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Efficacy and safety of regorafenib or fruquintinib plus camrelizumab in patients with microsatellite stable and/or proficient mismatch repair metastatic colorectal cancer: an observational pilot study

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This study was to investigate the efficacy and safety of regorafenib or fruquintinib combined with camrelizumab in patients with microsatellite stable (MSS) and/or proficient mismatch repair (pMMR) metastatic colorectal cancer (mCRC). Medical records of MSS/pMMR mCRC patients who received regorafenib (80 mg) or fruquintinib (3 mg) once a day (21 days on/7 days off) plus camrelizumab (200 mg) every three weeks in Yuhuangding Hospital between January 2020 and June 2020 were retrospectively collected. Follow-up data up to November 1st, 2020 was gathered. The primary endpoint was the objective response rate (ORR) and disease control rate (DCR). The safety profile was the secondary endpoint. A total of 16 patients were enrolled. The ORR was 25.0% (4/16) and the DCR was 62.5% (10/16). The main adverse events (AEs) included reactive cutaneous capillary endothelial proliferation (RCCEP) (81.3%), fatigue (43.8%), hypertension (37.5%), hand-foot skin reaction (25.0%), and thyroid dysfunction (25.0%). Most AEs were grade 1 or 2, with only 1 patient of grade 3 liver dysfunction. All the AEs were ameliorated by effective symptomatic treatment. Regorafenib or fruquintinib plus camrelizumab exhibited promising efficacy in patients with MSS/pMMR mCRC. The toxicity was moderate and manageable.

Key words: regorafenib, fruquintinib, camrelizumab, MSS/pMMR, metastatic colorectal cancer

Colorectal cancer (CRC) is the third most common and the second most deadly cancer worldwide [1]. Annually, approximately 900,000 individuals die from CRC and the number of deaths is expected to rise by 60–70% in 2035 due to population growth and aging [2]. Most CRC patients have metastases at the time of diagnosis, which indicates a poor prognosis. The 5-year overall survival (OS) rate of CRC was only 13% [3]. The first- and second-line standard treatments for metastatic colorectal cancer (mCRC) are fluoropyrimidine- or capecitabine-based chemotherapies with or without anti-VEGF or anti-EGFR targeted therapy [4, 5]. In terms of third-line treatment, regorafenib or fruquintinib monotherapy is the first recommendation and immune checkpoint inhibitors (ICIs) are the second recommendation for mCRC patients in China. It should be noted that ICIs are only recommended for patients with microsatellite instability-high (MSI-H) and/or mismatch repair-deficient (dMMR) mCRC as few studies had reported on the efficacy of immunotherapy in microsatellite stability (MSS) and/or proficient mismatch repair (pMMR) tumors. As is known, the microsatellite status of nearly 95% CRC is MSS and/or pMMR phenotype, which implies that the treatment options in the third- or later-line setting for most mCRC are so limited and the treatment demands are largely unmet.

A recently published study named REGNIVO [6] has attracted much attention as the results showed that the combination of nivolumab and regorafenib achieved an ORR of 33% in MSS/pMMR mCRC. Nivolumab is one of the ICIs used to treat a variety of solid tumors. The data in REGNIVO indicated that patients with MSS/pMMR mCRC may benefit from immunotherapy under an appropriate combined therapeutic strategy.

Camrelizumab (SHR-1210), a high-affinity, fully humanized and selective IgG4-κ monoclonal anti-PD-1 antibody, has shown promising antitumor activity in several kinds of solid tumors [7–11]. It has been approved by CFDA for the treatment of advanced non-small-cell lung cancer, advanced hepatic cancer, advanced esophageal cancer, and classic Hodgkin's lymphoma. Camrelizumab was also proven to have efficacy in MSI-H/dMMR advanced or metastatic

colorectal cancer in a study with a small sample size [12]. However, the clinical benefit of camrelizumab to the therapy of MSS/pMMR mCRC has not yet been reported. Based on the results of the REGNIVO study, camrelizumab combined with regorafenib or fruquintinib may have a clinical benefit to MSS/pMMR mCRC patients. Hence, we conducted this observational study to explore the efficacy and safety of camrelizumab in combination with regorafenib or fruquintinib in patients with MSS/dMMR mCRC.

Patients and methods

Study design. The medical records of patients with MSS/pMMR mCRC who were treated with regorafenib or fruquintinib plus camrelizumab in Yuhuangding Hospital Affiliated to Qingdao University between January 2020 and June 2020 were retrieved. The follow-up data from June 2020 to November 1st, 2020 were prospectively gathered.

This study was approved by the Medical Ethical Committee of Yuhuangding Hospital Affiliated with Qingdao University. The written informed consent was obtained from each patient.

Patients. Inclusion criteria: 1) age ≥18; 2) patients were histologically or cytologically diagnosed with mCRC; 3) the tumor genotype was confirmed as MSS/pMMR; 4) Eastern Cooperative Oncology Group performance score (ECOG PS) of 0–1; 5) at least one measurable lesion as defined by RECIST (version 1.1); 6) patients had received more than 2 previous lines of treatment, including chemotherapy and anti-EGFR or anti-VEGF targeted therapy; 7) the measured values of liver and kidney functions tested in routine blood test were ≤2.5 and ≤1.5 times of the threshold values of the normal ranges, respectively; 8) life expectancy of more than 12 weeks. Exclusion criteria: 1) patients previously treated with other ICIs; 2) history of autoimmune disease; 3) patients with other serious diseases.

Table 1. Clinicopathologic features of mCRC (N=16).

Characteristic	N of patients (%)
Age, years	
Median	54
Range	31–72
Gender	
Male	11 (68.8)
Female	5 (31.2)
ECOG PS	
0	6 (37.5)
1	10 (62.5)
Primary tumor location	
Left	9 (56.2)
Right	7 (43.8)
Number of previous treatment lines	
2	7 (43.7)
3	5 (31.3)
4	4 (25.0)
Site of distant metastasis	
Liver	11 (68.8)
Lung	9 (56.3)
Lymph nodes	8 (50.0)
Peritoneum	5 (31.3)
Bone	2 (25.0)

Abbreviations: ECOG PS-Eastern Cooperative Oncology Group performance score

Treatment regimen. Regorafenib 80 mg or fruquintinib 3 mg was orally given once a day on days 1–21 in a 28-day cycle. Camrelizumab 200 mg was intravenously administrated every 3 weeks. All patients received regorafenib or fruquintinib plus camrelizumab until disease progression, death, or intolerable toxicity.

Outcome evaluation. The primary endpoints were objective response rate (ORR) and disease control rate (DCR). The tumor response was evaluated with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) every 6–8 weeks by computed tomography (CT) scan. ORR was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR). DCR was defined as the proportion of patients who had CR, PR, or stable disease (SD).

The second endpoint was safety. Adverse events (AEs) were assessed by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).

Results

Patient characteristics. A total of 16 MSS/pMMR mCRC patients were included in this study. The baseline characteristics are summarized in Table 1. The median age was 54 years (range 31–72 years). Among all patients, 11 (68.8%) were males and 5 (31.2%) were females; 6 (37.5%) were ECOG PS 0, and 10 (62.5%) were ECOG PS 1; 9 (56.3%) had a left-side primary tumor and 7 (43.2%) had a right-side primary tumor. All patients had received at least two prior lines of therapy, including 7 cases with two previous treatment lines; 5 cases with three previous treatment lines, and 4 cases with four previous treatment lines. Liver metastases were the most common metastasis type found in 11 cases (68.8%), followed by lung metastases 9 (56.3%), lymph nodes metastases 5 (31.3%), peritoneum metastases 5 (31.3%), and bone metastases 2 (12.5%). Multiple metastases were found in 10 patients (62.5%).

Efficacy. Of the 16 patients, no one achieved CR, 4 (25.0%) achieved PR, and 7 (43.7%) were evaluated as SD. The ORR and DCR were 25.5% (4/16) and 68.8% (11/16), respectively (Table 2). Figure 1 showed that one patient with lung metastasis achieved PR after 4 cycles of treatment. Figure 2 showed that one patient with liver metastasis achieved PR after 6 cycles of treatment.

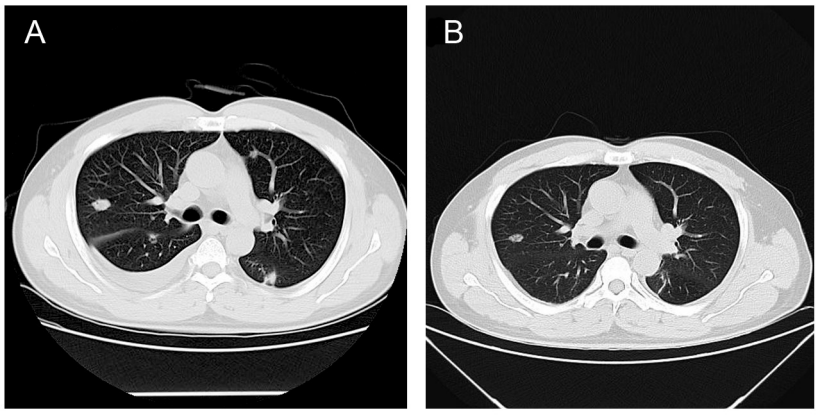

Figure 1. CT scan of a patient with lung metastasis achieved PR after 4 cycles of treatment. A) before treatment; B) after treatment.

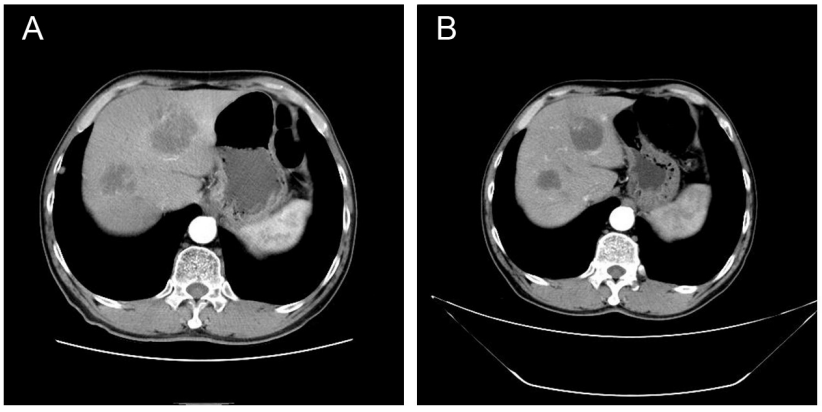

Figure 2. CT scan of a patient with liver metastasis achieved PR after 6 cycles of treatment. A) before treatment; B) after treatment.

Adverse events. All patients were generally well tolerated during the treatment. No treatment-related grade 4 or grade 5 toxicities were observed. The commonest AEs were reactive cutaneous capillary endothelial proliferation (REECP) (81.3%) (Figure 3), fatigue (43.8%), hypertension (37.5%), hand-foot skin reaction (25.0%), and thyroid dysfunction (25.0%). Grade 2 hand-foot syndrome was found in 2 patients, one of whom was treated with regorafenib (Figure 4) and the other one was treated with fruquintinib (Figure 5). Most AEs were grade 1 or 2 and only one patient had grade 3 liver dysfunction. The elevated alanine aminotransferase (ALT) of the patient with grade 3 liver dysfunction decreased to the normal level within 1 week after treatment with glucocorticoid. This patient received only camrelizumab in the next cycles and no subsequent liver abnormalities were observed. The occurrence information of AEs at different levels is presented in Table 3.

Table 2. Tumor response after the combination therapy.

Response (N=16)	N (%)
CR	0
PR	4 (25.5)
SD	7 (43.7)
PD	5 (31.3)
ORR	4 (25.5)
DCR	11 (68.8)

Abbreviations: CR-complete response; PR-partial response, SD-stable disease; PD-progression of disease; ORR-objective response rate; DCR-disease control rate

Discussion

In recent years, immunotherapy has achieved great progress in the treatment of lung cancer, kidney cancer, melanoma, and other solid tumors, whereas in mCRC treatment, only the MSS/pMMR mCRC, which accounts for a small proportion of all the mCRC, responds to immune checkpoint inhibition [5]. In the present study, we tried to explore the antitumor activity of immunotherapy in MSS/pMMR mCRC by evaluating the clinical efficacy of regorafenib or fruquintinib plus camrelizumab in patients with MSS/pMMR mCRC. The results showed that the ORR and DCR of this combination regimen were 25.0% (4/16) and 68.8% (11/16), respectively. Most of the AEs were grade 1–2, with only one case being grade 3. All the AEs were manageable.

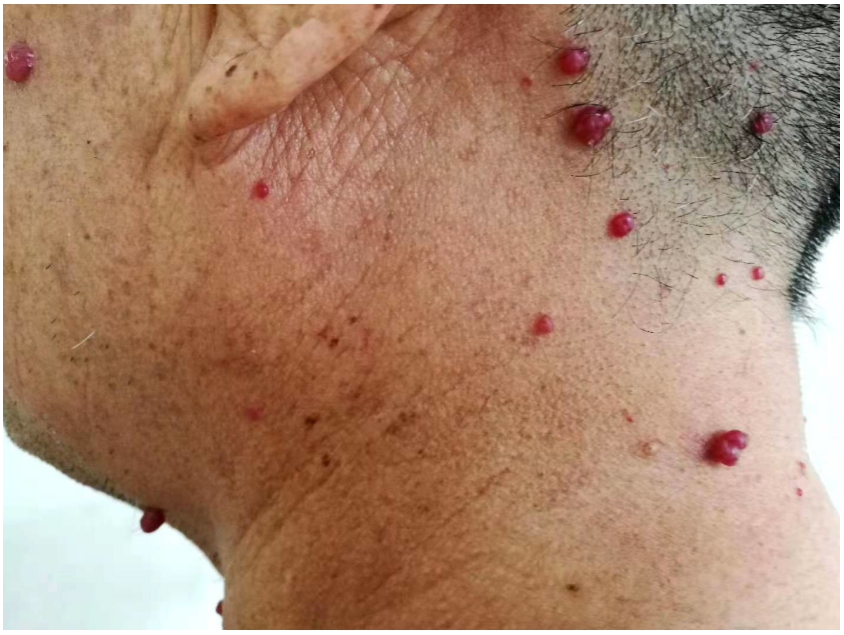

Figure 3. The AE of reactive cutaneous capillary endothelial proliferation caused by camrelizumab treatment.

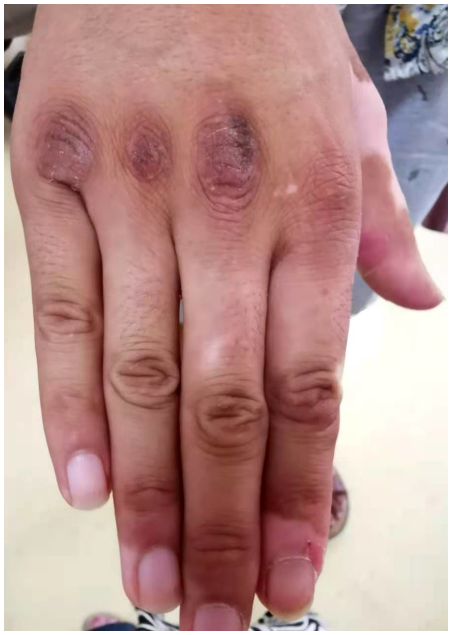

Figure 4. Grade 2 hand-foot syndrome caused by regorafenib treatment.

Table 3. Adverse events.

Adverse Event	Grade 1–2, N (%)	Grade 3–4, N (%)	All Grade, N (%)
Reactive cutaneous capillary endothelial proliferation	12 (75.0)	1 (6.3)	13 (81.3)
Fatigue	7 (43.8)	0 (0)	7 (43.8)
Oral mucositis	2 (12.5)	0 (0)	2 (12.5)
Nausea	3 (18.8)	0 (0)	3 (18.8)
Vomiting	3 (18.8)	0 (0)	3 (18.8)
Hand-foot skin reaction	5 (31.3)	0 (0)	4 (25.0)
Fever	1 (6.3)	0 (0)	2 (12.5)
Hypertension	6 (37.5)	0 (0)	6 (37.5)
Liver dysfunction	2 (12.5)	1 (6.3)	3 (18.8)
Thyroid dysfunction	4 (25.0)	0 (0)	4 (25.0)
Proteinuria	2 (12.5)	0 (0)	2 (12.5)

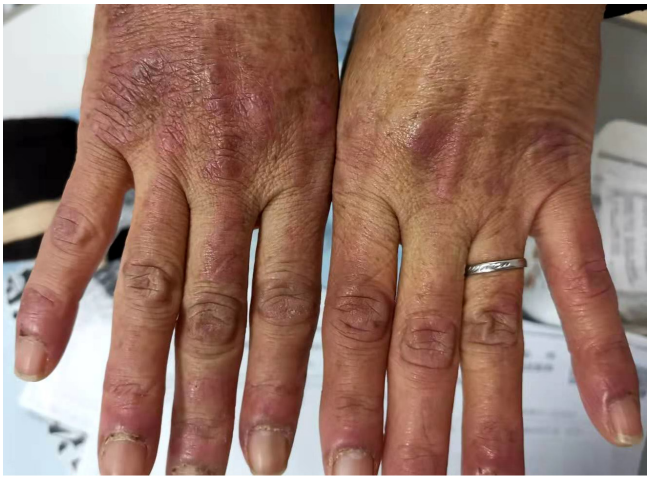

Figure 5. Grade 2 hand-foot syndrome caused by fruquintinib.

Regorafenib and fruquintinib are all oral small-molecule angiogenesis inhibitors approved for the standard salvage-line treatment for patients with mCRC in China. The approval of regorafenib was based on a phase 3 clinical trial named CONCUR [13] and the approval of fruquintinib was based on another phase 3 clinical trial named FRESCO [14]. In both the CONCUR study and the FRESCO study, part of the patients had been previously given VEGF-targeted or EGFR-targeted therapy, or both, which is similar to our study. Regorafenib monotherapy in the CONCUR study achieved an ORR of 4% and a DCR of 51%, and fruquintinib monotherapy in the FRESCO study achieved an ORR of 4.7% and a DCR of 62.2%. Interestingly, the ORR of regorafenib or fruquintinib plus camrelizumab in our study reached 25%, and the DCR reached 68.8%, which indicated that the addition of camrelizumab improved the clinical efficacy of regorafenib or fruquintinib in mCRC patients. In the aspect of immunotherapy, it should be noted that MSS mCRC was generally resistant to PD-1 blockade [15, 16]. For example, pembrolizumab monotherapy had an ORR of 40% in dMMR mCRC patients, but an ORR of 0% in pMMR mCRC patients [17]. Thus, the ORR of 25% in our study which included only MSS/pMMR mCRC patients is relatively satisfactory. In a recently published phase Ib

study named REGNIVO [6], the combination of regorafenib plus nivolumab was applied to 25 advanced CRC patients and this combination therapy achieved an ORR of 36%. In this study, all the advanced CRC patients had been previously treated with angiogenesis inhibitors and almost all the tumor genotypes were MSS/pMMR, which was similar to our study. We found that the biggest difference in patient characteristics between the REGNIVO study and our study was that all the patients in the REGNIVO study were ECOG PS 0, whereas, in our study, most of the patients were ECOG PS 1, which may be the reason why REGNIVO achieved a higher ORR. It's worth noting that in our study, one patient who was refractory to previous regorafenib therapy achieved PR after regorafenib plus camrelizumab treatment. This finding further confirmed the superiority of antiangiogenic therapy in combination with immunotherapy in treating MSS/pMMR mCRC.

Immunotherapy aims to improve the efficacy of T cells and the antitumor immune response by blocking CTLA-4, PD-1, or its ligand, PD-L1, with specific monoclonal antibodies called checkpoint inhibitors. As multi-kinase inhibitors, regorafenib inhibits angiogenic kinases VEGFR1/3, PDGFR, and FGFR [13] and fruquintinib inhibits kinases VEGFR-1, -2, and -3, both two blocking new blood vessel growth [18]. Some researchers believed that anti-angiogenesis therapy may improve the immune situation of the tumor microenvironment and alleviate the immunosuppressive status, thereby facilitating immunotherapy [19]. In our study, three of 9 patients with lung metastasis achieved PR, while only one of 11 patients with liver metastasis had PR, which was similar to a previous study [20]. This may be due to the reason that the liver had a relatively high fraction of immunosuppressive cells [21].

In this study, the most common AE was RCCEP, which was also observed in most of the studies concerning ICIs. The patient with grade 3 liver dysfunction was treated with glucocorticoid and the aminotransferase rapidly decreased to the normal level within 1 week. Subsequent camrelizumab monotherapy did not cause liver dysfunction. Therefore, the occurrence of this grade 3 liver dysfunction was considered to be related to regorafenib treatment.

Despite the encouraging results obtained in this study, we have to admit that the major limitations of our study are the small sample size and the retrospective nature, which inevitably reduced statistical effectiveness and caused bias. Besides, the follow-up period was short and the long-term efficacy of regorafenib or fruquintinib plus camrelizumab in MSS/pMMR mCRC patients had not been observed. Our study is a pilot observational study, in which the mechanism underlying the therapeutic effect of regorafenib or fruquintinib plus camrelizumab on MSS/pMMR mCRC was unable to speculate. Further clinical trials with a larger sample size are needed to confirm the clinical benefit of this combination regimen MSS/pMMR mCRC patients, and the mechanisms need to be disclosed.

In conclusion, our study presented an encouraging short-term efficacy of regorafenib or fruquintinib plus camrelizumab in MSS/pMMR mCRC patients, with an ORR of 25% and a DCR of 68.8%. The AEs were controllable. More data are needed to confirm the clinical efficacy of this combination regimen.

References

[1] BRAY F, FERLAY J, SOERJOMATARAM I, SIEGEL RL, TORRE LA et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424. https://doi.org/10.3322/caac.21492

[2] ARAGHI M, SOERJOMATARAM I, JENKINS M, BRIERLEY J, MORRIS E et al. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer 2019; 144: 2992–3000. https://doi.org/10.1002/ijc.32055

[3] GIANTONIO BJ, CATALANO PJ, MEROPOL NJ, O'DWYER PJ, MITCHELL EP et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25: 1539–1544. https://doi.org/10.1200/JCO.2006.09.6305

[4] DHILLON S. Regorafenib: A Review in Metastatic Colorectal Cancer. Drugs 2018; 78: 1133–1144. https://doi.org/10.1007/s40265-018-0938-y

[5] BRAHMER JR, TYKODI SS, CHOW LQ, HWU WJ, TOPALIAN SL et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366: 2455–2465. https://doi.org/10.1056/NEJMoa1200694

[6] FUKUOKA S, HARA H, TAKAHASHI N, KOJIMA T, KAWAZOE A et al. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). J Clin Oncol 2020; 38: 2053–2061. https://doi.org/10.1200/JCO.19.03296

[7] SONG Y, WU J, CHEN X, LIN T, CAO J et al. A Single-Arm, Multicenter, Phase II Study of Camrelizumab in Relapsed or Refractory Classical Hodgkin Lymphoma. Clin Cancer Res 2019; 25: 7363–7369. https://doi.org/10.1158/1078-0432.CCR-19-1680

[8] LIU J, LIU Q, LI Y, LI Q, SU F et al. Efficacy and safety of camrelizumab combined with apatinib in advanced triple-negative breast cancer: an open-label phase II trial. J Immunother Cancer 2020; 8: e000696. https://doi.org/10.1136/jitc-2020-000696

[9] FANG W, YANG Y, MA Y, HONG S, LIN L et al. Camrelizumab (SHR-1210) alone or in combination with gemcitabine plus cisplatin for nasopharyngeal carcinoma: results from two single-arm, phase 1 trials. Lancet Oncol 2018; 19: 1338–1350. https://doi.org/10.1016/S1470-2045(18)30495-9

[10] HU Y, QIN T, LI S, ZHANG T, XUE J. Efficacy and Safety of SBRT Combined With Camrelizumab and Apatinib in HCC Patients With PVTT: Study Protocol of a Randomized Controlled Trial. Front Oncol 2020; 10: 1589. https://doi.org/10.3389/fonc.2020.01589

[11] YAN Z, YAO ZH, YAO SN, WANG HY, CHU JF et al. Camrelizumab plus apatinib successfully treated a patient with advanced esophageal squamous cell carcinoma. Immunotherapy 2020; 12: 1161–1166. https://doi.org/10.2217/imt-2020-0197

[12] CHEN J, QUAN M, CHEN Z, ZENG T, LI Y et al. Camrelizumab in advanced or metastatic solid tumour patients with DNA mismatch repair deficient or microsatellite instability high: an open-label prospective pivotal trial. J Cancer Res Clin Oncol 2020; 146: 2651–2657. https://doi.org/10.1007/s00432-020-03251-5

[13] LI J, QIN S, XU R, YAU TC, MA B et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2015; 16: 619–629. https://doi.org/10.1016/S1470-2045(15)70156-7

[14] LI J, QIN S, XU RH, SHEN L, XU J et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA 2018; 319: 2486–2496. https://doi.org/10.1001/jama.2018.7855

[15] O'NEIL BH, WALLMARK JM, LORENTE D, ELEZ E, RAIMBOURG J et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. PLoS One 2017; 12: e0189848. https://doi.org/10.1371/journal.pone.0189848

[16] MCGREGOR M, PRICE TJ. IMblaze 370: lessons learned and future strategies in colorectal cancer treatment. Ann Transl Med 2019; 7: 602. https://doi.org/10.21037/atm.2019.08.119

[17] ASAOKA Y, IJICHI H, KOIKE K. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015; 373: 1979. https://doi.org/10.1056/NEJMc1510353

[18] HICKLIN DJ, ELLIS LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. J Clin Oncol 2005; 23: 1011–1027. https://doi.org/10.1200/JCO.2005.06.081

[19] KWILAS AR, DONAHUE RN, TSANG KY, HODGE JW. Immune consequences of tyrosine kinase inhibitors that synergize with cancer immunotherapy. Cancer Cell Microenviron 2015; 2: e677. https://doi.org/10.14800/ccm.677

[20] MARTINELLI E, SFORZA V, CARDONE C, CAPASSO A, NAPPI A et al. Clinical outcome and molecular characterisation of chemorefractory metastatic colorectal cancer patients with long-term efficacy of regorafenib treatment. ESMO Open 2017; 2: e000177. https://doi.org/10.1136/esmoopen-2017-000177

[21] BRODT P. Role of the Microenvironment in Liver Metastasis: From Pre- to Prometastatic Niches. Clin Cancer Res 2016; 22: 5971–5982. https://doi.org/10.1158/1078-0432.CCR-16-0460