Isoform Switching as a Mechanism of Acquired Resistance to Mutant Isocitrate Dehydrogenase Inhibition

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ABSTRACT

Somatic mutations in cytosolic or mitochondrial isoforms of isocitrate dehydrogenase (IDH1 or IDH2, respectively) contribute to oncogenesis via production of the metabolite 2-hydroxyglutarate (2HG). Isoform-selective IDH inhibitors suppress 2HG production and induce clinical responses in patients with IDH1- and IDH2-mutant malignancies. Despite the promising activity of IDH inhibitors, the mechanisms that mediate resistance to IDH inhibition are poorly understood. Here, we describe four clinical cases that identify mutant IDH isoform switching, either from mutant IDH1 to mutant IDH2 or vice versa, as a mechanism of acquired clinical resistance to IDH inhibition in solid and liquid tumors.

SIGNIFICANCE: IDH-mutant cancers can develop resistance to isoform-selective IDH inhibition by “isoform switching” from mutant IDH1 to mutant IDH2 or vice versa, thereby restoring 2HG production by the tumor. These findings underscore a role for continued 2HG production in tumor progression and suggest therapeutic strategies to prevent or overcome resistance. Cancer Discov; 8(12); 1540–7. ©2018 AACR.
INTRODUCTION

Somatic mutations in isocitrate dehydrogenase (IDH) enzymes are observed in a wide spectrum of human cancers, most commonly gliomas (1, 2), myeloid malignancies (3), chondrosarcomas (4), and intrahepatic cholangiocarcinomas (ICC; ref. 5). IDH enzymes normally function as components of the tricarboxylic acid cycle, catalyzing the interconversion of isocitrate and alpha-ketoglutarate (αKG; ref. 6). Cancer-associated IDH mutations occur at catalytic-site arginine residues in cytoplasmic IDH1 (R132) and mitochondrial IDH2 (R140 and R172), altering the enzymatic activity to promote efficient reduction of αKG to the “oncometabolite” 2-hydroxyglutarate (2HG; refs. 7, 8). Cellular accumulation of 2HG inhibits αKG-dependent dioxygenases that mediate histone and DNA demethylation, leading to a repressive chromatin landscape that disrupts normal cellular differentiation and contributes to oncogenesis (9–12).

Importantly, the effects of 2HG on chromatin and cell differentiation are largely reversible (11); therefore, drugs that inhibit 2HG production by mutant IDH1 represent potential therapies for IDH-mutant malignancies (13). Small-molecule inhibitors of IDH1 or IDH2 inhibit 2HG production by IDH-mutant enzymes, induce cellular differentiation, and inhibit cancer growth in preclinical models (6, 13). In phase I/II trials, the mutant IDH1 inhibitor ivosidenib (AG-120) and the mutant IDH2 inhibitor enasidenib (AG-221) induced clinical responses in patients with relapsed/refractory IDH-mutant myeloid malignancies (14, 15). Clinical trials with ivosidenib are under way for the treatment of relapsed/refractory IDH1-mutant solid tumors, including glioma, ICC, and chondrosarcoma (16).

The mechanisms that mediate response and resistance to small-molecule IDH inhibition are not fully understood (17–19). Here, we identify mutant IDH isoform switching, either from cytoplasmic mutant IDH1 to mitochondrial mutant IDH2 or vice versa, as a mechanism of acquired clinical resistance to IDH inhibition. The first two cases describe patients with relapsed/refractory IDH1 R132C-mutant acute myeloid leukemia (AML) who achieved durable remissions in response to the mutant IDH1 inhibitor ivosidenib followed by leukemic progression on therapy, rise of blood 2HG levels, and emergence of IDH2 R140Q mutations. The third case describes a patient with treatment-refractory IDH1 R132C-mutant ICC who attained a sustained partial response to ivosidenib followed by progression of disease associated with acquisition of a new IDH2 R172V mutation. The fourth case describes a patient with relapsed/refractory IDH2 R140Q-mutant AML who achieved a durable remission to the mutant IDH2 inhibitor enasidenib, followed by progression on therapy associated with emergence of a new IDH1 R132C mutation that was sensitive to combined IDH1/2 blockade with AG-881. These findings provide evidence of selective pressure to maintain 2HG production in IDH-mutant malignancies, as well as suggest potential strategies for disease monitoring and therapies that might overcome acquired resistance to IDH inhibition.

RESULTS

Case Reports 1 and 2

A 54-year-old man with normal karyotype AML relapsed 100 days after allogeneic bone marrow transplantation with progressive pancytopenia and a bone marrow biopsy showing 30% leukemic blasts (Fig. 1A and B). Targeted next-generation sequencing (NGS) of bone marrow cells using a microdroplet-PCR assay (20) demonstrated the presence of an IDH1 R132C mutation and two DNMT3A mutations (Fig. 1C; Supplementary Tables S1 and S2). The patient began treatment with the mutant IDH1 inhibitor ivosidenib 500 mg orally daily, with a complete remission evident after three 28-day cycles of therapy. After completing twelve 28-day cycles of ivosidenib, the blast count and blood 2HG levels began to rise and a new IDH2 R140Q mutation was detected (Fig. 1A, C and D). Droplet digital PCR (ddPCR) analysis of DNA from bone marrow cells demonstrated that the IDH2 R140Q mutation was not detectable prior to treatment but was present at low levels early in the course of ivosidenib treatment (Supplementary Fig. S1A; Supplementary Table S3). Ivosidenib was discontinued, and the mutant IDH2 inhibitor enasidenib was started. After several days of treatment with enasidenib, the patient developed fever and hypoxia suspected to be secondary to IDH inhibitor differentiation syndrome (21); enasidenib was discontinued.

A 72-year-old man presented with AML arising from preexisting JAK2 V617F-mutant myelofibrosis. For several years prior, the myelofibrosis had been treated successfully with single-agent ruxolitinib and then combination therapy with ruxolitinib plus decitabine. However, at the time of presentation with secondary AML, there were 37% blasts in the bone marrow, and the patient was neutropenic (Fig. 1E and F). Targeted NGS of bone marrow mononuclear cells using a microdroplet-PCR assay (20) identified JAK2 V617F and IDH1 R132C mutations (Fig. 1G), as well as mutations in ASXL1, EZH2, and RUNX1 (Supplementary Tables S1 and S4). The patient began treatment with ivosidenib 500 mg orally daily, and a complete response was evident after one 28-day cycle of therapy. The IDH1 mutation became undetectable after four 28-day cycles of ivosidenib, but then reappeared after the 11th 28-day cycle (Fig. 1G). The patient remained in complete morphologic remission until the start of the 12th cycle when the bone marrow blasts increased to 12%, then 28% four weeks later (Fig. 1E). The increase in AML blasts was associated with the emergence of a new IDH2 R140Q mutation and a rise in the serum 2HG levels (Fig. 1G and H). ddPCR analysis of DNA from bone marrow cells demonstrated that the IDH2 R140Q mutation was detectable at low levels both before treatment and early during the course of therapy with ivosidenib, well before overt clinical resistance developed (Supplementary Fig. S1B; Supplementary Table S5). Ivosidenib was discontinued. The patient subsequently pursued treatment elsewhere with low-dose cytarabine and venetoclax (22), but was lost to follow-up.

Case Report 3

A 79-year-old woman with American Joint Committee on Cancer stage IV (T3N1M1) ICC presented for evaluation. One month prior to presentation, she had developed anorexia, unintentional weight loss, and abdominal distention. Cross-sectional imaging with computed tomography revealed an 8 × 5 × 7.5 cm hypoattenuating mass with peripheral enhancement and capsular retraction in the right hepatic lobe,
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Figure 1. Acquired resistance to mutant IDH1 inhibition associated with emergence of oncogenic IDH2 mutations in AML. Clinical and laboratory features of two patients (case 1 = A–D; case 2 = E–H) with IDH1 R132C-mutant AML treated with the mutant IDH1 inhibitor ivosidenib (gray boxes), including A, E, bone marrow blast percentage; B, F, absolute neutrophil count (ANC); C, G, variant allele frequency (VAF) for IDH1 and IDH2 mutations identified by targeted NGS of bone marrow cells; and D, H, plasma 2-hydroxylglutamate (2HG) concentration measured by gas chromatography–mass spectrometry. Dotted line indicates limit of detection.

Case Report 4

A previously healthy 70-year-old man was found to be pan-cytopenic on routine bloodwork. Bone marrow aspiration and core biopsy demonstrated a hypercellular marrow with dysplastic neutrophils, erythroid precursors, and megakaryocytes. Myeloblasts were increased and comprised 15% of the marrow cellularity. These morphologic findings were consistent with myelodysplastic syndrome (MDS), subtype refractory anemia with excess blasts 2 (RAEB-2). Cytogenetics and FISH were normal. Clinical ampiclon-based genotyping of bone marrow cells demonstrated the presence of an IDH2 R140Q mutation without mutation of NPM1, CEBPA, FLT3, or KIT (not shown).
IDH Inhibitor Resistance Arising from IDH Isoform Switching

After 4 cycles of azacytidine, pancytopenia persisted (Supplementary Fig. S3A–S3C). Repeat bone marrow evaluation demonstrated a hypercellular marrow with persistent trilineage dysplasia (Supplementary Fig. S3D) and increased myeloid blasts comprising up to 20% of the marrow cellularity (Fig. 3A). Targeted NGS of bone marrow cells using a microdroplet-PCR assay (20) confirmed persistence of the IDH2 R140Q mutation (Fig. 3B; Supplementary Tables S1 and S9). On the basis of these findings, the patient met the diagnostic criteria for IDH2-mutant secondary AML evolved from MDS.

The patient began treatment with the mutant IDH2 inhibitor enasidenib 100 mg orally twice daily. Monthly bone marrow evaluation demonstrated a progressive decrease in the myeloid blast percentage with a complete response (blasts <5%) evident after completing three 28-day cycles of therapy (Fig. 3A; Supplementary Fig. S3D). Although the pancytopenia persisted, there was a modest improvement in the absolute neutrophil count (Supplementary Fig. S3A–S3C). The variant allele frequency (VAF) for IDH2 R140Q remained in the ~20% to 40% range (Fig. 3B), consistent with the observation that enasidenib promotes differentiation of IDH2-mutant blasts rather than cytotoxicity (14, 17). Serial measurements of plasma 2HG concentration demonstrated a decrease from 0.5 to 1.5 μmol/L while on therapy with enasidenib (Fig. 3C).

The patient remained in complete remission until the start of cycle 17 of enasidenib (day 448), at which time the bone marrow blast percentage increased to 10% (Fig. 3A), leukemic blasts appeared in the blood (not shown), and two CEBPA mutations became detectable by NGS of bone marrow cells (Supplementary Table S9). On day 497, the dose of enasidenib was increased to 200 mg orally twice daily, resulting in a transient decrease in bone marrow blasts (Fig. 3A). However, 8 weeks later there was an increase in bone marrow blasts accompanied by a progressive rise in plasma 2HG concentration (Fig. 3A, C, and D). Targeted NGS of bone marrow cells identified a new IDHI R132C mutation (Fig. 3B) coinciding with the leukemic progression and rise in plasma 2HG levels. ddPCR analysis of DNA from bone marrow cells demonstrated that the IDHI R132C mutation was not detectable prior to treatment but was present at low levels relatively early in the course of enasidenib treatment, well before the development of overt clinical resistance (Supplementary Fig. S3E; Supplementary Table S10).

Enasidenib was discontinued on day 700, and the patient began therapy on a clinical study of the dual IDH1/2 inhibitor AG-881 at 400 mg orally daily. There were rapid decreases in the plasma 2HG concentration, bone marrow blast percentage, and VAF for IDHI R132C (Fig. 3A–C). These effects were transient, as the patient underwent a prolonged hospitalization for Clostridium difficile infection and gastrointestinal bleeding and ultimately expired approximately 3 months after starting therapy with AG-881. In the interval prior to expiration, there was progression of leukemic blasts despite ongoing suppression of blood 2HG levels.

IDH Inhibition in Cells Expressing Both Mutant IDH Isoforms

As the IDH2 R172V mutation identified in case 3 has not been previously reported in patients, we examined the effect...
of introducing this mutation into IDH1-mutant cancer cells. Expression of the IDH2 R172V mutation in IDH1 R132G-mutant chondrosarcoma cells resulted in 2HG production that was resistant to ivosidenib but susceptible to combined treatment with ivosidenib and enasidenib (Fig. 4A). Likewise, we examined the effect of introducing a neomorphic IDH1 R132H mutation into chondrosarcoma cells harboring an endogenous IDH2 R172S mutation. Although the IDH2-mutant chondrosarcoma cells did not tolerate transient transfection of the IDH1 R132H mutation, we were able to achieve low-level expression of the IDH1 R132H mutation via a doxycycline-inducible retroviral system (Fig. 4B). Expression of the IDH1 R132H mutation conferred enasidenib-resistant 2HG production (albeit less than the uninhibited endogenous IDH2 mutation), which was suppressed by combined inhibition of both IDH isoforms (Fig. 4B). IDH inhibition impaired cellular fitness in both experimental systems as evidenced by decreased cellular biomass (Supplementary Fig. S4A and S4B) and modestly induced apoptosis (Supplementary Fig. S4B). Taken together, these findings demonstrate that bidirectional mutant IDH isoform switching can restore 2HG production in the face of isoform-selective IDH inhibition and that this effect can be overcome by combined inhibition of both isoforms of mutant IDH.

**DISCUSSION**

We have identified mutant IDH isoform switching as a mechanism of acquired resistance to IDH-targeted therapy. Both IDH1 and IDH2 mutations are observed in liquid tumors, whereas in solid tumors IDH1 mutations vastly outnumber IDH2 mutations (6). The biological underpinning for the preferential selection of cytosolic IDH1 mutation versus mitochondrial IDH2 mutation in different cancer types remains poorly understood. Experimental evidence suggests that the level of 2HG production can vary based on the subcellular location of the IDH mutation (23). Our findings suggest that the selective pressure of inhibiting mutant IDH activity in one subcellular compartment might provide a growth advantage for malignant subclones with unimpeded mutant IDH activity in another subcellular compartment.

Resistance alleles assessed using ddPCR were detectable prior to and/or early during treatment. This suggests that rare subclones harboring neomorphic mutations in both IDH1 and IDH2 can emerge under the selective pressure of isoform-selective IDH inhibition. Indeed, the VAFs of the IDH mutations in cases 1, 2, and 4 allow us to speculate that the IDH1 and IDH2 mutations are present within the same subclone. However, it remains possible that resistance to isoform-selective IDH inhibitors might also occur through parallel acquisition of IDH1 and IDH2 mutations in distinct clones. Single-cell analyses will be required to formally delineate the clonal architecture of IDH inhibitor resistance, particularly for solid tumors such as case 3. Likewise, it will be important to determine whether additional co-occurring genomic alterations contribute to acquired resistance to IDH inhibition.

Mutant IDH isoform switching represents a mechanism of acquired resistance to isoform-selective IDH-targeted therapy with potential therapeutic import. Experimental evidence demonstrated that cancer cells expressing both mutant IDH1 and mutant IDH2 exhibit 2HG production that is resistant to monotherapy yet sensitive to combined inhibition of both isoforms (Fig. 4). The patient in case 4 exhibited potent inhibition of 2HG production and a transient clinical response to the dual IDH1/2 inhibitor AG-881, although there was...
subsequent 2HG-independent disease progression resulting from unknown molecular mechanisms. Alternatively, a strategy of cotargeting of mutant IDH1 and IDH2 from the outset might delay or prevent resistance and should be explored in clinical trials. These efforts could be focused on patients with low levels of the alternative mutant IDH isoform detectable by sensitive sequencing assays (e.g., ddPCR) prior to or early during therapy with an isoform-selective IDH inhibitor.

The frequency of mutant IDH isoform switching as a mechanism of resistance to IDH inhibition remains uncertain. Prior studies in liquid tumors have begun to elucidate potential mechanisms of resistance to mutant IDH2 inhibitors. We previously reported IDH2 dimer–interface mutations in 2 of 9 patients with IDH2-mutant AML and acquired resistance to enasidenib therapy (18). The current study identifies isoform switching to mutant IDH1 in an additional case (case 4) from this cohort (1 of 9; 11%). Similarly, a recent report using single-cell sequencing to study clonal dynamics of IDH2-mutant AML in response to enasidenib found that 2 of 12 (17%) cases developed resistance associated with emergence of new IDH1 mutations (19). Here, we establish bidirectional mutant IDH isoform switching, either from cytoplasmic mutant IDH1 to mitochondrial mutant IDH2 or vice versa, as a generalized mechanism of acquired clinical resistance to IDH inhibition in both liquid and solid tumors. As larger numbers of patients with IDH-mutant malignancies are treated with isoform-selective IDH inhibitors, it will be important to determine the precise frequency of isoform switching and to elucidate other mechanisms of de novo and acquired resistance (17–19). These cases underscore the potential utility of serial DNA sequencing and 2HG measurement in patients treated with IDH inhibitors as means to monitor response, define resistance mechanisms, and inform treatment recommendations.

METHODS

Clinical Specimens

The patients described were enrolled on the phase I/II studies NCT01915498 (14), NCT02073994, or NCT02074839 (15). Enrollment was open to all patients with relapsed or refractory AML with a mutation in IDH1 (NCT02074839) or IDH2 (NCT01915498) or patients with advanced solid tumors with a mutation in IDH1 (NCT02073994). IDH mutations were identified locally and confirmed centrally. Patients were required to be 18 years or older at the time of study entry. Both men and women were enrolled on the studies. Patients were required to have acceptable performance status and adequate organ function as defined in the study protocols. Neutrophil count, hemoglobin concentration, platelet count, and blast percentage were determined by standard clinical assays. Targeted NGS and determination of VAF were performed by Raindance microdroplet PCR (20) for AML or MSK-IMPACT hybrid capture (24) for cholangiocarcinoma as previously described (see Supplementary Tables S1, S6, and S8 for gene lists). Sequencing data are deposited in the European Nucleotide Archive under accession number PRJEB29344.

cDNA Isolation and Sequencing

Whole blood was collected in 10-mL Cell-Free DNA BCT tubes (STRECK) and centrifuged at 800 × g for 10 minutes at ambient...
temperature. Plasma was separated from red blood cells and subjected to an additional centrifugation at 18,000 × g for 10 minutes at ambient temperature. Cell-free plasma was aliquoted and stored at −80°C. Extraction of cfDNA was performed using a fully automated QIAGEN platform, QIAasympolymer SP, and QIAasympolymer DSP Virus/Pathogen Midi Kit (QIAGEN). This is a bead-based custom protocol, optimized to work with 3 mL of plasma as starting material. The extraction process includes lysis, binding, wash, and elution steps. The final product was a 60 µL elution of cfDNA with an average size of ~170 to 200 bp. Quality and quantity of cfDNA were evaluated with automated electrophoresis using a fragment analyzer with a 170 to 200 bp droplets positive for mutant or wild-type DNA.

Cell Culture

The chondrosarcoma cell lines JJJ012 with an endogenous IDH1 R132G mutation and CS-1 with an endogenous IDH2 R172S mutation were obtained from Dr. Justin Cross (Memorial Sloan Kettering) and previously validated by sequencing the IDH1 and IDH2 genes as described (23, 25). Cells were maintained at low passage number (<10 passages after thawing) in high-glucose DMEM with 10% FBS, glucose 25 mmol/L, and glutamine 2 mmol/L and split every 2 to 3 days before reaching confluence. Cultured cells tested negative for Mycoplasma at least monthly throughout the experimental period.

Statistical Analyses

Statistical analyses for 2HG levels in Fig. 4 were performed with Prism 7.0 (GraphPad), using one-way ANOVA with Tukey multiple comparisons test.

DNA Constructs

Please refer to the Supplementary Methods.

Gel Electrophoresis and Western Blotting

Please refer to the Supplementary Methods.

Metabolite Extraction and Analysis

Please refer to the Supplementary Methods.

Disclosure of Potential Conflicts of Interest

J.J. Harding reports receiving a commercial research grant from Bristol-Myers Squibb and is a consultant/advisory board member for Bristol-Myers Squibb, Eli Lilly, Eisai, and CytoMx. M.A. Lowery is a consultant/advisory board member for Agios, Celgene, EMD Serono, and Roche. J.M. Schwartzman is an Associate Physician at Best Doctors. M. Roshal reports receiving a commercial research grant from Agios and is a consultant/advisory board member for Agios and Celgene. R.K. Do is a consultant/advisory board member for Bayer. M.S. Tallman reports receiving commercial research grants from Arog, Cellerant, Orsenis, ADCT Therapeutics, and AbbVie and is a consultant/advisory board member for Daiichi Sankyo, AbbVie, Novo, Danbury Hospital, and American Society of Hematology. D.M. Hyman reports receiving commercial research grants from Loxo Oncology, Puma Biotechnology, and AstraZeneca and is a consultant/advisory board member for Atara Biotherapeutics, Chugai Pharma, CytoMx Therapeutics, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, Debiopharm Group, and Genentech. E. Papaemmanuelli reports receiving a commercial research grant from MDS Foundation, has been a speaker at conference symposia, and is a consultant/advisory board member for the Novartis Scientific Advisory Board. A. Tosolini is Director, Clinical Science at Celgene Corporation and has ownership interest (including stock, patents, etc.) in the same. M.G. Frattini is Executive Medical Director at Celgene Corporation and has ownership interest (including stock, patents, etc.) in the same. K.J. MacBeth is Senior Director at Celgene Corporation and has ownership interest (including stock, patents, etc.) in the same. G. Liu is Director at Agios Pharmaceuticals and has ownership interest (including stock, patents, etc.) in the same. S. Cade has ownership interest (including stock, patents, etc.) in Aigios. B. Wu has ownership interest (including stock, patents, etc.) in Aigios. Y.Y. Janjigian reports receiving commercial research grants from Boehringer Ingelheim, Bayer, Genentech/Roche, Bristol-Myers Squibb, Eli Lilly, and Merck and is a consultant/advisory board member for Merck Serono, Bristol-Myers Squibb, Eli Lilly, Pfizer, Bayer, Imugene, and Merck. L.K. Mellinhoff reports receiving commercial research support from GE Global Research and is a consultant/advisory board member for Agios, Puma Biotechnology, Merck, Deciphera, Roche, and Debiopharm Group. L.A. Diaz is a member of the Board of Directors of Jounce Therapeutics and Personal Genome Diagnostics, has ownership interest (including stock, patents, etc.) in PappGen, Personal Genome Diagnostics, Phoremost, Jounce Therapeutics, and Zydexem, and is a consultant/advisory board member for Merck, Personal Genome Diagnostics, Caris, Lyndra, and Genocea. R.L. Levine is on the Supervisory Board of Qiagen and the Scientific Advisory Board of Loxo, reports receiving commercial research grants from Celgene, Roche, and Prelude, has received honoraria from the speakers bureau of Gilead and Lilly, has ownership interest (including stock, patents, etc.) in Qiagen and Loxo, and is a consultant/advisory board member for Novartis, Roche, Janssen, Celgene, and Incyte. G.K. Abou-Alfa is a consultant/advisory board member for 3DMedcare, Agios, Beigene, Bioline, BMS, Boston Scientific, Bridgebio, Carsgen, Celgene, Casi, Cipla, CytoMx, Alignmed, Daiichi, DeBio, Delcath, Eisai, Etxelisix, Genoscience, Gilead, Halozyme, Hengrui, Incyte, Amgen, Invivo, Jazz, Janssen, Kyowa Kirin, Lmamococo, Lilly, Loxo, Merck, Mina, Newlink Genetics, Antengene, Novella, Ozoneo, PCI Biotech, Pfizer, Pharmacyte, Pharmaclicks, Piers, QED, Redhill, Sanofi, Aptus, Servier, Silenseed, Sillajen, Sobi, Targovax, Tekmira, Twoxar, Vicus, Yakult, Yiviva, Aslan, Astellas, AstraZeneca, and Bayer. E. Stein reports receiving commercial research grants from Celgene Pharmaceuticals, Agios Pharmaceuticals, Syros Pharmaceuticals, and Bayer Pharmaceuticals, and is a consultant/advisory board member for Celgene Pharmaceuticals, Agios Pharmaceuticals, Daiichi Sankyo Pharmaceuticals, Astellas Pharmaceuticals, AbbVie Pharmaceuticals, Bayer Pharmaceuticals, Syros Pharmaceuticals, Novartis Pharmaceuticals, Pfizer Pharmaceuticals, and Seattle Genetics. A.M. Intlekofer is a consultant/advisory board member for Foundation Medicine. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.A. Lowery, A. Tosolini, M.G. Frattini, Y.Y. Janjigian, G.K. Abou-Alfa, E.M. Stein, A.M. Intlekofer


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