid cancer. Subsequent positron emission tomography imaging revealed mediastinal lymphadenopathy that was treated with external beam radiation. Two years after diagnosis, imaging identified a solitary left pleural lesion pathologically confirmed to be metastatic thymoma. When the lesion began enlarging after another 2 years, she was treated with sandostatin LAR and prednisone. Over the next 10 years, she was treated with multiple regimens, including a combination of carboplatin and etoposide, single-agent gemcitabine, CAP (cyclophosphamide, doxorubicin, and cisplatin), single-agent pemetrexed, capecitabine, and single-agent everolimus. She was also treated with the anti-insulin-like growth factor 1 receptor antibody cixutumumab on a clinical trial. Although cixutumumab halted significant progression for nearly 2 years, in each case she eventually progressed on treatment and ultimately developed extensive, bulky pleural metastases (Fig. 1).

To identify additional treatment options, a sample of her tumor was sent for FoundationOne next-generation sequencing (NGS), which identified mutations in *BRCA2*, tyrosine kinase 2 (*TYK2*), and SET domain containing 2 (SETD2). Although neither *TYK2* nor *SETD2* mutations are clinically actionable, cancers harboring inactivation mutations in *BRCA1* or *BRCA2* can respond to poly (ADP-ribose) polymerase (PARP) inhibitors [1]. Thus, the patient was started on olaparib and has remained on treatment for 14 months with overall stable disease. The patient had some reduction in tumor size (approximate of 20% reduction in the sum of the longest diameter for all target lesions); however, this did not meet RECIST criteria for a partial response (Fig. 1). Because of toxicity of nausea and fatigue, the patient has remained on dose-reduced olaparib and has since been able to wean down her pain regimen for management of pleural-based cancer pain.

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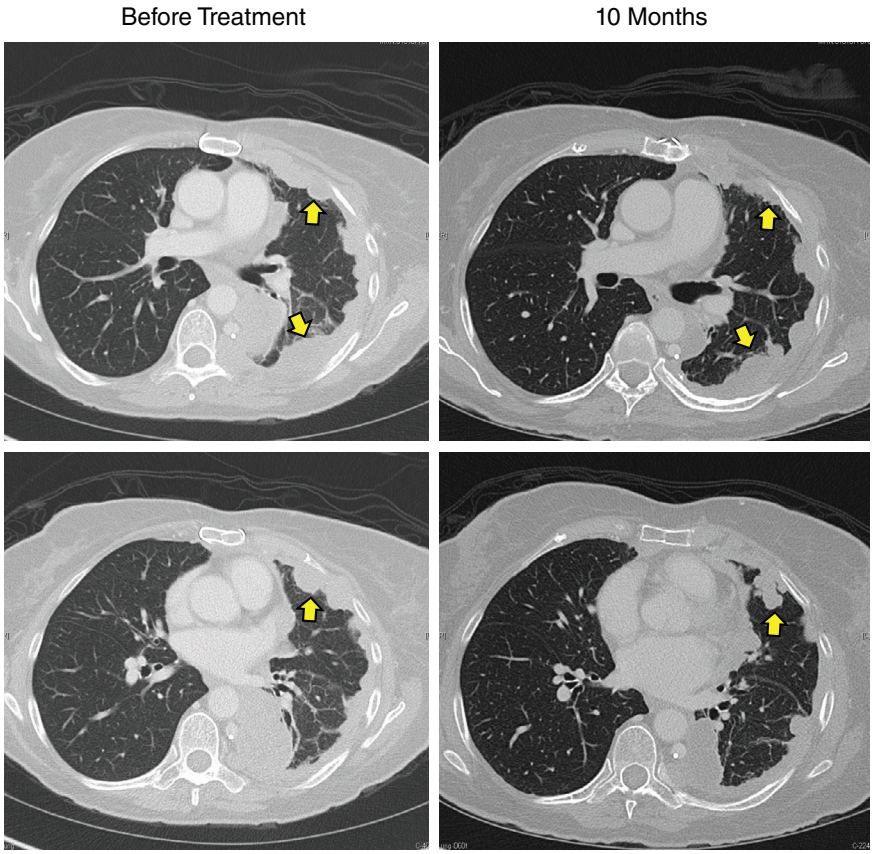

Figure 1. Computed tomography (CT) image of the chest before and after treatment. Baseline chest CT imaging showing extensive metastatic pleural-based nodules on the left (arrows) from metastatic thymoma, and overall stable disease after 10 months on olaparib.

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Precision medicine has become standard of care in several cancers. Tyrosine kinase inhibitors targeting the BCR-ABL fusion protein have revolutionized the treatment of chronic myeloid leukemia [2], and many therapies targeting molecular alterations have made an impact in breast cancer [3], non-small cell lung cancer, and others. Comprehensive genomic profiling is also changing the treatment paradigm toward molecularly targeted therapies, regardless of histology. For instance, a trial of 1,144 patients with any solid tumor evaluated in a large phase I program showed that patients harboring distinct molecular aberrations treated with a matched targeted therapy had significant improvements in overall response rates, time to treatment failure, and overall survival [4]. Although a patient with thymic carcinoma overexpressing mutant KIT responded to imatinib [5], such approaches have yet to enter the management of metastatic thymomas. Although thymic epithelial tumors frequently harbor mutations in *GTF2I*, *HRAS*, *NRAS*, and *TP53*, none of these mutations are clinically actionable at this time [6]. Similarly, although thymic epithelial tumors can be clustered into four genetic subtypes (38% *GTF2I* mutant, 33% T-cell enriched, 21% chromosome unstable, 8% chromosome stable), these groupings have yet to influence clinical practice [7].

Genotyping Results and Interpretation of Molecular Results

The FoundationOne Heme (Foundation Medicine, Cambridge, MA) assay is recommended by the manufacturer for thymomas, and it uses whole-genome shotgun library construction and hybrid-capture NGS to provide a focused interrogation of 406 genes and 31 introns, 265 RNAs associated with gene fusions, and information regarding the tumor mutational burden and microsatellite instability status. Briefly, massively parallel sequencing is done using 50–200 ng of DNA from a formalin-fixed paraffin-embedded tissue specimen. Hybrid-capture–selected libraries are sequenced to high uniform depth. FoundationOne sequences patient tissues to a median depth of approximately 500× unique coverage for DNA and RNA to an average of ∼6.9 million unique pairs (targeting >500× coverage by non–polymerase chain reaction duplicate read pairs, with >99% of exons at coverage >100×) using the Illumina HiSeq 2500 platform (Illumina, San Diego, CA, https://www.illumina.com). The panel identifies base substitutions, insertions and deletions, copy number alterations, and rearrangements [8]. In our patient, the results revealed three distinct mutations: *TYK2*^{V15A}, *SETD2*^{T1652fs*14}, and *BRCA2*^{K1800fs*16}.

Although each of these genes has been investigated in other cancers, none has a clearly defined role in thymic cancers. For instance, *TYK2* encodes for a nonreceptor JAK family tyrosine kinase with contradictory roles in inflammation. Although TYK2 is involved in interleukin (IL)-12 and interferon signaling, it also acts downstream of IL-10, and *Tyk2* knockout mice are unable to fully generate or respond to IL-10 [9, 10]. In cancer, the effects of TYK2 are similarly dichotomous. Although TKY2 is seemingly required for oncogenic fibroblast growth factor and epidermal growth factor signaling, TYK2 inhibition also appears to impede anticancer CD8 responses [11]. Interestingly, in

Table 1. Frequency of BRCA mutations in breast, ovarian, and thymic cancers in genomic databases

Data set	Sample size	*BRCA1* mutation	*BRCA2* mutation	Combined
Breast Cancer (MSK)	1,918	1.30%	3.18%	4.38%
Breast Cancer (METABRIC)	2,506	1.68%	1.80%	3.43%
Breast Cancer (TCGA)	1,066	2.53%	2.72%	5.07%
Ovarian Cancer (TCGA)	585	3.08%	2.56%	5.64%
Thymoma (TCGA)	124	0%	1.61%	1.61%

Abbreviations: METABRIC, Molecular Taxonomy of Breast Cancer International Consortium; MSK, Memorial Sloan Kettering; TCGA, The Cancer Genome Atlas.

murine models of allografted thymoma cells, genetic deletion of *TYK2* accelerated tumor development largely because of defects in CD8-mediated cytotoxicity [12]. Although interesting, the *TYK2*^{V15A} mutation has not been described in metastatic thymoma and its clinical significance is unknown.

SETD2 is a histone methyltransferase specific for lysine-36 of histone H3, and it is generally considered a tumor suppressor gene [13]. SETD2 is frequently altered in other malignancies, including approximately 30% of pediatric high-grade gliomas and 15% of clear cell renal cell carcinomas [14, 15]. In breast cancer, SETD2 is often downregulated, and lower SETD2 mRNA levels have been associated with both local and distant recurrences and poor survival [16]. Similarly, in B-cell acute lymphoblastic leukemia, loss of SETD2 is associated with chemotherapy resistance through loss of DNA damage recognition and impaired apoptotic signaling [17]. Although the specific *SETD2*^{T1652fs*14} frame-shift mutation observed in our patient has not been described, it occurs in the coding region for the SET domain (AA 1561-1667) and is likely analogous to the oncogenic *SETD2*^{R1625C} mutation [18]. However, the clinical significance of this mutation is unclear at this time.

Finally, our patient's tumor harbored a *BRCA2*^{K1800fs*16} frame-shift mutation with presumptive loss of function. After learning this, our patient was referred to a hospital geneticist. A blood sample was sent for *BRCA2* sequencing ($\pm$20 base pairs of adjacent intronic sequence) through Invitae, and this mutation was found to be germline, although the patient had no personal or family history of BRCA-associated cancers. Whereas the role of *BRCA2* in thymic cancers is largely unexplored, familial *BRCA1* and *BRCA2* mutations have been well described in breast and ovarian cancers. Although familial BRCA mutations drive only a relatively small percentage of these cancers, women with an inherited *BRCA1* mutation have a lifetime risk of 65%–80% of developing breast cancer and 37%–62% for ovarian cancer. Similarly, women carrying familial *BRCA2* mutations have a lifetime risk of 45%–85% for breast cancer and 11%–23% for ovarian cancer [19]. *BRCA1* and *BRCA2* are established tumor suppressor genes with distinct but important roles in DNA damage response and repair pathways [20]. Given the strong evidence supporting the use of PARP inhibitors in BRCA-mutant ovarian cancers [1], our patient was started on olaparib.

Functional and Clinical Significance of the Specific Mutation in Thymic Cancer

Little is known regarding the role of BRCA mutations in thymic cancers. To date, there has only been one reported case of a *BRCA1*-mutant metastatic thymoma, although this patient also developed thyroid and ovarian cancers during her lifetime [21]. A similar report described a family with frequent thymomas, potentially attributed to a germline translocation of the *BRCA2*-associated DNA repair protein RAD51B [22]. Another family was reported to have high rates of BRCA-linked breast/ovarian cancers and thymomas, although there was insufficient evidence to suggest a familial cancer syndrome caused by a single unifying mutation [23]. Of note, one series of 72 patients with thymoma or thymic carcinoma identified 1 patient with an ataxia-telangiectasia mutated (*ATM*) gene mutation, which can affect DNA repair mechanisms similar to BRCA mutations [24]. Interestingly, deletion of ATM *in vivo* is associated with spontaneous thymoma formation, whereas restoration of ATM expression reverses this phenotype [25].

Despite these observations, the frequency of BRCA mutations in thymomas is unknown. We therefore evaluated the established The Cancer Genome Atlas (TCGA) genomic database for mutations in either *BRCA1* or *BRCA2* using cBioportal [26, 27]. Of 123 thymoma patients, none had a *BRCA1* mutation, and two (1.61%) had mutations in *BRCA2* (Table 1). Of the observed *BRCA2* mutations, one consisted of a single amino acid substitution of unknown significance (M3118V) at the oligonucleotide/oligosaccharide-binding domain 3 (AA: 3052 – 3190). The second mutation was another substitution (R2336C) analogous to the oncogenic R2336H/P mutations [28, 29]. Our patient displayed a frame-shift mutation at the 1800 position (Fig. 2). While this particular mutation has not been characterized, several similar *BRCA2* frame-shift mutations have been identified in breast and ovarian cancers, many leading to missing or nonfunctional proteins [30]. However, given the small sample size of the TCGA cohort, the overall rate of oncogenic BRCA mutations in patients with thymomas remains unclear. Given the efficacy of olaparib in our patient, PARP inhibition in BRCA-mutated advanced thymomas warrants further investigation.

Potential Strategies to Target the Pathway and Implications for Clinical Practice

The mechanistic link between BRCA and PARP inhibition is well established. In brief, PARP is critical for single-strand break repair (SSBR) [31]. As such, PARP inhibitors such as olaparib prevent SSBR, leading to double strand breaks (DSBs). As *BRCA1* and *BRCA2* play key roles in DSB repair, namely, through homologous recombination [32], the use of olaparib in BRCA-mutant cancers leads to the accumulation of irreparable DSBs, ultimately causing cell death (Fig. 3). As discussed, this approach has shown significant efficacy in BRCA-mutant ovarian and breast cancers. Olaparib became the first Food and Drug Administration (FDA)-approved PARP inhibitor for patients with ovarian cancer with germline BRCA mutations in 2014. This was based on results

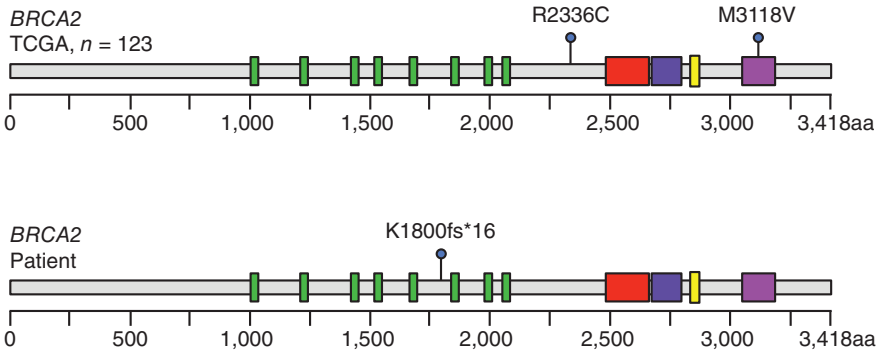

Figure 2. Known *BRCA2* mutations in patients with thymomas. Using the TCGA genomic dataset, we evaluated the known mutations of *BRCA1* and *BRCA2* in 123 patients with thymomas. Two patients harbored point mutations leading to single amino acid substitutions either at R2236C or M3118V at the oligonucleotide/oligosaccharide-binding, domain 3. In contrast, our patient had a frameshift mutation at the K1800 position, presumptively causing loss of function.
Abbreviation: TCGA, The Cancer Genome Atlas.

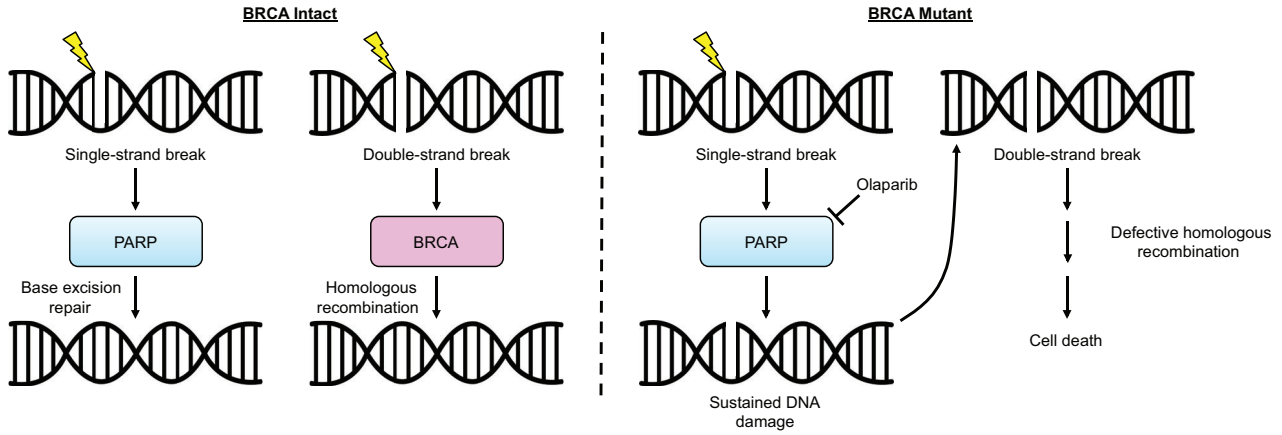

Figure 3. Schema describing the efficacy of PARP inhibition in BRCA-deficient tumor cells. Under physiologic conditions, DNA damage causing single-strand breaks (SSBs) leads to the rapid synthesis and recruitment of PARP. This promotes base excision repair, leading to repair of SSBs. In the case of double-strand breaks (DSBs), BRCA proteins interact with a variety of additional factors to promote repair via homologous recombination. In the setting of BRCA deficiency, the repair of DSBs is significantly impaired. Therefore, when PARP is inhibited with olaparib, cells lack the ability to repair SSBs, leading to the accumulation of DSBs. With no means of repairing these DSBs, cells eventually undergo programmed cell death.
Abbreviation: PARP, poly (ADP-ribose) polymerase.

from Study 19, a randomized, placebo-controlled trial showing a statistically significant improvement in both progression-free and overall survival [33]. Three PARP inhibitors, olaparib, rucaparib, and niraparib, have now been FDA approved as maintenance therapy after platinum-based chemotherapy in patients with ovarian cancer with either germline or somatic BRCA mutations or homologous recombination deficiency [34–36]. Olaparib was also FDA approved in 2018 for germline BRCA-mutated breast cancer based on the randomized, phase III OlympiAD trial showing an improved response rate (59.9% vs. 28.8%) and progression-free survival (7.0 vs. 4.2 months) compared with standard therapy [37].

Additionally, emerging evidence suggests there are additional mutations that may be indicative of homologous recombination deficiencies. These include alterations in *ATM*, *BARD1*, *BRIP1*, *CHEK2*, *FAAP20*, *FAN1*, *FANCE*, *FANCM*, *PALB2*, *POLQ*, *RAD51B*, *RAD51C*, and *RAD51D* [38–40]. Several of these mutations, namely, *ATM* and *PALB2*, have correlated with responsiveness to PARP inhibition in other malignancies including metastatic prostate cancer [41]. Given these results, and those seen in our patient, PARP inhibition warrants further investigation in other malignancies with germline or somatic BRCA mutations and potentially other mutations in DNA repair pathways.

Patient Update

After 14 months on treatment, the patient reports that her pain is under control without new chest/abdominal pain or other related symptoms. The first 3 months on olaparib were complicated by nausea and fatigue, but after a dose adjustment, the patient is tolerating treatment well. Her most recent imaging demonstrates overall stable disease with no new pleural-based nodules.

Glossary of Genomic Terms and Nomenclature

DSBs: double-strand breaks
NGS: next-generation sequencing
SSBs: single strand breaks
SSBR: single-strand break repair

Acknowledgments

We thank our patient for giving us the permission to include her clinical information in this report, and we wish

her well in her continued recovery. This work was supported by NIH F30CA236031 to D.R.P.

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Disclosures

The authors indicated no financial relationships.

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