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Case Report

Sustained Clinical Response to Ivosidenib in Previously Treated Patients with Advanced Intrahepatic Cholangiocarcinoma Harboring an IDH1 R132 Mutation: Two Case Reports

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Keywords
Intrahepatic cholangiocarcinoma · IDH1 · Ivosidenib · Sustained clinical response

Abstract
Introduction: Patients with progressing intrahepatic cholangiocarcinoma (iCCA) harboring an isocitrate dehydrogenase 1 (IDH1) mutation who received ivosidenib showed a median progression-free survival (PFS) benefit of 1.3 months compared to placebo in the phase 3 ClarIDHy trial. ***Case Presentations:*** We describe 2 consecutive patients with previously treated unresectable and metastatic iCCA harboring an IDH1 R132 mutation who achieved durable clinical responses with ivosidenib 500 mg once daily for >12 months until disease progression. In one case with a mixed response, a single progressive liver metastasis was additionally treated locally with interstitial brachytherapy, while ivosidenib was continued until further progression. Ivosidenib therapy resulted in long-term disease control with PFS of 20 and 13 months and duration of treatment of 26 and 13 months, respectively, with no relevant side effects. ***Conclusion:*** Patients with unresectable or metastatic IDH1-mutated iCCA can achieve sustained clinical responses for >12 months with ivosidenib. No new safety signals were observed during long-term treatment with ivosidenib.

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Introduction

Cholangiocarcinoma (CCA) is the second most common primary liver tumor after hepatocellular carcinoma. CCA includes malignancies of the intrahepatic cholangiocarcinoma (iCCA) and extrahepatic bile ducts and the gallbladder [1]. CCA has been steadily increasing worldwide over the past few decades, with a current incidence of 6 per 100,000 [2]. Only 30% of patients are eligible for resection at the time of diagnosis [3], and the risk of recurrence is up to 40% [4].

Chemotherapy with gemcitabine and cisplatin has been the standard of care for patients with unresectable or metastatic disease for more than a decade. At this stage, median overall survival (mOS) is less than 12 months and the 5-year survival rate is less than 20% [5]. Recently, the phase 3 TOPAZ-1 and KEYNOTE-966 trials both showed a small but significant additional improvement in mOS with the addition of the checkpoint inhibitors durvalumab or pembrolizumab to gemcitabine and cisplatin [6, 7].

The mOS of patients with CCA after progression on first-line therapy is less than 3 months [8, 9]. For eligible patients, second-line chemotherapy provides a small survival benefit, with the best therapeutic regimen selected based on its specific side effects [1].

CCA, especially iCCA with small duct histology, is enriched by genomic alterations which can be exploited as actionable therapeutic targets. Therefore, molecular profiling of the tumor is strongly recommended for these patients. The most common targetable alteration found in iCCA is a heterozygous point mutation in codon 132 of the isocitrate dehydrogenase 1 (IDH1) gene encoding arginine (R132), which occurs in approximately 14% of cases [10]. IDH1 normally functions to catalyze the oxidative carboxylation of isocitrate to α-ketoglutarate. Instead, mutated IDH1 has neomorphic activity that converts α-ketoglutarate to the oncometabolite 2-hydroxyglutarate, resulting in intracellular 2-hydroxyglutarate accumulation with enhanced proliferation and impaired differentiation [11].

In the randomized, double-blind, placebo-controlled, global phase 3 ClarIDHy trial, the selective IDH1 inhibitor ivosidenib significantly improved progression-free survival (PFS) (median 2.7 months, 95% confidence interval 1.6–4.2) compared to placebo (1.4 months, 95% confidence interval 1.4–1.6) in patients with inoperable or metastatic IDH1-mutated iCCA who had progressed after up to two prior therapies [12, 13]. Patients randomized into the placebo arm were allowed to receive ivosidenib upon progression. More than 70% crossed over to the ivosidenib arm. This cross-over study design skewed the OS results. However when adjusting for cross-over, mOS was approximately doubled in patients treated with ivosidenib (mOS 10.3 months, 95% CI: 7.8–12.4 months) compared to placebo (5.1 months, 95% CI: 4.8–11.1 months).

Based on the ClarIDHy trial, ivosidenib is now approved by both the FDA (August 2021) and the EMA (May 2023) for the treatment of patients with locally advanced or metastatic CCA and a confirmed IDH1 R132 mutation who have received at least one prior systemic therapy. Of note, the median duration of treatment with ivosidenib in the ClarIDHy study was 2.8 months (range, 0.1–34.4 months). Treatment-related serious adverse events were reported in only 2% of patients receiving ivosidenib.

Here, we present 2 cases of patients with IDH1-mutated iCCA who received ivosidenib prior to EMA approval and achieved an exceptionally durable remission for more than 12 months. Importantly, no new safety signals were observed during this long-term treatment with ivosidenib.

Case Reports

Two patients with IDH1-mutant iCCA treated with ivosidenib 500 mg once daily at our institution (University Hospital Magdeburg) were identified. Ivosidenib was not yet approved in Germany, and the reimbursement requests for off-label ivosidenib were both approved by the responsible health insurance company prior to the start of treatment.

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For molecular pathological diagnoses, formalin-fixed paraffin-embedded tissue of the iCCA from the included patients was used. DNA/RNA preparation was performed from ten paraffin sections after macrodissection. Tumor cell content was 50% in case 1 and 80% in case 2. Mutation analysis was performed using HANDLE Classic next-generation sequencing (NGS) panel and NGS. The following genes are included: AKT1, **ALK**, BRAF, CDK4, CTNNB1, DDR2, DPYD, EGFR, **ERBB2**, ESR1, **FGFR1, FGFR2, FGFR3**, FGFR4, HRAS, IDH1, IDH2, KEAP1, KIT, KRAS, MAP2K1, MET, MYC, NFE2L2, NKX2-1, NRAS, **NRG1, NTRK1, NTRK2, NTRK3**, PDGFRA, PIK3CA, POLE, PTEN, RB1, **RET**, **ROS1**, STK11, TP53, and UGT1A1. Genes were additionally tested for the detection of copy number variations, and fusions are shown in bold. NGS included microsatellite instability molecular testing.

For each patient, we analyzed PFS, defined as the time from treatment initiation to disease progression or death; OS, defined as the time from ivosidenib initiation to death from any cause; and treatment duration, defined as the time from treatment initiation to treatment discontinuation. A safety analysis was performed on both patients. Patient characteristics, a comprehensive timeline summarizing the major events of this case series, survival outcomes, and the time course of carbohydrate antigen 19-9 (CA19-9) from first diagnosis to last presentation of the 2 patients treated with ivosidenib are shown in Table 1, Figures 1 and 2. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539665).

Case 1

In August 2013, a 60-year-old female patient presented to our clinic with a feeling of pressure in the right upper quadrant of the abdomen. A magnetic resonance imaging of the liver showed a 10 × 9 cm large liver lesion involving segments IVa, IVb, and V. The serum tumor marker CA19-9 level was not increased. The patient underwent oncological tumor resection. Histological examination revealed a pT3 pN1 L1 V0 Pn1 G2 R1 CCA with gallbladder invasion. After recovery, the patient received additive systemic therapy with gemcitabine. Sixteen months after the resection, a new CCA manifestation in the liver segment II was surgically resected. Additional isolated metachronous lung, liver, and peritoneal lesions (i.e., oligometastatic disease) were then treated with local ablative procedures (microwave ablation, radiofrequency ablation, and interstitial brachytherapy) or surgical resection (the sequence of local therapies is shown in Table 1). In April 2018, because of progressive peritoneal disease not amenable for surgical resection, palliative systemic therapy with gemcitabine/cisplatin was initiated, resulting in partial remission after four cycles. On October 2018, in a chemotherapy-free interval, localized progressive disease in the liver was treated by transarterial radioembolization with partial response of the hepatic lesions. Subsequently, further progressive peritoneal disease necessitated re-exposing the patient to gemcitabine/cisplatin, resulting in disease control. At this stage, in addition to fatigue CTCAE 1° and persistent thrombocytopenia CTCAE 2°, the chemotherapy was also not well tolerated psychologically. After a period of rest from therapy, progressive hepatic and peritoneal metastases were documented in January 2020 (shown in Fig. 3a). Molecular analysis of the tumor by NGS revealed an R132C mutation in the IDH1 gene with an allele frequency of 11.1% and no other pathogenic alterations. The reimbursement request for off-label ivosidenib to the responsible health insurance company was approved, and treatment with ivosidenib 500 mg once daily was started in March 2020. At 20 months, the best response was partial remission. Notably, serum CA19-9, which was normal prior to ivosidenib initiation, showed a steady increase over 4 months to 79.8 U/mL and then stabilized (range 71.2–83.7 U/mL) throughout the duration of ivosidenib therapy. Overall, the treatment was well tolerated by the patient. No side effects

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Table 1. Baseline characteristics and detailed treatment of the 2 cases reported

	Case 1	Case 2
Patient characteristics		
Gender	Female	Male
Year of diagnosis	2013	2021
Age at diagnosis, years	60	80
ECOG performance status	0	1
Tumor-specific data at diagnosis		
Initial tumor stage	pT3 pN1 (1/9) L1 V0 Pn1 R1	cT2 cN0 cM0
Tumor grading	G2	G2
CA19-9 level at diagnosis, U/mL	13.4	35.5
IDH1 mutation	R132C	R132L
Allele frequency, %	11.1	32.94
Prior resection	Yes	No
Adjuvant chemotherapy	Gemcitabine	–
Local treatment	Yes	No
	March 2015, MWA lung	–
	June 2015, iBT liver	
	January 2016, iBT lung	
	December 2016, iBT liver	
	August 2017, RFA lung	
	December 2018, TARE liver	
	November 2021, iBT liver	
First-line therapy	Gemcitabine/cisplatin	Gemcitabine/cisplatin
Cycles, *N*	10*	4
Dose reduction	Yes	Yes
Therapy with ivosidenib		
Duration of therapy, months	26	13
Best response	Partial remission	Stable disease
Overall survival, months	34	16, still alive
Dose reduction	No	No

TARE, transarterial radioembolization; MWA, microwave ablation; iBT, interstitial brachytherapy; RFA, radiofrequency ablation.

*Indicates repeated exposure to gemcitabine/cisplatin.

were observed in laboratory chemistry and electrocardiography. Clinical side effects were intermittent myalgia, fatigue, and mild nausea, all CTCAE 1°. The patient did not require treatment interruption at any time. In November 2021, a single progressive liver metastasis was documented and treated locally with interstitial brachytherapy, while ivosidenib was continued as all other hepatic and peritoneal manifestations were stable. Six months later, in July 2022, hepatic and peritoneal metastases progressed and ivosidenib was discontinued after a treatment period of 24 months. Neither subsequent FOLFIRI

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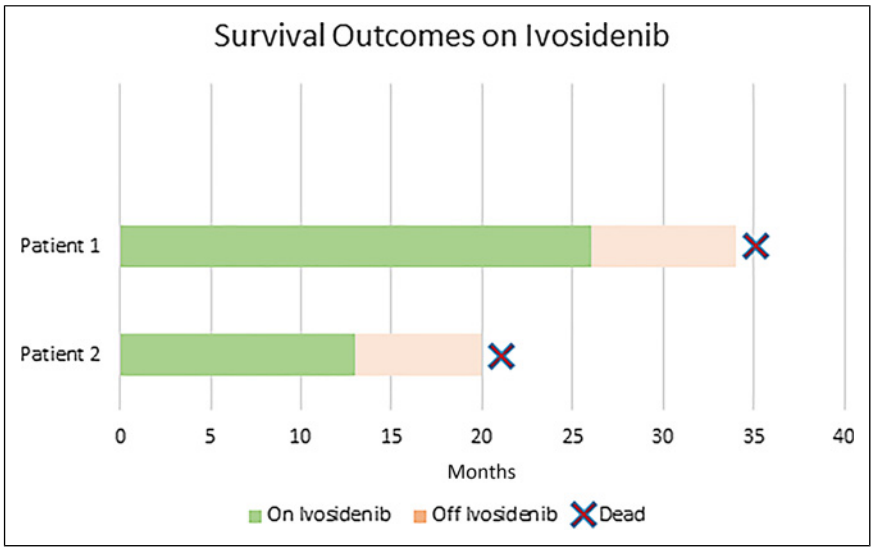

Fig. 1. Swimmer plot of survival outcomes for patients treated with ivosidenib.

protocol systemic chemotherapy nor re-exposure to gemcitabine/cisplatin resulted in disease control. Notably, serum CA19-9 measured 3 months after ivosidenib discontinuation returned to normal levels. In November 2022, a biopsy of a parietal peritoneal metastasis in the right upper quadrant of the abdomen was performed for repeat molecular diagnostics, but a new NGS did not reveal any new actionable mutation. Only the known R132C mutation in the IDH1 gene was confirmed. Despite a good performance status (ECOG 1), no further tumor-directed therapy was attempted due to insufficient evidence, and she died 4 months later from complications related to the peritoneal metastases.

Case 2

In September 2021, an 80-year-old male patient with known diabetes mellitus type II was admitted with recurrent fever and chills due to diabetic foot syndrome of the right big toe. Other comorbidities included diabetic sensory polyneuropathy, chronic heart disease with heart failure and NYHA II dyspnea, stage 2 chronic renal failure, controlled arterial hypertension, and a history of nicotine abuse up to 40 years ago. A screening CT of the lungs for further infectious foci revealed a liver lesion. The subsequent magnetic resonance imaging with liver-specific contrast agent showed two hypervascular lesions of 67 × 58 mm and 10 × 15 mm, respectively, in segment VII/VIII. Histology of the CT-guided biopsy revealed a moderately differentiated bile duct carcinoma. An R132L mutation in the IDH1 gene with an allele frequency of 32.9% and a missense mutation of the TP53 (c.743G>A) with an allele frequency of 17.6% were detected by NGS of the tumor sample. The serologic tumor marker CA19-9 was slightly elevated at 35.5 U/mL. After surgical exploration excluding further tumor manifestations, multidisciplinary tumor board recommended contralateral liver lobe hypertrophy induction by portal vein embolization followed by right hemihepatectomy. However, after a surgical explanation of the benefits and risks of this procedure, the patient declined this treatment option. Therefore, chemotherapy with gemcitabine/cisplatin was started in December 2021 with dose reduction due to the advanced age of the patient. Restaging after four cycles of chemotherapy showed a partial remission and normalization of the tumor marker CA19-9. However, the patient developed anemia CTCAE 2° and the sensory polyneuropathy

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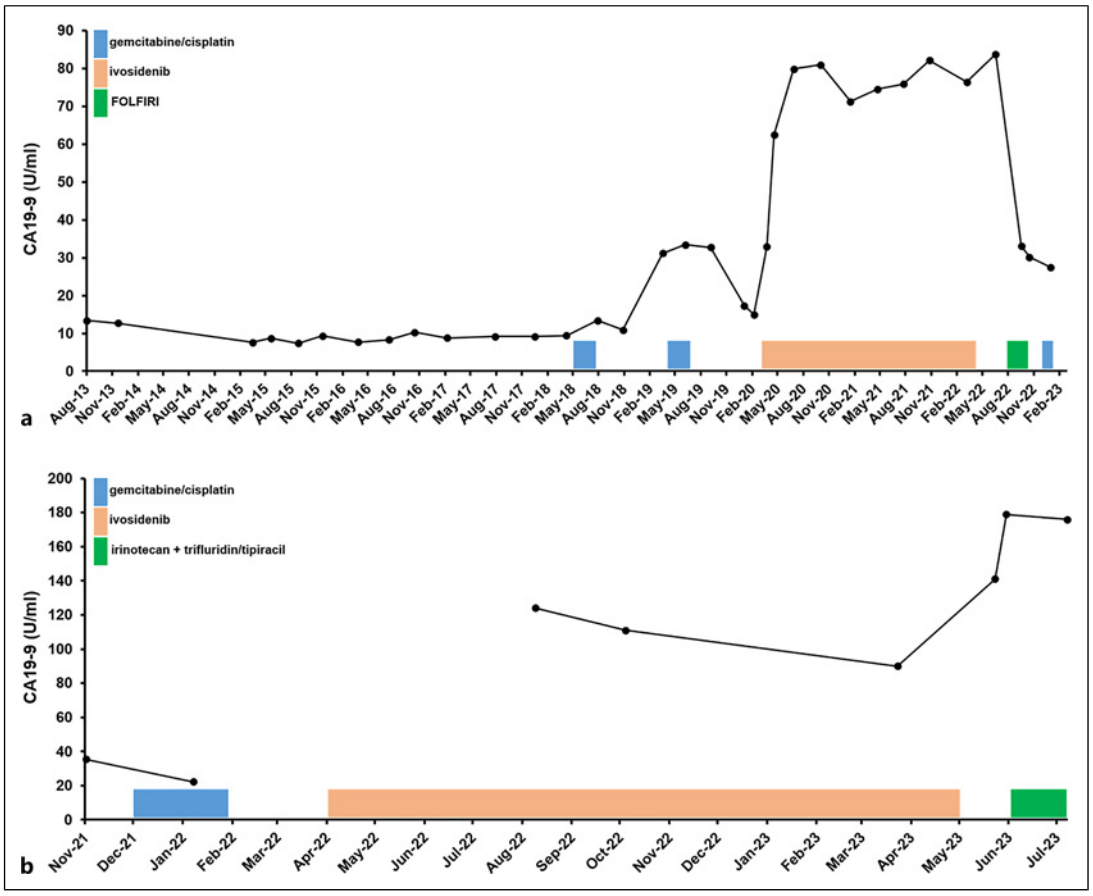

Fig. 2. Time course of CA19-9 from initial diagnosis to last presentation. Time course of the serologic tumor marker CA19-9 (values in U/mL) from initial diagnosis to last presentation in our department for case 1 shown in (**a**) and case 2 shown in (**b**). Both graphs also show the time course of systemic therapy (blue: gemcitabine/cisplatin; orange: ivosidenib; green: 5-irinotecan-based therapy). In case 2, tumor marker assessment prior to treatment with ivosidenib is not available.

CTCAE 1° in both legs, which was already present before the start of chemotherapy due to a long history of diabetes, and worsened to CTCAE 2°. Therefore, despite a good performance status ECOG 1, chemotherapy was discontinued in January 2022. The reimbursement request for off-label ivosidenib to the responsible health insurance company was approved and treatment with ivosidenib 500 mg once daily was started in April 2022. A CT scan performed prior to ivosidenib initiation showed stable disease (shown in Fig. 3b). Unfortunately, serum CA19-9 levels prior to ivosidenib are not available. The therapy was well tolerated by the patient with no relevant clinical, laboratory, or electrocardiographic side effects for 13 months. In particular, CA19-9 decreased steadily from 124 to 90 U/mL, the last and best value achieved in March 2023. In May 2023, a CT scan showed progressive disease with a slight increase in the size of lesions in the liver, a new lesion in the left upper lobe of the lung, and an increase in serum CA19-9 levels to 179 U/mL. In this case, no re-biopsy was performed. Irinotecan-based chemotherapy as part of a phase 2 clinical trial resulted in further disease progression as documented by a CT scan in July 2023, along with deterioration of performance status (ECOG 3). No further tumor-specific therapy was attempted, and he died 4 months later from complications related to local tumor growth with liver failure.

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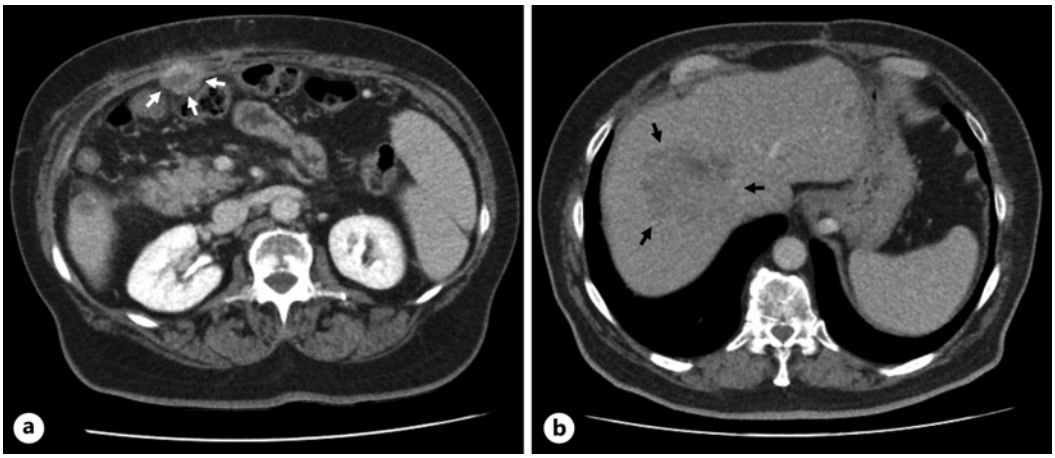

Fig. 3. Representative CT scans of both cases prior to starting ivosidenib. Representative axial CT scan in venous contrast phase prior to ivosidenib treatment. **a** Representative image of case 1 showing evidence of peritoneal carcinomatosis (white arrows). **b** Representative image of case 2 with evidence of a flat diffuse mass in the liver (black arrows).

Discussion

Here, we describe two real-world cases of patients with IDH1-mutated iCCA who achieved exceptionally durable remissions for more than 12 months on ivosidenib. In a recent real-world case series of 8 patients with unresectable or metastatic CCA, the longest duration of treatment with ivosidenib was 9 months [14]. Thus, to our knowledge, we report the longest duration of response to ivosidenib described to date outside of a prospective study. Our data are consistent with the ClarIDHy trial, where despite a median treatment duration of 2.8 months (range: 0.1–34.4 months), a small percentage of patients (15%) received ivosidenib for more than 12 months.

A peculiarity of case 1 is that the PFS was 20 months, but the total treatment duration was 26 months. In fact, after 20 months on ivosidenib a single progressive liver metastasis was documented and treated locally with interstitial brachytherapy, while ivosidenib was continued for another 6 months until the next unequivocal progression. A similar strategy has been adopted in ClarIDHy, where 12% of patients receiving ivosidenib were permitted to continue treatment beyond radiographic progression [12]. Indeed, ivosidenib had an excellent safety profile in our case, and in the absence of convincing alternative therapies, patients with a mixed radiographic response may be better off remaining on ivosidenib rather than switching to best supportive care or even another chemotherapy regimen.

Of note, in case 1, serum CA19-9 increased during ivosidenib therapy despite clear clinical disease control and decreased after ivosidenib discontinuation. The observational nature of our report does not allow an explanation of this phenomenon. With respect to case 2, the unavailability of CA19-9 levels prior to ivosidenib initiation does not allow this observation to be confirmed or refuted.

In case 2, chemotherapy-induced worsening of pre-existing polyneuropathy and hematotoxicity precluded continuation of chemotherapy and necessitated a change in treatment. In this case, treatment with ivosidenib resulted in disease control for 13 months, with the best response being stable disease.

Prognostic markers that can identify patients with IDH1-mutated CCA who would benefit most from ivosidenib, such as the patients we have reported, are highly desirable. Based on a 52-gene NGS panel (Oncomine™ Focus Assay), no association of baseline co-variants in any single gene with OS, PFS, or treatment duration was observed in ClarIDHy [13]. Nevertheless, in a

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multicenter real-world study analyzing samples from 125 patients with IDH1-mutated CCA using a more comprehensive NGS panel (FoundationOne® CDx), three distinct genomic clusters with prognostic significance were proposed [14, 15]. However, the genetic tumor profile detected in our patients is not consistent with the described clusters. For example, our patient 2 was treated with ivosidenib for 13 months despite a TP53 alteration that is clustered with the worse prognosis.

While our real-world data support the use of ivosidenib in patients with advanced CCA, further real-world data are needed to confirm the benefits and risks observed in the phase 3 ClarIDHy trial, providing additional evidence on the drug's performance in a broader, more diverse patient population. Whether combination strategies of ivosidenib with other therapies can further improve patient outcomes is yet to be determined. Initial results from an ongoing phase I/II study investigating the combination of ivosidenib with nivolumab and ipilimumab are expected in 2027 (EudraCT Number 2023-503236-41).

Conclusion

In our cases, ivosidenib was effective in a heavily pretreated patient as well as in a patient who required a change in therapy due to chemotherapy-induced side effects. Despite long-term treatment with ivosidenib, no new safety signals were observed.

Acknowledgments

We would like to thank the patients and family members who consented to the publication of their data.

Statement of Ethics

This study protocol was reviewed and approved in February 2023 by the local Ethics Committee of the Medical Faculty and University Hospital of the Otto-von-Guericke University in Magdeburg, reference number 26/23. Written informed consent for publication of these case reports and any accompanying images was obtained from the patients during the time they were alive, in the presence of their next of kin. The completed consent form can be made available to the editor at any time if requested.

Conflict of Interest Statement

C.M. and S.F. have no conflicts of interest to declare. T.R. is an employee of Servier Deutschland GmbH. V.K. received honoraria for speakers' corner from AbbVie, Gilead, Falk, Albireo, and CSL Behring, and participated in an advisory board for AstraZeneca. M.V. received honoraria for speaker, consultancy, and advisory role from Servier, Roche, BMS, MSD, EISAI, Bayer, Lilly, AstraZeneca, Merck Serono, Sirtex, Ipsen, Nordic Pharma, and Amgen.

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Author Contributions

M.V. conceived and is the guarantor of the manuscript. C.M. and M.V. drafted the manuscript, analyzed the data, and interpreted the data in the context of the literature. S.F., T.R., and V.K. supported the development of the manuscript and critically revised the manuscript. All authors approved the final version of the manuscript, read and approved the published version, and took responsibility for the accuracy and integrity of the data presented.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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