Complete Response Associated With Combination Treatment Regorafenib and Sintilimab in a Sorafenib-refractory Hepatocellular Carcinoma Patient

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Case report

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Abstract

Background

Most of patients diagnosed with Hepatocellular carcinoma (HCC) have advanced diseases and many are not eligible for curative therapies. There is a growing evidence suggesting that combination treatment of PD-1/PD-L1 inhibitors and tyrosine kinase inhibitors (TKIs) becomes a prospective trend for advanced HCC. For those HCC patients with sorafenib resistance, the efficacy of regorafenib combined with PD-1/PD-L1 inhibitors remains unclear.

Case presentation:

Herein, we represent a case of HCC with lung metastasis in the setting of HBV-induced liver cirrhosis responding dramatically to the combination treatment of sorafenib-regorafenib sequential and PD-1 inhibitor after initial liver resection. A 56-year-old man diagnosed with AFP-negative HCC underwent liver resection in September 2015, and was found to have solitary liver recurrence and lung metastases in March 2017. He received microwave coagulation therapy and trans-arterial chemoembolization (TACE) for liver tumor and treatment was started with sorafenib 400 mg twice daily for controlling lung metastases. In December 2018, abdominal computerized tomography (CT) scan showed two new lesions in liver. In March 2019, disease progression of lung metastases was measured and he received 160 mg regorafenib once daily. After a short period of partial response, he started treatment with regorafenib 160 mg in combination with sintilimab (200 mg, 3 weeks as a cycle) in December 2019 due to disease progression. Surprisingly, after 5 cycles of sintilimab injection, it showed complete response in target lesions. There is no clinical evidence of disease progression and the side effects were mild and well tolerated. The current overall survival is 57 months.

Conclusion

Data from this clinical case report suggests that combination therapy of regorafenib and PD-1 inhibitor is a promising therapeutic option for the treatment of advanced HCC. This is the first article reporting the complete response to regorafenib combination therapy with PD-1 inhibitor for sorafenib-refractory HCC.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death in the world and its incidence rate is rising in recent years [1]. In China, the number of HCCs accounts for nearly half of the world's new cases [2]. Both the incidence and mortality rates are 2 to 3 times higher in China than those in majority of other countries [3]. Liver resection, liver transplantation and local ablation are curative treatments for earlier stages of HCC, which achieve good surgical outcomes. However, HCC frequently relapses and most patients have locally advanced or extrahepatic metastasis when curative treatments are no longer available. For these patients, evidence for highly effective therapies on overall survival (OS) is still lacking.

Trans-arterial chemoembolization (TACE) can be used to treat HCC confined to the liver and the therapeutic effect is limited.

Sorafenib, a small-molecule multi-kinase inhibitor, is the first systemic therapeutic agent for patients with advanced HCC after a landmark study which revealed improvements in time to progression (TTP) and OS [4, 5]. However, the therapeutic impact of sorafenib remains limited, and patients often acquire resistance soon after treatment. Thus, for HCCs who are refractory or intolerant to sorafenib, the second-line treatment for HCC is very important. Regorafenib is a multikinase inhibitor that blocks the activity of several protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumour immunity [6]. It has a distinct molecular target profile and had more potent pharmacological activity than sorafenib in previous studies [6, 7]. Nevertheless, this therapy remains unsatisfactory. Therefore, there is an urgent need for more effective systemic therapies for HCC, particularly after treatment with sorafenib and regorafenib.

There is growing evidence suggesting that HCC was considered as an immunogenic tumor, stemming from an immunosuppressive environment. In the past few years, breakthroughs in immune therapy have offered new therapeutic options for many tumors [8]. The inhibitors of the programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have emerged as a promising therapeutic strategy in a variety of cancers, such as melanoma, lung cancer and renal cell carcinoma [8, 9]. The chronic inflammation, viral infection and liver cirrhosis underlying the formation of most HCC tumors highlight a complicated relationship between the immune biology and the development of HCC [10]. The liver is constitutively immunosuppressive as it promotes systemic tolerance to foreign antigens, which prevents excessive reactions to toxins and antigens absorbing from the enteric circulation [11]. HCC takes advantage of the immune tolerance to initiate and promote HCC carcinogenesis and progression. These characteristics of HCC may steer immunotherapeutic strategies to those that prevent immune suppressive mechanisms, rather than directly increase the immune function of HCC patients. The recently published open-label, phase 3 (IMbrave150) trial reported atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib with a objective response rate (ORR) of 33.2% versus 13.3% in patients with advanced HCC, which was granted as a first-line treatment for patients with advanced or metastatic HCC by the FDA [12]. Studies show that the anti-VEGF and PD-1/PD-L1 inhibitor combination improves antigen-specific T-cell migration. These results provide evidence for efficiency of immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) combination in advanced and metastatic HCC, indicating the combination therapy might become a prospective trend for advanced HCC.

To evaluate clinical efficacy of the combination rationale including ICIs and TKIs, we represent a case of HCC with lung metastasis in the setting of HBV-induced liver cirrhosis responding dramatically to the combination of sorafenib-regorafenib sequential treatment and PD-1 inhibitor after initial liver resection and we hope to explore further study for combination therapy of regorafenib and PD-1/PD-L1 inhibitor for HCC in the future.

Case Presentation

A 56-year-old man with a history of chronic HBV infection for more than 30 years, presented to our department with abdominal malaise in September 2015. Enhanced abdominal magnetic resonance imaging (MRI) revealed a mass with the largest measuring up to 11.0*9.5 cm in size in segment 7 and 8 within the right lobe of liver (Fig. 1A and 1B). The patient was diagnosed of HCC with the background of cirrhosis secondary to HBV infection based on imaging and confirmed with the clinical diagnosis of Barcelona Clinic Liver Cancer (BCLC) A and Child-Pugh class A. Entecavir treatment was routinely used once per day from then on. His alpha-fetoprotein (AFP) level was in the normal range. On September 23, 2015, he underwent segment 7 and 8 resection and cholecystectomy. The postoperative pathological examination showed hemorrhage with necrosis in the middle of the tumor, with moderate differentiation and vascular cancer embolus. The incisal edge was negative and not invaded the hepatic capsule (Fig. 1C and 1D). He recovered well and discharge from hospital. With regular examination, unfortunately, in March, 2017, he was found to liver recurrence and had lung metastases (BCLC C). According to the guidelines, he started systemic treatment with sorafenib (400 mg, twice per day) and could tolerated this dose. Enhanced abdominal CT showed a heterogeneous irregular mass measuring up to 2.3*2.2 cm with arterial phase enhancement and venous phase washout in the left lobe of liver (**Fig.S1**). Chest CT revealed that multiple pulmonary nodules on both sides of the lung which were diagnosed as lung metastases, the largest up to 8-mm diameter (Fig. 2A/B). The patient received percutaneous microwave coagulation for the liver tumor on March 23, 2017. On April 5, 2017, he proceeded with TACE and then pulmonary arterial infusion (PAI) on December 27, 2017. On December 24, 2018, enhanced abdominal CT showed two lesions with the largest diameter 3 cm in both sides of liver (Fig. 3A-D). He had radiographic progression in lung metastases after 3 months (Fig. 2C/D). Disease progression was measured using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v 1.1) or modified RECIST for HCC (mRECIST). Under this circumstance, he received 160 mg regorafenib orally once daily for 3 weeks in each 4-week cycle. The patient had no dose reductions in the period of medical treatment. On June 12, 2019, restaging chest CT showed partial response in lung metastases (Fig. 2E/F). Despite good tolerability of regorafenib, repeat MRI scans on December 3, 2019 revealed obvious tumor progression in liver and lung (Fig. 2G/H and Fig. 3E/F). The patient started treatment with regorafenib 160 mg in combination with sintilimab on December 4. Sintilimab was given 200 mg over a period of 30–60 min for every 3 weeks as a cycle. The patient tolerated treatment well except potentially treatment associated general pruritus grade 2 with mild skin changes but without rash. After 5 cycles of sintilimab injection, a follow-up abdominal MRI scan showed complete response in target lesions of liver without any tumor activity, as assessed by mRECIST (Fig. 3G/H), while chest CT revealed complete response in target lesions of lung, as evaluated by RECIST v 1.1 (Fig. 2I/J). Figure 4 showed local and systemic treatment and summary diameter of target lesions according to RECIST v 1.1 or mRECIST. During systematic treatment process, the patient has no severe complications and shows good liver function (Child-Pugh A) (Table 1). At his last follow-up, nearly 5 years have elapsed since the diagnosis of HCC and up to 40 months since lung metastases was diagnosed. He was observed to be in a very good condition, without evidence of disease progression. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Table 1
The liver function and full blood test analysis corresponding to the treatment.

Date	Child-Pugh	Ascites	T-BIL (umol/L)	ALB (g/L)	PT (s)	WBC (*10 ⁹)	HB (g/L)	PLT (*10 ⁹)
17.3.21	A	N	11	41.3	13.7	3.97	138	104
17.5.14	A	N	35.8	39.7	14.7	3.66	128	96
17.12.27	A	N	33.8	41.2	14.1	5.26	129	88
18.12.24	A	N	19.3	39.8	13.5	5.03	146	103
19.3.21	A	N	14.2	44.1	12.4	4.77	148	100
19.6.12	A	N	36.0	36.7	14.8	7.38	140	127
19.12.5	A	N	16.2	38.8	11.9	5.49	132	172
20.5.11	A	N	24.2	39.6	12.1	5.67	138	166

Discussion

Liver resection is recommended as the first line of treatment for patients with early stage HCC with well-preserved liver function [13]. However, resection of even very early tumors, less than 2 cm and without vascular invasion or satellites (BCLC stage 0), is associated with a recurrence rate of approximately 60% at 5 years [13, 14]. HCC patients are often diagnosed at advanced stages when recurrence occurs, and curative therapy options are limited. The prognosis is extremely poor, leading to a 5-year overall survival rate of 2% [3].

The systemic treatment options available for HCC patients with advanced stages are limited. Overall, more than 50% of patients receive systemic therapies at some point during the disease process [15]. Sorafenib, a molecular kinase inhibitor, was thought to be a breakthrough in treating unresectable HCC although only 3 months longer OS was found in SHARP trial [4]. For a decade, sorafenib was the only FDA-approved therapy and the benefits were limited for lack of either therapeutic alternative or second-line treatment for those who are intolerant or resistant. However, since 2017, treatment for patients with advanced HCC is dramatically changed by novel multi-target inhibitors approved, such as regorafenib, lenvatinib and cabozantinib, or immune checkpoint inhibitors, such as nivolumab and pembrolizumab. Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumour immunity [6, 7]. Regorafenib is the only systemic treatment shown to provide survival benefit in advanced HCC patients progressing on sorafenib treatment. RESORCE trial indicated that regorafenib improved OS with a hazard ratio of 0.63 (95% CI: 0.50–0.79; one-sided $p < 0.0001$); median survival was 10.6 months (95% CI: 9.1–12.1) for regorafenib versus 7.8 months (6.3–8.8) for placebo [6]. Although regorafenib has been approved as a second-line treatment for patients with advanced HCC who show progression after sorafenib therapy, the treatment efficacy remains insufficient. With the development of immune therapy, the treatment effects on HCC need to be urgently explored.

PD-1 is expressed by activated T lymphocytes and is a pivotal immune checkpoint receptor that mediates immunosuppression upon binding to the PD-L1 expressed by tumor cells [9]. In recent years, immune checkpoint blockade has brought a paradigm shift in the treatment of a number of solid tumors. Various immune checkpoint blocking agents are being tested for their efficacy in HCC. Furthermore, PD-1 pathway offers a potential treatment strategy based on the encouraging results of KEYNOTE-224 [16] and Checkmate 040 trials [17]. Recently, IMbrave150 trial showed better overall and progression-free survival outcomes of atezolizumab plus bevacizumab as compared with sorafenib in patients with unresectable hepatocellular carcinoma who had not previously received systemic therapy, which inspired us to administrate this combination therapy in advanced or metastatic HCC [12]. Sintilimab (Innovent Biologics, Suzhou, China) is a highly selective, humanised, monoclonal antibody that blocks interactions between PD-1 and its ligands and has been tested regarding the safety and activity in patients with advanced-stage solid tumor and was approved for lymphoma by Chinese Center for Drug Evaluation in China in 2018 [18–20]. Findings from a phase 1 study of sintilimab in advanced solid tumours suggested 200 mg every 3 weeks as the recommended dose, and clinical benefit from the therapy was observed [19, 21].

For those HCC patients with sorafenib resistance, the efficacy of regorafenib combined with PD-1/PD-L1 inhibitors remains unclear. Regorafenib was proved to be an immunomodulator in tumor microenvironment while PD-1 antibody blocks the co-inhibitory signals and unlocks the negative regulation of the immune response [22, 23]. Therefore, further investigations for the combination treatment of regorafenib and PD-1/PD-L1 inhibitors are warranted to provide its efficacy data in clinical trials. Unfortunately, there are no published data from randomized controlled trials in HCC which were registered on clinicaltrials.gov currently (Table 2). Standard combination and sequencing of the therapy need to be established with deeper insight into the rationale of combined action and further RCTs. What's more, for most of the patients enrolled in, present with preserved liver function, while the advanced HCC patients in real clinical phase may have a much worse performance. Whether they can tolerate the combination treatment is still unknown and the clinical trials won't take the risk to enroll these patients. Joerger *et al.* [24] presented the case of a sorafenib-refractory patient probably experiencing progressive disease during immune checkpoint inhibitor combination treatment with the anti-PD-1 monoclonal antibody nivolumab and the anti-GITR monoclonal antibody BMS-986156 within a clinical phase-1 trial followed by a prolonged tumor response according to RECIST v 1.1 during third-line treatment with regorafenib. In this case, sorafenib-immunotherapy-regorafenib sequential treatment was applied and the last evaluation was documented as partial response and the patient started taking regorafenib at a reduced dose of 80 mg and later further reduced to 40 mg per day. The patient in our report was evaluated as complete response after combination therapy of regorafenib with standard dose and sintilimab. No life-threatening adverse events were found in our patient. The combination of regorafenib and PD-1/PD-L1 inhibitor will be a novel therapy method for the future gold standard in the systemic treatment of sorafenib-refractory HCC.

Table 2
Ongoing clinical trials with regorafenib and PD-1/PD-L1 inhibitors in hepatocellular carcinoma.

NCT Number	Study Title	N	Interventions	Trial phase	Primary endpoint	Current status
NCT 04170556	Regorafenib Followed by Nivolumab in Patients With Hepatocellular Carcinoma	60	Regorafenib + Nivolumab	1 and 2	AE TTP	Recruiting
NCT 04183088	Regorafenib Plus Tislelizumab as First-line Systemic Therapy for Patients With Advanced Hepatocellular Carcinoma	125	Regorafenib+ Tislelizumab	2	AE ORR	Not yet recruiting
NCT 03347292	Regorafenib Plus Pembrolizumab in First Line Systemic Treatment of HCC	57	Regorafenib+ Pembrolizumab	1	AE	Recruiting
NCT 03475953	A Phase I/II Study of Regorafenib Plus Avelumab in Solid Tumors	362	Regorafenib+ Avelumab	1 and 2	Phase 1 : Recommended phase 2 Dose Phase 2 : Assessment of the antitumor activity of regorafenib	Recruiting
NCT 04310709	Combination of Regorafenib and Nivolumab in Unresectable Hepatocellular Carcinoma	42	Regorafenib+ Nivolumab	2	RR	Not yet recruiting
AE, Adverse Events; TTP, Time to progression; ORR, Objective response rate; RR, Response rate.						

The precise mechanism of synergistic effect between regorafenib and PD-1/PD-L1 inhibitors remains unclear. Previous study indicated that inhibition of JAK1/2-STAT1 signaling pathway blocked MHC-I expression while suppressing the MAPK pathway increased MHC-I expression [25]. Through inhibiting both the RET-Src axis/JAK1/2-STAT1 and MAPK pathway, regorafenib had little influence on MHC-I expression. Taken together, through blocking the IFN- γ induced PD-L1 and IDO1 expression with little influence on MHC-I expression, regorafenib unleashed the IFN- γ side effect without compromising the antigen presentation processes. What's more, tumor-associated macrophage (TAM) is major population of immune cells that affects tumor development. One of the mechanisms described for the failure of anti-angiogenic therapy and tumor evasion is the strong infiltration of TAMs. TAM serves as an important driving factor in

immunosuppressive tumor microenvironment (TME) and, for instance, the secreted TGF- β inhibits CD8 + T-cell responses to kill the cancer cells [26, 27]. Regorafenib modulates TAM re-polarization and relieved the immunosuppressive effect of TAM via binding to CSF-1R [27]. Terme *et al.* [28] demonstrated that regorafenib reduces the proportion of Tregs and inhibits tumor-induced Treg proliferation via targeting the vascular endothelial growth factor A (VEGFA)/VEGF receptor 2 (VEGFR2) signaling pathway. Regorafenib targets a variety of kinases involved in angiogenic, tumor growth-promoting and tumor micro-environmental signalling pathways [7]. The probable mechanism of synergistic effects of regorafenib and PD-1/PD-L1 inhibitors are showed in Fig. 5.

In summary, this study provided the first case of complete tumor response to the combination of regorafenib and sintilimab as second line treatment for a patient with advanced, pulmonary metastatic HCC which was refractory to first-line sorafenib. Data from this clinical case report support future exploration of combination treatment of the oral multi-kinase inhibitor regorafenib with PD-1/PD-L1 inhibitors in sorafenib-refractory HCC patients. Regorafenib plus PD-1 or PD-L1 inhibitor may present a new potential treatment option for the advanced HCC patient with sorafenib resistance. However, their synergistic effects and safety need further investigation in a randomized phase 3 study.

Declarations

Acknowledgements

None

Authors' contributions

ZYH was the chief physician who provided the case. ELZ provided funding and was a major contributor in writing the manuscript and performing the analysis and interpretation of data. ZYZ and LZ collected clinical data. SX and XPC revised the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

Not applicable as all information and data is presented in manuscript.

Ethics approval and consent to participate

Ethical approval is not required as patient consent for publication was obtained.

Consent for publication

Written informed consent was obtained from the patient's father for publication of the present study; the patient authorized her father to provide informed consent as she was in ill health at the time.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin.* 2018;68(6):394–424.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *Cancer J Clin.* 2016;66(2):115–32.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *Cancer J Clin.* 2019;69(1):7–34.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359(4):378–90.
5. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *The Lancet Oncology.* 2009;10(1):25–34.
6. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10064):56–66.
7. Abou-Elkacem L, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, Lederle W. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. *Mol Cancer Ther.* 2013;12(7):1322–31.
8. Dermani FK, Samadi P, Rahmani G, Kohlan AK, Najafi R. PD-1/PD-L1 immune checkpoint: Potential target for cancer therapy. *Journal of cellular physiology.* 2019;234(2):1313–25.
9. Constantinidou A, Alifieris C, Trafalis DT. Targeting Programmed Cell Death – 1 (PD-1) and Ligand (PD-L1): A new era in cancer active immunotherapy. *Pharmacol Ther.* 2019;194:84–106.
10. Khan H, Pillarisetty VG, Katz SC. The prognostic value of liver tumor T cell infiltrates. *J Surg Res.* 2014;191(1):189–95.
11. Chan T, Wiltrott RH, Weiss JM. Immunotherapeutic modulation of the suppressive liver and tumor microenvironments. *Int Immunopharmacol.* 2011;11(7):879–89.
12. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med.* 2020;382(20):1894–905.

13. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. *Annals of surgery*. 2015;261(5):947–55.
14. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, Labow D, Llovet JM, Schwartz M, Mazzaferro V. Resection of hepatocellular cancer ≤ 2 cm: results from two Western centers. *Hepatology*. 2013;57(4):1426–35.
15. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nature reviews Clinical oncology*. 2018;15(10):599–616.
16. Zhu AX, Finn RS, Edeline J, Cattani S, Ogasawara S, Palmer D, Verslype C, Zagonel V, Fartoux L, Vogel A, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. *The Lancet Oncology*. 2018;19(7):940–52.
17. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling THR, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–502.
18. Boku N, Ryu MH, Kato K, Chung HC, Minashi K, Lee KW, Cho H, Kang WK, Komatsu Y, Tsuda M, et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4). *Annals of oncology: official journal of the European Society for Medical Oncology*. 2019;30(2):250–8.
19. Gao S, Li N, Gao S, Xue Q, Ying J, Wang S, Tao X, Zhao J, Mao Y, Wang B, et al. Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer*. 2020;15(5):816–26.
20. Shi Y, Su H, Song Y, Jiang W, Sun X, Qian W, Zhang W, Gao Y, Jin Z, Zhou J, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *The Lancet Haematology*. 2019;6(1):e12–9.
21. Duan X, Zhang H, Zhou L, Jiang B, Mao X: Complete response to the combination of sintilimab and IBI305 for a patient with HBV-associated hepatocellular carcinoma with multiple lung metastasis. *Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2020.
22. Kudo M. Immuno-Oncology in Hepatocellular Carcinoma: 2017 Update. *Oncology*. 2017;93(Suppl 1):147–59.
23. Lin YY, Tan CT, Chen CW, Ou DL, Cheng AL, Hsu C. Immunomodulatory Effects of Current Targeted Therapies on Hepatocellular Carcinoma: Implication for the Future of Immunotherapy. *Semin Liver Dis*. 2018;38(4):379–88.
24. Joerger M, Guller U, Bastian S, Driessen C, von Moos R. Prolonged tumor response associated with sequential immune checkpoint inhibitor combination treatment and regorafenib in a patient with advanced pretreated hepatocellular carcinoma. *Journal of gastrointestinal oncology*. 2019;10(2):373–8.

25. Wu RY, Kong PF, Xia LP, Huang Y, Li ZL, Tang YY, Chen YH, Li X, Senthilkumar R, Zhang HL, et al. Regorafenib Promotes Antitumor Immunity via Inhibiting PD-L1 and IDO1 Expression in Melanoma. *Clinical cancer research: an official journal of the American Association for Cancer Research*. 2019;25(14):4530–41.
26. Zhao P, Wang Y, Kang X, Wu A, Yin W, Tang Y, Wang J, Zhang M, Duan Y, Huang Y. Dual-targeting biomimetic delivery for anti-glioma activity via remodeling the tumor microenvironment and directing macrophage-mediated immunotherapy. *Chemical science*. 2018;9(10):2674–89.
27. Hume DA, MacDonald KP. Therapeutic applications of macrophage colony-stimulating factor-1 (CSF-1) and antagonists of CSF-1 receptor (CSF-1R) signaling. *Blood*. 2012;119(8):1810–20.
28. Terme M, Tartour E, Taieb J. VEGFA/VEGFR2-targeted therapies prevent the VEGFA-induced proliferation of regulatory T cells in cancer. *Oncoimmunology*. 2013;2(8):e25156.

Figures

Figure 1

MRI showed a mass with the largest measuring up to 11.0*9.5cm in size in segment 7 and 8 within the right lobe of liver before surgical resection (A and B). Postoperative pathology revealed moderate differentiation and vascular cancer embolus (C and D).

Figure 2

Chest CT scans showing the course of lung metastases. A and B show baseline tumor situation of the targets at the start of sorafenib systemic treatment. C and D show progressive disease upon treatment with sorafenib. E and F show partial response in lung metastases after treatment with regorafenib for 3 months. G and H show marked tumor progression in the lung metastases. I and J show complete response in target lesions of lung after treatment with sintilimab for 5 cycles.

Figure 3

Abdominal CT and MRI showing the course of hepatocellular cancer in the liver. A-D show two masses in both sides of liver. E and F show marked tumor progression in the liver. G and H show complete response in target lesions of liver.

Figure 4

Local and systemic treatment (C) and tumor volume (A/B), summary diameter of target lesions according to RECIST v.1.1.

Figure 5

The probable mechanism of synergistic effect between regorafenib and PD-1/PD-L1 inhibitors.

Supplementary Files

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