

A Refractory Case of *CDKN2A/B* Loss Metastatic Intrahepatic Cholangiocarcinoma Achieving a Partial Response After First-Line Treatment with Palbociclib

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Abstract: Intrahepatic cholangiocarcinoma (ICC) is a highly aggressive and malignant subtype of biliary duct tumors. The poor prognosis of advanced ICC brings great challenges to clinical treatment, and chemotherapy-based therapy remains the standard first-line regimen. In recent years, the development of clinical research on targeted therapy for biliary duct tumors has brought new strategies for clinical treatment, but the targets are limited. Herein, we reported a 68-year-old patient with metastasis ICC harboring *CDKN2A/B* loss, who achieved a partial response (PR) after the first-line treatment with a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor called palbociclib, and no obvious side effects were observed. As of the latest follow-up time, the progression-free survival (PFS) had lasted for 20 months. This case reveals the molecular characteristic of ICC patients who respond to palbociclib treatment and illustrates the importance of performing a multiple-gene panel test in ICC patients.

Keywords: intrahepatic cholangiocarcinoma, ICC, *CDKN2A/B* loss, palbociclib, CDK4/6 inhibitor, next-generation sequencing, NGS

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a subtype of cholangiocarcinoma often characterized by acinar or small tubular adenocarcinoma, and its incidence continues to increase in both eastern and western countries.^{1,2} ICC has a poor prognosis due to its high degree of malignancy, susceptibility to recurrence and metastasis.² It is well known that radical surgical resection is the best choice for ICC patients to obtain a long-term survival outcome, especially those in the early stages. However, even with radical resection, ICC is still highly susceptible to postoperative recurrence and metastasis, with a postoperative recurrence rate of 40–80%.² In addition, most ICC patients were already in the middle and late stages at the time of initial diagnosis, and lost the opportunity of radical surgery, which made diagnosis and treatment more difficult.¹ As for patients with unresectable or metastatic ICC, the gemcitabine and cisplatin regimen (GemCis) remains the standard systemic treatment.¹ Although the response rate of GemCis is about 80%, the median overall survival (OS) is only 11.7 months and the median progression-free survival (PFS) is only 8.0 months, and not all patients can tolerate the side effect of chemotherapy,³ so a number of patients who can benefit from chemotherapy are limited. Targeted therapies for cholangiocarcinoma have made encouraging progress in recent years, in particular drugs targeting *FGFR2* fusions or rearrangements (pemigatinib, infigratinib, etc) and *IDH1* mutations (ivosidenib), which have been approved by the FDA as a subsequent-line therapy option for patients with cholangiocarcinoma.^{4,5} The frequency of *FGFR2* and *IDH1* alterations in ICC patients is much higher than that of other cholangiocarcinoma subtypes,⁴ suggesting

that targeted therapy has a better clinical application prospect in ICC. Even so, the proportion of ICC patients with *FGFR2* fusion or rearrangement and *IDH1* mutation is only 11–45%¹ and 10–20%,⁵ respectively, indicating that a significant proportion of patients would not benefit from either type of targeted therapy described above. Therefore, it is necessary to explore other biomarkers that can guide the targeted therapy of ICC patients in order to promote the development of patient-specific therapy. Herein, we report an ICC patient with *CDKN2A/B* loss, who underwent postoperative metastasis, achieved a partial response (PR) after first-line treatment with palbociclib (cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor), and the PFS had lasted for 20 months.

Case Presentation

A 68-year-old man was admitted to the hospital on May 28, 2020, due to the discovery of a liver mass. He had a history of gout and hypertension, but no history of viral hepatitis, chronic disease, hereditary disease, or surgery. Laboratory examinations of the patient before therapy revealed alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) remained in the normal range. A computed tomography angiography (CTA) of the upper abdomen showed a lumpy mixed-density lesion in the left lobe of the liver with an unclear boundary with the gallbladder (Figure 1A). An ultrasonography showed a fatty liver, and parenchymal lesions in the left inner lobe and right anterior lobe of the liver, indicating a suspected mixed liver cancer. The patient underwent drug-eluting-beads transhepatic arterial chemotherapeutic embolism (D-TACE) under local anesthesia on June 5, 2020, and was in stable condition after D-TACE.

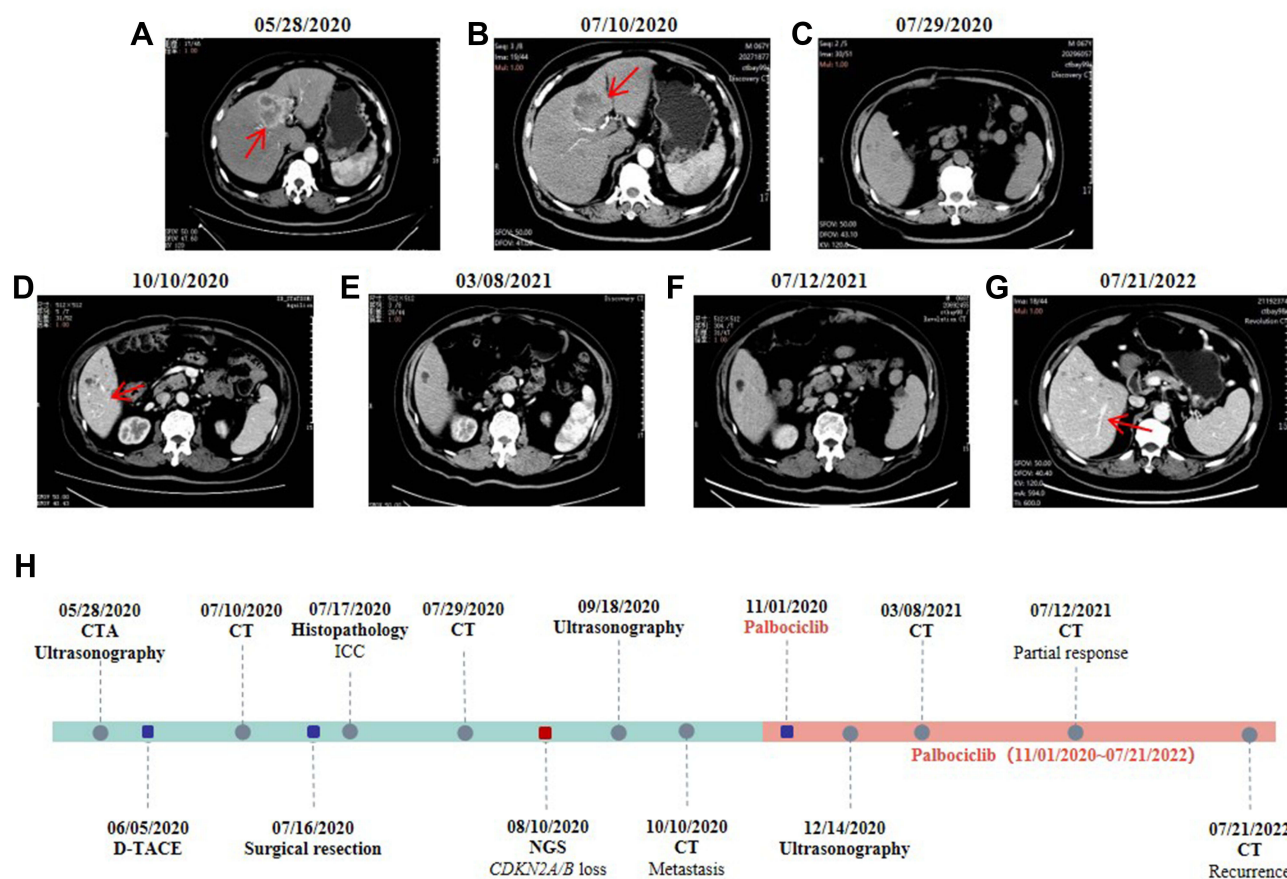


Figure 1 Representative upper abdominal imaging throughout the treatment period. (A) Preoperative CTA showed a lumpy mixed-density lesion in the liver with an unclear boundary with the gallbladder. (B) CT showed tumor cells were partially necrotic after D-TACE. (C) Postoperative CT showed new nodules in the S6 segment of the residual liver. (D) CT showed two small nodules in the S6 segment of the liver. (E) CT showed some shadows were smaller than before after palbociclib treatment. (F) CT showed a tumor reduction (reaching the criteria for a PR according to RECIST 1.1). (G) The latest CT showed the sign of recurrence. (H) The main clinical diagnosis and treatment process.

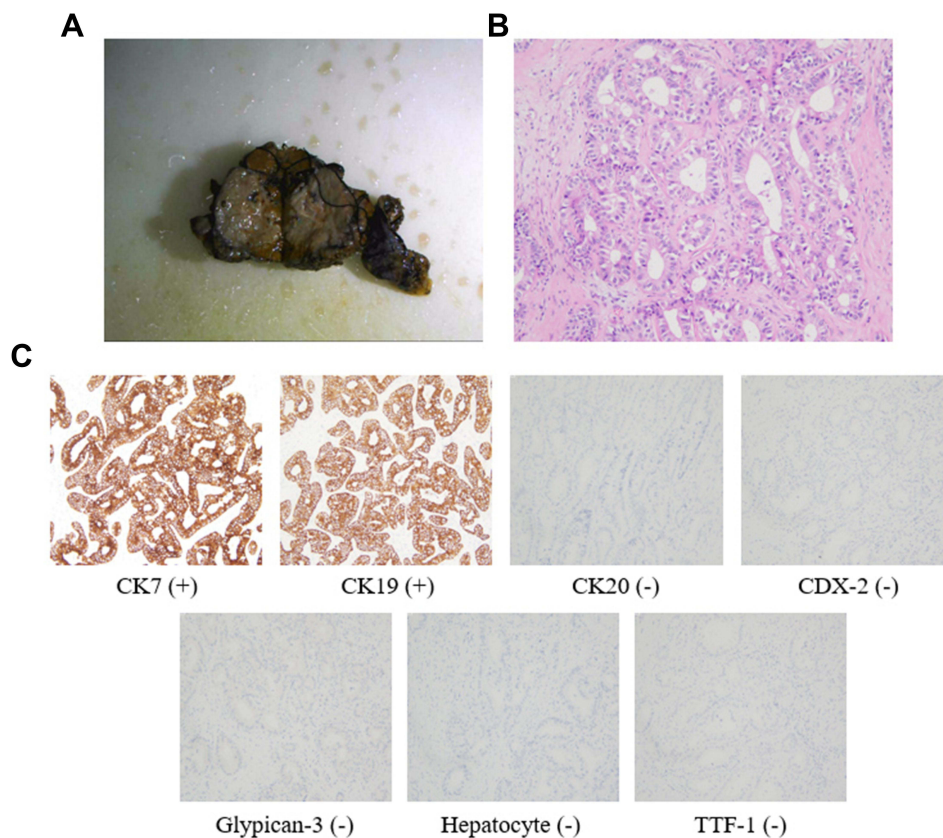


Figure 2 Excised tissue and postoperative pathological examination of the patient. **(A)** Excised gallbladder and liver tissue: a gray mass of 6 cm × 4.5 cm × 3 cm in size on section view. **(B)** Pathological examination: hematoxylin and eosin (H&E) stain, original magnification ×200. **(C)** Immunohistochemical results: CK7 (+); CK19 (+); CK20 (-); CDX-2 (-); Glypican-3 (-); Hepatocyte (-); TTF-1 (-).

Compared with the examination result in May 2020, the abdominal computed tomography (CT) on July 10, 2020, revealed the mass of the left lobe of the liver showed annular enhancement as before, and there were several small cystic areas without enhancement between the right lobe of the liver (Figure 1B). The patient underwent resection of liver tumor, cholecystectomy, biliary tract exploration, T tube drainage, and abdominal adhesion release under general anesthesia on July 16, 2020. Histological examination of paraffin-embedded (FFPE) specimens from surgically removed tumor tissue led to a pathological diagnosis of stage II (cT2N0M0) ICC (Figure 2), which was moderately differentiated, with no intratumoral tumor plug and nerve fiber invasion, no satellite nodules, and no involvement of liver capsule and liver resection margin. Immunohistochemical staining indicated the sample being positive for CK7 and CK19, and negative for CK20, CDX-2, TTF-1, glypican-3, and hepatocyte marker. After surgery, the patient's vital signs were normal, the T tube and abdominal drainage tube were unobstructed, and the wound healed (level II/A). On July 29, 2020, the postoperative CT examination revealed new nodules in the S6 segment of the residual liver, which suggested the possibility of intrahepatic metastasis (Figure 1C).

To optimize the follow-up treatment plan, FFPE samples with the morphological characteristics of ICC, as well as a blood control sample, were used for the detection of genetic alterations on August 10, 2020. Targeted next-generation sequencing (NGS) was performed using a panel covering the whole exon region and partial intron region of 733 cancer-related genes in 3D Medicines Laboratory (3D Medicines Inc., Shanghai, China). The captured libraries were loaded onto a NovaSeq 6000 platform (Illumina) for sequencing with a mean sequencing depth of 500×. The patient was identified to harbor four somatic genetic variations, including *BAP1* mutation (Q40*), *IDH2* mutation (R172W) as well as the co-deletion of *CDKN2A* and *CDKN2B* genes (*CDKN2A/B* loss, Figure 3). *CDKN2A* and *CDKN2B* encode the p16^{INK4a} and p15^{INK4b} proteins, respectively, both of which are inhibitors of CDK4/6 kinases.⁶ Multiple studies suggest that *CDKN2A* may be a potential predictive biomarker for CDK4/6 inhibitors,^{7–10} so palbociclib, a CDK4/6 inhibitor, becomes a follow-up treatment option.

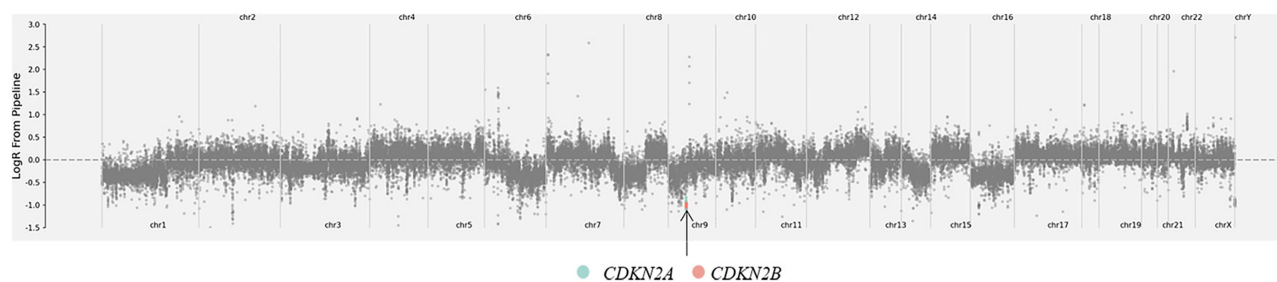


Figure 3 Copy number analysis of all genes showing the *CDKN2A/B* loss. The horizontal axis represents the location of the gene on the chromosome, and the vertical axis represents the copy number calculated by the NGS method.

A regular postoperative examination was performed. The B-scan ultrasonography on September 18, 2020, showed no obvious nodules and lumpy echoes in the residual liver. An enhanced CT scan of the upper abdomen on October 10, 2020, showed two small nodules in the S6 segment of the liver, with a diameter of about 7–12 mm (Figure 1D), suggesting that the patient might have undergone metastasis. Even though GemCis was the preferred treatment for metastatic ICC, chemotherapy was not administered due to the patient's inability to tolerate chemotherapy after surgery and his strong rejection of chemotherapy. Based on the *CDKN2A/B* loss in NGS test results and related research reports, palbociclib becomes the first-line treatment choice for this patient. The palbociclib treatment (125 mg daily for 21 days, then 7 days off) was subsequently started on November 1, 2020. Routine blood tests were performed on the day before each medication cycle. Once white blood cell count and neutrophil absolute value appear below the normal range, palbociclib was taken in combination with leucogen tablets (a drug used to treat leukopenia and thrombocytopenia) and batilol tablets (a drug used to treat leukopenia). Since then, the patient has continued to receive palbociclib treatment and blood routine tests were performed on the 15th day of each medication cycle. Liver function, kidney function, and CA19-9 were examined every 2 months.

B-scan ultrasonography on December 14, 2020, showed no obvious occupying of the residual liver. Enhanced CT scan of the upper abdomen on March 8, 2021, showed that, compared with the CT result on October 10, 2020, there were several clusters of low-density shadows in the liver, with a maximum size of about 27 mm×17 mm, some of which were smaller than before and none of which had enhanced (Figure 1E). And a follow-up CT scan of the upper abdomen on July 12, 2021, showed that, compared with the CT result on March 8, 2021, there were several clusters of low-density shadows in the liver, with a maximum size of about 17 mm×10 mm, some of which were smaller than before, and no enhancement was observed (Figure 1F). According to the CT imaging, the tumor size reduced slightly, which was rated as PR based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria. No adverse reactions were observed during the treatment, and the patient reported better physical and mental condition than before. Except for uric acid (653 umol/L) and cystatin C (1.61 mg/L) were slightly higher, all blood indexes were within the normal range. Moreover, the concentration of CEA, AFP, and CA19-9 remained in the normal range from June 2020 to July 2021. These indicated that the patient had a good response to palbociclib treatment.

Therefore, the patient continued to receive palbociclib, and follow-up CT examinations were carried out every 3 months during the medication period. Liver function and tumor-related biomarkers examinations were performed every 6 months. Blood routine examinations were performed every month. At the latest follow-up on July 21, 2022, CT scan showed that there were multiple slightly low-density nodules in the liver, suggesting that the patient had a recurrence of the disease (Figure 1G). In summary, the patient received PFS for 20 months from November 2020, when he was treated with palbociclib, until July 2022. Currently, the patient has been switched to lenvatinib treatment. The main clinical diagnosis and treatment process of the patient is shown in Figure 1H.

Discussion

The long-term survival rate of ICC patients who underwent radical surgical excision remains poor.¹¹ In addition, the median OS of advanced ICC patients without systematic treatment is 3.9 months.¹² There are few treatment options available for patients with advanced ICC, and the effectiveness of standard chemotherapy for advanced ICC is limited.

GemCis, the standard first-line systemic treatment for advanced cholangiocarcinoma, provides a median survival of only about 1 year.³ Few molecularly targeted drugs have been approved for ICC, even though the emergence of molecular targeted therapy has provided new ideas for the individualized treatment of advanced ICC. In this case, intrahepatic metastasis was observed in the ICC patient after D-TACE and surgical resection. The patient was found to have *CDKN2A/B* loss by NGS analysis using a 733-gene panel, and subsequently treated with palbociclib. After 4 months of treatment, the metastatic lesions were found to have shrunk. Following treatment until 8 months later, the patient was shown to have achieved PR and PFS lasted for 20 months.

Palbociclib (known as PD-0332991 in previous studies), a CDK4/6 inhibitor, is approved by the Food and Drug Administration (FDA) for using in combination with the anti-estrogen therapy in hormone receptor positive breast cancer.¹³ As palbociclib has shown a good efficacy in breast cancer, many preclinical or clinical trials of palbociclib have also been carried out in other malignant tumors and preliminarily obtained good results.¹⁴ *CDKN2A* and *CDKN2B* are both included in the CDK4/6-cyclin-Rb pathway and located in the chromosome 9p21 region so that the co-deletion of them often occurs simultaneously due to their chromosomal proximity,¹⁵ which accounts for 5.6% to 25.9% in ICC.⁴ The *CDKN2A* gene encodes two different tumor suppressor proteins, p16^{INK4a} and p14^{ARF}, respectively. The *CDKN2B* gene encodes the tumor suppressor protein called p15^{INK4b}. Loss or inactivation of p16^{INK4a} and p15^{INK4b} proteins will lead the CDK4/6-cyclin-Rb signaling pathway to be abnormal.⁶ Multiple tumor cell lines have demonstrated that the *CDKN2A/p16^{INK4a}* function is related to palbociclib sensitivity, including glioblastoma,⁷ ovarian cancer,⁸ melanoma,⁹ pancreatic cancer,¹⁰ etc. Besides, there are two case reports that provide clinical evidence for *CDKN2A/B* as a target of palbociclib. A patient with metastatic collecting duct carcinoma who harbor *CDKN2A/B* homozygous deletions achieved a PR in pulmonary metastases after 3 months of palbociclib treatment.¹⁶ Another case was a serous ovarian cancer patient, who detected bi-allelic *CDKN2A* loss and p16^{INK4a} expression loss, responded to the combination of palbociclib and letrozole.¹⁷

However, little has been reported about CDK4/6 inhibitors in ICC. A study using patient-derived xenograft cells and ICC cells to evaluate the efficacy of palbociclib in the treatment of ICC showed that palbociclib had no effects on ICC cytotoxicity or necrocytosis *in vitro* and no inhibition on tumor proliferation *in vivo*.¹⁸ Another study confirmed the efficacy of CDK4/6 inhibitors in cholangiocarcinoma using cell lines and patient-derived xenograft models, and found that the expression of a tumor suppressor called retinoblastoma protein (pRB) is necessary for the CDK4/6 inhibitor activity, suggesting that the gene in the CDK4/6-cyclin-Rb pathway may be a suitable therapeutic target for ICC treated with CDK4/6 inhibitors.¹⁹ In clinical studies, there was a basket trial evaluating antitumor activity of palbociclib in pancreatic and biliary cancer patients with *CDKN2A/B* alterations, but the results were not satisfactory.²⁰ A total of 10 biliary cancer patients were enrolled in the study,²⁰ all of whom had previously received first-line or more systemic therapies, so we cannot exclude the possibility that previous exposure to systemic chemotherapy may induce resistance to palbociclib, which might have led to the poor efficacy in this trial.

In this case, the patient was in poor physical condition after surgery, with emaciation, weight loss, poor mental condition and mobility problems, and therefore could not tolerate chemotherapy. In addition, the patient and his family strongly refused to treat with chemotherapy. Therefore, despite limited clinical evidence, palbociclib was eventually adopted as the first-line treatment for this patient. It must be acknowledged that there are certain risks associated with using treatment regimens that exceed clinical guidelines. Obviously, in this case, the partial response to palbociclib in a metastatic ICC patient harboring *CDKN2A/B* loss is unusual, illustrating the importance of performing a multiple-gene panel test to find potentially sensitive drugs in ICC patients. However, we could not distinguish whether the *CDKN2A/B* were homozygous deletion or heterozygous deletion due to the original design of the NGS assay. We also could not exclude the possibility that homozygous deletion and heterozygous deletion of *CDKN2A/B* may exhibit different clinical features. It is necessary to use another method, such as fluorescence *in situ* hybridisation, to identify the type of deletion. But further verification was not performed because of the patient's family finances. Besides that, NGS analysis revealed that the patient also had *BAP1* (Q40*) and *IDH2* (R172W) mutations. However, currently, there are no preclinical or early clinical data suggesting that *BAP1* and *IDH2* can be used as biomarkers for ICC targeted therapy. In addition, the genetic test result we referred to was derived from surgical primary lesions, rather than metastatic lesions, and the genetic variation of the primary lesions seems to be insufficient to guide the treatment of metastatic lesions.

However, it is difficult to collect the tumor tissue of metastatic lesions for patients with postoperative metastases. A previous study showed similar ICC somatic variation profiles between primary and metastatic tumor tissues,²¹ suggesting that it is reasonable to make a medication regimen based on the genetic test results of the primary tumor tissue removed by surgery.

To sum up, this case report described a metastatic ICC patient harboring *CDKN2A/B* loss responded to palbociclib as the first-line therapy, suggesting that comprehensive genomic variation detection can provide new strategies for individualized treatment of advanced ICC patients. Given the good response to palbociclib observed in this case report, it is necessary to further explore whether *CDKN2A/B* variants are associated with the response of ICC patients to CDK4/6 inhibitors.

Abbreviations

AFP, alpha-fetoprotein; CA19-9, carbohydrate antigen 19-9; CDK4/6, cyclin-dependent kinases 4 and 6; CEA, carcinoembryonic antigen; CT, computed tomography; CTA, computed tomography angiography; D-TACE, drug-eluting-beads transhepatic arterial chemotherapeutic embolism; FDA, Food and Drug Administration; FFPE, formalin-fixed paraffin-embedded; GemCis, gemcitabine and cisplatin regimen; ICC, intrahepatic cholangiocarcinoma; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; PR, partial response; pRB, retinoblastoma protein.

Ethical Statement

This study has been approved by Ethic Committee of the First People's Hospital of Foshan (Guangdong, China). The written informed consent was obtained from the patient in order to publish this case report.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

XZ, YZ, and MH are current employees of 3D Medicines, Inc. TC is a former employee of 3D Medicines, Inc. The other authors have no conflicts of interest to declare for this work.

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