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Clinical Benefit in Response to Palbociclib Treatment in Refractory Uterine Leiomyosarcomas with a Common *CDKN2A* Alteration

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

Key Words. Palbociclib • Uterine leiomyosarcoma • CDKN2A • Comprehensive genomic profiling • Targeted therapy • Precision medicine

Abstract

Background. Uterine leiomyosarcoma (uLMS) responds poorly to conventional chemotherapeutic agents, and personalized therapies have yet to be systematically explored. Comprehensive genomic profiling (CGP) can identify therapeutic targets and provide insight into the biology of this highly aggressive tumor. We report a case of uLMS treated with the CGP-matched therapy palbociclib, a CDK4/6 inhibitor, with sustained clinical benefit in this rare and deadly malignancy.

Materials and Methods. This study analyzed 279 clinically advanced/recurrent uLMS samples. Median patient age was 54 years (range, 23–83 years). DNA was extracted from 40 μm of formalin-fixed, paraffin-embedded sections, and CGP was performed on hybridization-captured, adaptor ligation-based libraries for up to 405 cancer-related genes plus introns from up to 31 genes frequently rearranged in cancer. Sequencing data were analyzed for base pair substitutions, insertions/deletions, copy number alterations, and rearrangements.

Results. CGP shows that 97.1% of uLMS harbor at least one alteration, and approximately 57% harbor alterations in one or more therapeutically targetable pathways. *CDKN2A* mutations that inactivate p16INK4a were identified in 11% of uLMS. We report the first demonstration of clinical benefit in response to palbociclib treatment for a uLMS patient with a *CDKN2A* mutation, resulting in disease stabilization and significant symptom reduction.

Conclusion. A patient with uLMS harboring a *CDKN2A* mutation experienced clinical benefit from treatment with palbociclib, and genomic analysis of 279 uLMS samples revealed that 19% of patients had mutations affecting the cyclin-dependent kinase (CDK) pathway. These observations provide a rationale for a clinical trial investigating treatment with CDK pathway inhibitors for uLMS harboring relevant genomic alterations. ***The Oncologist*** 2017;22:416–421

Implications for Practice: Comprehensive genomic profiling (CGP) of individuals with uterine leiomyosarcoma (uLMS) indicates that nearly 20% of patients may harbor a mutation affecting the cyclin-dependent kinase (CDK) pathway. The case presented demonstrates that a CDK inhibitory drug may provide clinical benefit to such individuals. Given the lack of curative therapies for uLMS, CGP could be performed on all cases of advanced uLMS and a CDK inhibitor could be recommended (preferably as part of a clinical trial) for individuals harboring a mutation in the CDK pathway.

Introduction

Uterine leiomyosarcoma (uLMS) is the most common uterine sarcoma, accounting for 1%–2% of uterine malignancies and with an incidence of approximately 0.55 cases per 100,000 women per year [1]. It is a rare, highly aggressive tumor arising from smooth muscle of the uterine wall that frequently recurs and spreads hematogenously, responding poorly to standard chemotherapy. Common treatment modalities include resection followed by adjuvant chemotherapy, but most patients recur. Randomized phase II trials of gemcitabine plus docetaxel have shown objective response rates (ORRs) of approximately 20%, with median progression-free survival of about 6 months and overall survival of approximately 18 months [2, 3]. Newer

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Table 1. Characteristics of genomically profiled uterine leiomyosarcomas

Characteristic	Value
Total cases	279
Patient age (yr)	
Average	54.25
Median	54
Range	23–83
Specimen sites (*n*)	
Primary	
Uterus	117
Metastatic	
Pelvis	27
Soft tissue	17
Abdomen	12
Peritoneum	8
Omentum	5
Other	93
Genomics (*n*)	
Cases with reportable alterations	271
Cases without reportable alterations	8
Average genomic alterations	3.97
Median genomic alterations	4

treatment regimens using trabectedin or trabectedin plus doxorubicin have increased ORRs (up to 53%) but confer similar median survival rates [2, 4–9]. The use of targeted therapies for uLMS has been limited, despite the U.S. Food and Drug Administration approval of pazopanib for the treatment of soft tissue sarcomas. Comprehensive genomic profiling (CGP) detects a diverse range of mutations that may direct treatment with targeted therapies. In this report, we present the first published case of uLMS treated with palbociclib based on mutation of the cyclin-dependent kinase (CDK) pathway and place this in context of the full landscape of genomic alterations in uLMS.

Materials and Methods

Comprehensive genomic profiling (FoundationOne or FoundationOneHeme, Cambridge, MA, http://foundationone.com) testing was performed on 279 consecutive clinically advanced/recurrent uLMS (Table 1), as described previously [10]. In brief, DNA was extracted from 40 μm of formalin-fixed, paraffin-embedded sections, and CGP was performed on hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of 599X for up to 405 cancer-related genes plus introns from up to 31 genes frequently rearranged in cancer. Sequence data were analyzed for clinically relevant classes of genomic alterations, including base pair substitutions, insertions/deletions, copy number alterations, and rearrangements.

One sample analyzed was an initial tumor biopsy sample for a 72-year-old woman with progressive disease after several lines of treatment, including surgery, conventional chemotherapy (gemcitabine/docetaxel, bevacizumab, liposomal doxorubicin, and ifosfamide/paclitaxel), and an investigational therapy (AMG232). After genomic analysis of her initial tumor, treatment with palbociclib was initiated at the standard 125 mg dose for 21 days each month, but because of severe pancytopenia the dose was reduced to 75 mg.

Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, was obtained from the Western Institutional Review Board (IRB# 20152817).

Results

An analysis of 279 clinically advanced/recurrent uLMSs from women with a median age 54 years (range, 23–83 years) using FoundationOne assays showed that 97.1% of uLMSs harbor at least one alteration known or suspected to be important in cancer, and approximately 57% harbor alterations in at least one therapeutically targetable pathway (Fig. 1). Therapeutically targetable pathways and genes are defined later in the text or in supplemental online Table 1.

Alterations in uLMS are most frequently found in one or both of the critical tumor suppressors *TP53* (66%) and *RB1* (49%). In 11% of uLMSs, mutations within *CDKN2A* with potential to inactivate the p16INK4a protein were identified. Most *CDKN2A* mutations were homozygous loss of exons (90%), and the remaining mutations were rearrangements (7%) and short variants (3%). Many uLMSs (6.8%) harbored *CDKN2B* mutations, and 93% of these tumors had a co-occurring *CDKN2A* mutation. Other mutations affecting cyclin-dependent kinase pathway genes were found in *CDKN2C* (6%), *CDK4* (2.9%), *CCND3* (1.4%), *CCND2* (1.4%), *CDKN1B* (0.7%), and *CCND1* (0.3%). In total, 19% of uLMSs had a genomic alteration in one or more genes participating in the CDK4/6 pathway (*CDKN2A/B, CDKN2C, CDK4, CDK6, CCND1, CCND2,* and *CCND3*). The co-occurrence of alterations in the CDK pathway and *RB1* or *TP53* were observed significantly less often than expected ($p = 2.14 \times 10^{-10}$ and $p = 3.28 \times 10^{-6}$, respectively).

Within the 279 uLMS described here, genomic alterations (GA) predicted to activate the phosphatidyl inositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (*AKT1, AKT2, AKT3, FBXW7, MTOR, NF2, PIK3CA, PIK3R1, PTEN, RICTOR, RPTOR, STK11, TSC1, TSC2*) was identified in 29% of samples, predominantly through the loss of negative regulators (*PTEN,* 16.8%; *TSC1,* 2.5%; *STK11,* 1.8%; *TSC2,* 0.7%; *PIK3R1,* 2.9%; and *NF2,* 2.1%) and less frequently through gain of activity by positive regulators (*RICTOR,* 3.2%; *AKT2,* 1%; *AKT1,* 0.3%; *AKT3,* 0.7%; *PIK3CA,* 2.2%). Alterations in other genes of the mTOR pathway (*MTOR, RPTOR, and FBXW7*) were not observed in this cohort. The co-occurrence of alterations in the CDK and mTOR pathways were common, as illustrated in Figure 2.

We identified an illustrative case of a patient whose tumor harbors an alteration in the CDK pathway. A 72-year-old woman underwent a total abdominal hysterectomy, right salpingo-oophorectomy, and lymph node dissection at Yale-New Haven Hospital for a stage IIB (T2bN0) uLMS. Per original pathology analysis, the tumor showed a prominent myxoid component, and myxoid foci were apparent in the sequenced tissue (Fig. 3). She received six cycles of adjuvant chemotherapy with gemcitabine and docetaxel. Approximately 10 months later she was diagnosed with metastatic disease, characterized by multiple mesenteric masses. She was treated with bevacizumab, which was complicated by gastrointestinal bleeding, and required metastasectomy of omental tumors nearly 2 years

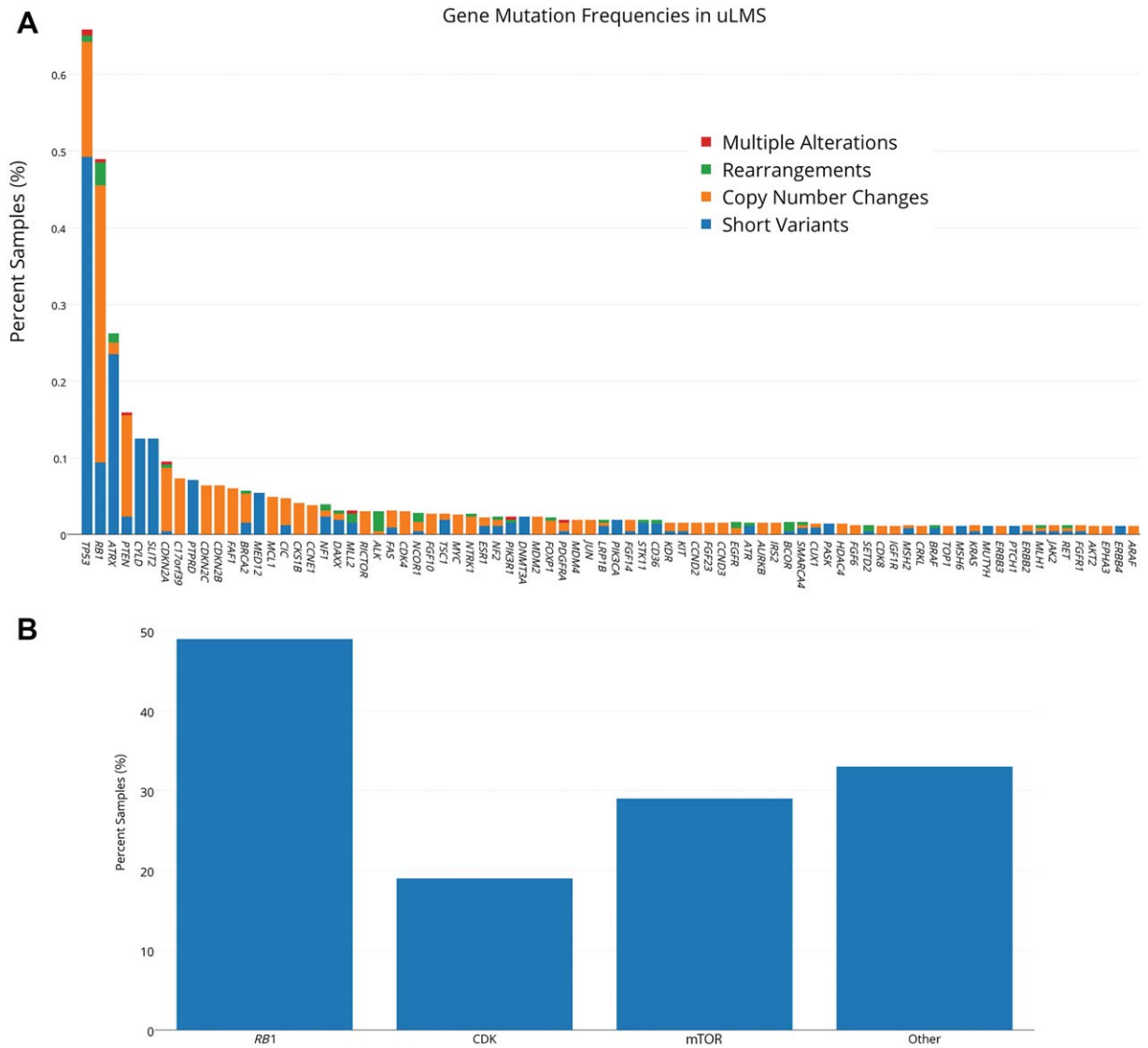

Figure 1. (A): Long tail plot illustrating the most frequently mutated genes in 279 uterine leiomyosarcoma (uLMS) samples. **(B)**: Frequency of mutation in *RB1*, the CDK pathway, the mTOR pathway, or other therapeutically targetable genes. Mutations in *RB1* were found in 49% of uLMS samples in this study, and targetable alterations in other genes were found in approximately 20%–35% of samples.

Abbreviations: CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin.

after diagnosis. This surgery and her subsequent care occurred at Norwalk Hospital.

After metastasectomy, she received liposomal doxorubicin for 6 months before disease progression. She was then treated in a phase I trial of the p53 inhibitor AMG232 (the *TP53* gene was wild type by sequencing) for 5 months before progression. Upon progression, she underwent repeat metastasectomy of omental tumors, with pathology showing high-grade, estrogen receptor (ER)/progesterone receptor (PR)-negative leiomyosarcoma. Upon disease progression, she was treated with two cycles of ifosfamide and paclitaxel, with no response but considerable bone marrow suppression.

Comprehensive genomic profiling was performed on the patient's initial tumor specimen, which revealed two mutations of known significance: one in the gene *CDKN2A* (homozygous loss of exons 2–3), a negative regulator of the cell cycle checkpoint kinases CDK4 and CDK6, and a co-occurring *NF2* alteration (Q147*). The *NF2* alteration observed here was heterozygous. No mutations were identified in *RB1*. Variants of unknown significance were identified in *EP300*, *FLT1*, *MED12*, *MPL*, *NOTCH2*, and *PRKDC*. The remaining 308 genes assayed were negative for alterations known or suspected to be important in cancer. The patient was ineligible for an available clinical trial involving a CDK inhibitor, but on the basis of the *CDKN2A* mutation, her insurance company approved coverage of the commercially available drug palbociclib (Ibrance, Pfizer Inc., New York, NY, http://www.pfizer.com). Palbociclib is an oral CDK4/6 inhibitor approved for the treatment of ER-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer.

Computed tomography (CT) performed at the initiation of palbociclib demonstrated at least eight discrete mesenteric masses and considerable disease progression compared with a scan obtained 8 weeks earlier. For example, a left upper quadrant mass was 6.6 cm × 5.3 cm versus 4.9 cm × 3.7 cm, and a left lower quadrant mass was 3.2 cm × 2.9 cm versus 2.2 cm × 2.1 cm (Fig. 4B). Palbociclib was initiated at the standard 125 mg dose for 21 days each month, but because of severe

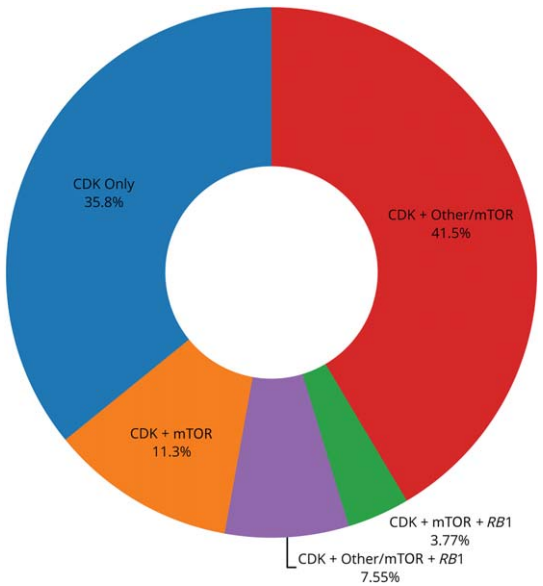

Figure 2. Frequency of CDK pathway mutation and co-occurrence with other clinically relevant genomic alterations (CRGA) in uterine leiomyosarcoma (uLMS). Mutations affecting the CDK, mTOR, or other targetable pathways are common in uLMS and frequently co-occur. In this dataset, targetable alterations in the CDK, mTOR or other pathways are commonly found in the absence of *RB1* mutations.

Abbreviations: CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin.

pancytopenia, the dose was reduced to 75 mg. CT performed after 2 and 4 months showed stable disease with no new masses and a slight reduction in some existing masses (Fig. 4A). The patient's overall sense of well-being dramatically improved and she was weaned off narcotics as her abdominal pain resolved. At present, although a CT scan at 8 months showed a small increase in the size of existing tumors, no new tumors have appeared and the patient continues to derive significant clinical benefit from palbociclib.

Discussion

Recurrent uLMS is a soft tissue sarcoma (STS) that carries a very poor prognosis, is nearly always fatal, and has few effective therapeutic options. The most recently approved agents for STS, pazopanib and trabectedin, have limited efficacy, highlighting the need for novel approaches. The case presented here is the first published example of a leiomyosarcoma successfully treated with the CDK4/6 inhibitor palbociclib, selected on the basis of a loss-of-function mutation identified in the CDK4/6 negative regulator *CDKN2A* (Fig. 5).

In this patient's tumor, CGP identified the homozygous loss of *CDKN2A* exons 2–3, which encode domains critical for the function of p16INK4a. *CDKN2A* encodes two distinct tumor suppressor proteins, p16INK4a and p14ARF [11], and this alteration leads to loss of both proteins. p16INK4a inhibits CDK4 and CDK6, thereby maintaining the growth-suppressive activity of the Rb tumor suppressor, and inactivation of p16INK4a contributes to dysregulation of the CDK4/6-cyclin-Rb pathway and loss of cell cycle control. The tumor suppressive functions of p14ARF involve stabilization and activation of p53, via MDM2 inhibition. Loss of p16INK4a and/or p14ARF has been

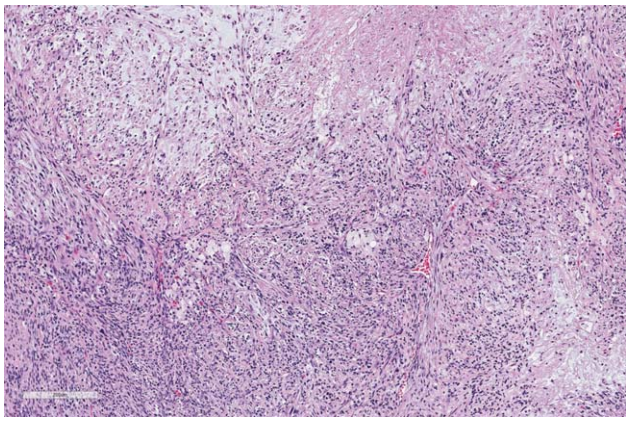

Figure 3. Sample from a stage IIB (T2bN0) leiomyosarcoma of the uterus with a prominent myxoid component (hematoxylin and eosin stain; magnification ×10).

associated with poor prognosis in several soft tissue sarcomas, including leiomyosarcoma [12]. Preclinical data suggest that tumors with loss of p16INK4a function may be sensitive to CDK4/6 inhibitors, such as palbociclib [13–16]. In contrast to the patient response reported herein and a similar response reported for a patient with breast cancer [17], large-scale clinical studies of breast cancer failed to show significant correlation between p16INK4a loss or inactivation and therapeutic benefit of palbociclib [18, 19].

In total, 19% of uLMS had a genomic alteration in one or more genes participating in the CDK4/6 pathway (*CDKN2A/B, CDKN2C, CDK4, CDK6, CCND1, CCND2,* and *CCND3*), identifying tumors for which palbociclib might be expected to provide clinical benefit. The loss of Rb in nearly half of uLMS predicts resistance to CDK4/6 inhibitors, such as palbociclib, abemaciclib, or LEE011 [20]. However, in our cohort of 279 patients, there were limited instances of co-occurring mutations between CDK4/6 pathway components and *RB1* (Fig. 2). Nearly 17% of uLMS samples in this study harbored CDK alterations without alteration of RB1. When CDK pathway mutations were expected to be the only targetable driver, there were no instances of co-occurring *RB1* mutation.

This patient's tumor also harbored a heterozygous truncating event in *NF2* (Q147*), which would disrupt the FERM domain and is predicted to be inactivating. This additional GA suggests a second line of potential targeted therapy that could result in clinical benefit, and it is worth noting that the presence of an alteration in *NF2* did not preclude clinical benefit from palbociclib. Strong clinical evidence from multiple case reports [21–24] indicates that *NF2* inactivation predicts sensitivity to mTOR inhibitors, including everolimus and temsirolimus. Other studies have shown that sensitivity to the pan-ERBB inhibitor lapatinib or mitogen-activated protein kinase (MEK) inhibitors, such as trametinib and cobimetinib [25–27] can arise from *NF2* inactivation. Within the 279 uLMS described here, GA predicted to activate the PI3K/AKT/mTOR pathway were identified in 29% of samples, predominantly through the loss of negative regulators (*PTEN,* 16.8%; *TSC1,* 2.5%; *STK11,* 1.8%; *TSC2,* 0.7%; *PIK3R1,* 2.9%; and *NF2,* 2.1%) and less frequently through gain of function by positive regulators (*RICTOR,* 3.2%; *AKT2,* 1%; *AKT1,* 0.3%; *AKT3,* 0.7%; *PIK3CA,* 2.2%).

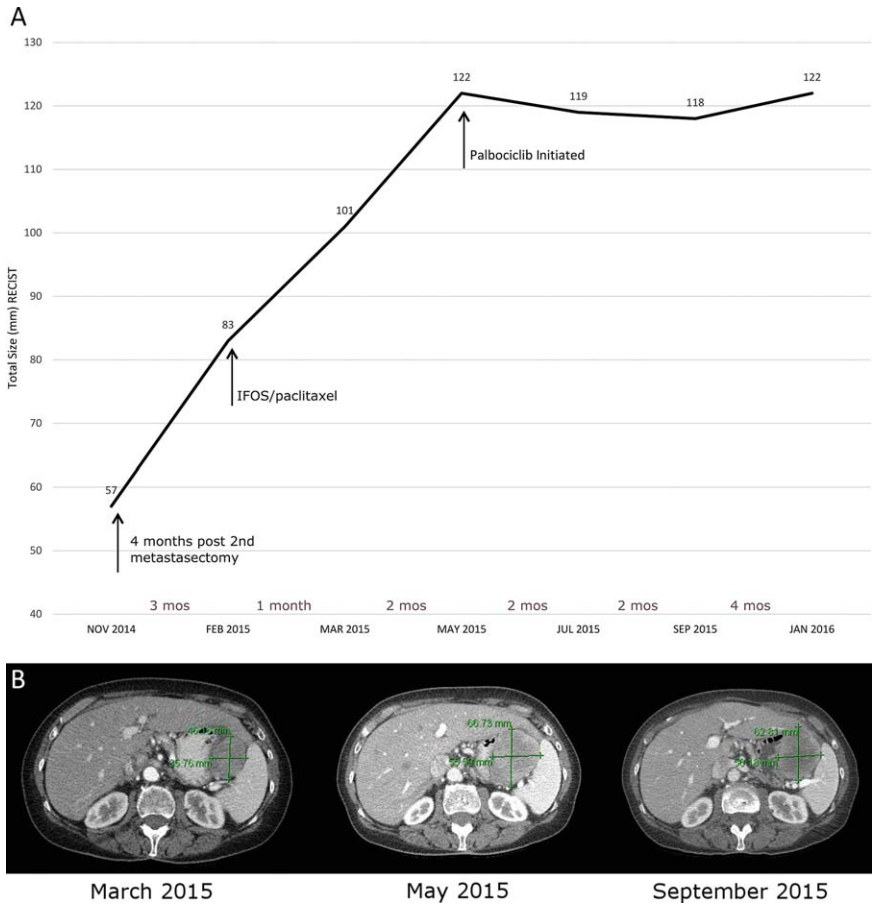

Figure 4. (A): Tumor growth over time. Tumor area over time, as measured by computed tomography (CT). **(B)**: CT scans taken 4 months apart showing rapid increase in tumor area. After initiation of palbociclib treatment (May 2015), stable disease was achieved with symptomatic improvement and no increase in tumor size.

Abbreviation: RECIST, Response Evaluation Criteria In Solid Tumors.

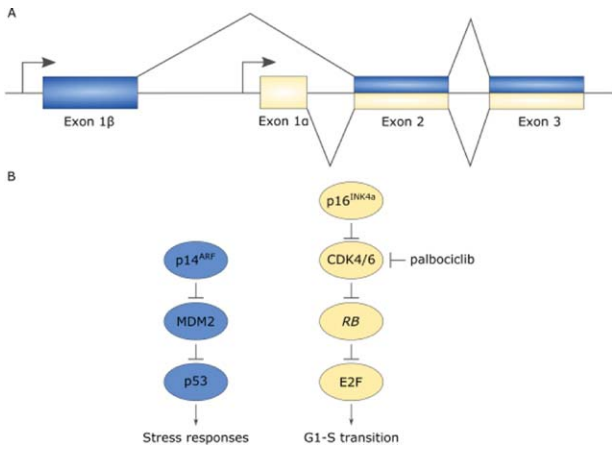

Figure 5. (A): Illustration of *CDKN2A* locus. *CDKN2A* encodes two transcripts using alternate initial exons, that share exons 2 and 3. Loss of exons 2 or 3 is expected to prevent production of both gene products, p14ARF and p16INK4A. **(B):** The gene products of *CDKN2A* regulate two related pathways that control cell growth and division, the p53-mediated stress response and the G1-S phase transition. Loss of *CDKN2A* releases inhibition on the cyclinD-CDK4/6 complex. Palbociclib is a small molecule inhibitor of both CDK4 and CDK6. Mutations affecting *RB*, which acts downstream of CDK4/6, are predicted to confer decreased sensitivity to palbociclib, although studies are ongoing.

Abbreviation: CDK, cyclin-dependent kinase.

Despite the high rate of mTOR pathway mutation in uLMS (Figs. 1 and 2), the presence of an alteration in the CDK4/6 pathway may still direct therapy with CDK-targeted inhibitors.

Conclusion

We report the first clinical response to palbociclib in uLMS, directed by the presence of a mutation in the CDK pathway regulator CDKN2A. Unlike many uLMS malignancies, this patient's tumor did not harbor co-occurring inactivation of *TP53* or *RB1*. Her response to treatment underscores the utility of CGP for identifying relevant targeted therapies, and analysis of 279 additional samples revealed that up to 19% of uLMS patients harbor alterations in the CDK pathway. These observations provide a rationale for the initiation of a clinical trial investigating treatment with CDK pathway inhibitors for uLMS, especially those harboring relevant genomic alterations.

Author Contributions

Conception/Design: Julia A. Elvin, Richard Frank
Provision of study material or patients: Rita Ort, Joseph Shuluk, Jennifer Long, Lauren Shelley, Ronald Lee, Richard Frank
Collection and/or assembly of data: Julia A. Elvin, Laurie M. Gay, Lauren Shelley, Ronald Lee, Zachary R. Chalmers, Garrett M. Frampton, Richard Frank
Data analysis and interpretation: Julia A. Elvin, Laurie M. Gay, Ronald Lee, Zachary R. Chalmers, Garrett M. Frampton, Siraj M. Ali, Alexa B. Schrock, Richard Frank
Manuscript writing: Julia A. Elvin, Laurie M. Gay, Richard Frank

Final approval of manuscript: Rita Ort, Siraj M. Ali, Alexa B. Schrock, Vincent A. Miller, Philip J. Stephens, Jeffrey S. Ross, Richard Frank

Disclosures

Julia A. Elvin: Foundation Medicine Inc. (E, O/I); **Laurie M. Gay**: Foundation Medicine Inc. (E, OI); **Zachary R. Chalmers**: Foundation Medicine Inc. (E, C/A, OI); **Garrett M. Frampton**: Foundation Medicine Inc. (E, OI); **Siraj M. Ali**: Foundation Medicine Inc. (E, OI); **Alexa B. Schrock**: Foundation Medicine Inc. (E, OI); **Vincent A. Miller**: Foundation Medicine Inc. (E, OI); **Philip J. Stephens**: Foundation Medicine Inc. (E, OI); **Jeffrey S. Ross**: Foundation Medicine Inc. (E, RF, OI); The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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