ESMO Open
Cancer Horizons

Rationale and design of the TRUSTY study: a randomised, multicentre, open-label phase II/III study of trifluridine/tipiracil plus bevacizumab versus irinotecan, fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer progressive during or following first-line oxaliplatin-based chemotherapy

Takayuki Yoshino,[1] Eiji Oki,[2] Hiroaki Nozawa,[3] Takako Eguchi-Nakajima,[4] Hiroya Taniguchi,[5] Satoshi Morita,[6] Naruhito Takenaka,[7] Daisuke Ozawa,[7] Kuniaki Shirao[8]

To cite: Yoshino T, Oki E, Nozawa H, *et al*. Rationale and design of the TRUSTY study: a randomised, multicentre, open-label phase II/III study of trifluridine/tipiracil plus bevacizumab versus irinotecan, fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer progressive during or following first-line oxaliplatin-based chemotherapy. *ESMO Open* 2018;**3**:e000411. doi:10.1136/esmoopen-2018-000411

Received 13 June 2018
Accepted 15 June 2018

For numbered affiliations see end of article.

Correspondence to
Dr Takayuki Yoshino, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa Chiba 277-8577, Japan; tyoshino@east.ncc.go.jp

ABSTRACT

Background Trifluridine/tipiracil is an oral agent approved for the treatment of patients with metastatic colorectal cancer (mCRC). Trifluridine is an antineoplastic thymidine analogue, and tipiracil improves its bioavailability. A phase I/II C-TASK FORCE study of trifluridine/tipiracil plus bevacizumab for patients with refractory mCRC demonstrated promising efficacy results with mild toxicity profile. It is important that quality of life be preserved in patients with mCRC without compromising their prognosis. Here, we outline the TRiflUridine/tipiracil in Second-line sTudY phase II/III study (JapicCTI-173618), designed to demonstrate non-inferiority in overall survival of trifluridine/tipiracil plus bevacizumab compared with irinotecan, fluoropyrimidine and bevacizumab combination regimens as second-line treatment in patients with mCRC.

Patients and methods Eligible patients have confirmed unresectable advanced or recurrent colorectal adenocarcinoma and have failed to respond to first-line oxaliplatin-based chemotherapy. A total of 524 patients are to be randomly assigned (1:1 ratio) to trifluridine/tipiracil plus bevacizumab or irinotecan, fluoropyrimidine and bevacizumab and stratified according to *RAS* status (wild type vs mutant). The primary endpoint of the phase II part is disease control rate with trifluridine/tipiracil plus bevacizumab therapy. Secondary endpoints are response rate and safety with trifluridine/tipiracil plus bevacizumab therapy. In the phase III part, the primary endpoint is overall survival, and secondary endpoints include quality of life, progression-free survival, response rate, disease control rate, safety, time to treatment failure, time to post-study treatment failure and the proportion of patients receiving post-study treatment. The first patient was enrolled in October 2017 and the study is anticipated to be completed in 2022.

Clinical trial registration JapicCTI-173618 (JapicCTI).

INTRODUCTION

Fluorouracil and leucovorin combined with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus bevacizumab is widely used as first-line or second-line chemotherapy for metastatic colorectal cancer (mCRC).[1] In Japan, the treatment of mCRC typically involves chemotherapy using oxaliplatin-based regimens as first-line treatment, with irinotecan-based regimens frequently used afterwards.[2–4] The FIRIS study showed that oral S-1 and irinotecan was non-inferior to FOLFIRI, in terms of progression-free survival (PFS), as second-line treatment for mCRC.[5] Additionally, the TRICOLORE trial showed that S-1 and irinotecan plus bevacizumab was non-inferior to FOLFOX or capecitabine/oxaliplatin plus bevacizumab as first-line treatment.[6] In the ML18147 study,[7] continuous use of bevacizumab from first-line to second-line treatment was associated with prolonged overall survival (OS). Bevacizumab therefore represents a viable treatment

option even for patients with mCRC and progression after bevacizumab-combined chemotherapy as first-line treatment. The treatment aims for mCRC are typically not curative but are instead focused on prolonging survival and improving quality of life (QOL). However, treatment regimens based on irinotecan are associated with severe toxicities, which can be detrimental to the treatment objectives.[8] It is therefore clear that treatment options that preserve QOL and improve prognosis while maintaining acceptable toxicity are required for this patient population.

Trifluridine/tipiracil consists of trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5. Trifluridine, an antineoplastic thymidine analogue, and tipiracil, a thymidine phosphorylase inhibitor that improves the bioavailability of trifluridine, are approved as an oral combination preparation for the treatment of mCRC in the USA, Europe, and Japan. The RECOURSE global phase III study demonstrated a significant improvement in OS with trifluridine/tipiracil compared with placebo in patients with refractory colorectal cancer (median OS, 7.1 vs 5.3 months; HR 0.68; 95% CI 0.58 to 0.81, p<0.001).[9] More recently, the TERRA study demonstrated similar findings in an Asian population with mCRC (median OS, 7.8 vs 7.1 months; HR 0.79; 95% CI 0.62 to 0.99, p=0.035) as well as improved PFS (2.0 vs 1.8 months; HR 0.43; 95% CI 0.34 to 0.54, p<0.001).[10] In both studies, the most frequent adverse event (AE) of grade 3 or higher was neutropenia, occurring in 38.0% and 20.3% of patients receiving trifluridine/tipiracil in the RECOURSE and TERRA studies, respectively.

In a xenograft model of human CRC, trifluridine/tipiracil in combination with bevacizumab demonstrated synergistic activity.[11] The C-TASK FORCE phase I/II study of trifluridine/tipiracil plus bevacizumab in patients with mCRC unresponsive to standard treatment demonstrated the potential of this regimen to extend PFS (5.6 months, 95% CI 3.4 to 7.6 by investigator assessment) and median survival time (MST; 11.4 months, 95% CI 7.6 to 13.9) with acceptable toxicity, although 68% of patients reported neutropenia as a treatment-emergent AE of grade 3 or worse.[12] However, the magnitude of the antitumour effect and severity of AEs for trifluridine/tipiracil plus bevacizumab as second-line treatment in patients with mCRC remain unclear.

Therefore, the purpose of this phase II/III TRiflUridine/tipiracil in Second-line sTudY (TRUSTY) is to demonstrate the non-inferiority in terms of OS of trifluridine/tipiracil plus bevacizumab compared with FOLFIRI plus bevacizumab or S-1 and irinotecan plus bevacizumab regimens as second-line treatment in patients with mCRC.

DISCUSSION

Study design and treatment

This open-label, multicentre, randomised, comparative phase II/III study will assess the efficacy and safety of trifluridine/tipiracil plus bevacizumab versus fluoropyrimidine and irinotecan plus bevacizumab as second-line treatment in Japanese patients with mCRC (figure 1). Patient enrolment commenced in October 2017 and is currently ongoing, and the estimated completion date of this trial is March 2022 (24 month enrolment period, with a 30-month follow-up period after the last patient is enrolled). Prior to enrolment, investigators select one of the following scheduled regimens for each patient assigned to the fluoropyrimidine and irinotecan plus bevacizumab (Group A) treatment arm: (1) FOLFIRI plus bevacizumab therapy (bevacizumab 5 mg/kg, irinotecan 150 mg/m^2, and L-leucovorin 200 mg/m^2 by intravenous infusion followed by bolus injection of fluorouracil (5-FU) 400 mg/m^2, all on day 1, followed by a 46 hours infusion of 5-FU 2400 mg/m^2 in a 14-day cycle); (2) S-1 and irinotecan plus bevacizumab therapy with a 3-week cycle (bevacizumab 7.5 mg/kg and irinotecan 150 mg/m^2 by intravenous infusion on Day 1 and oral administration

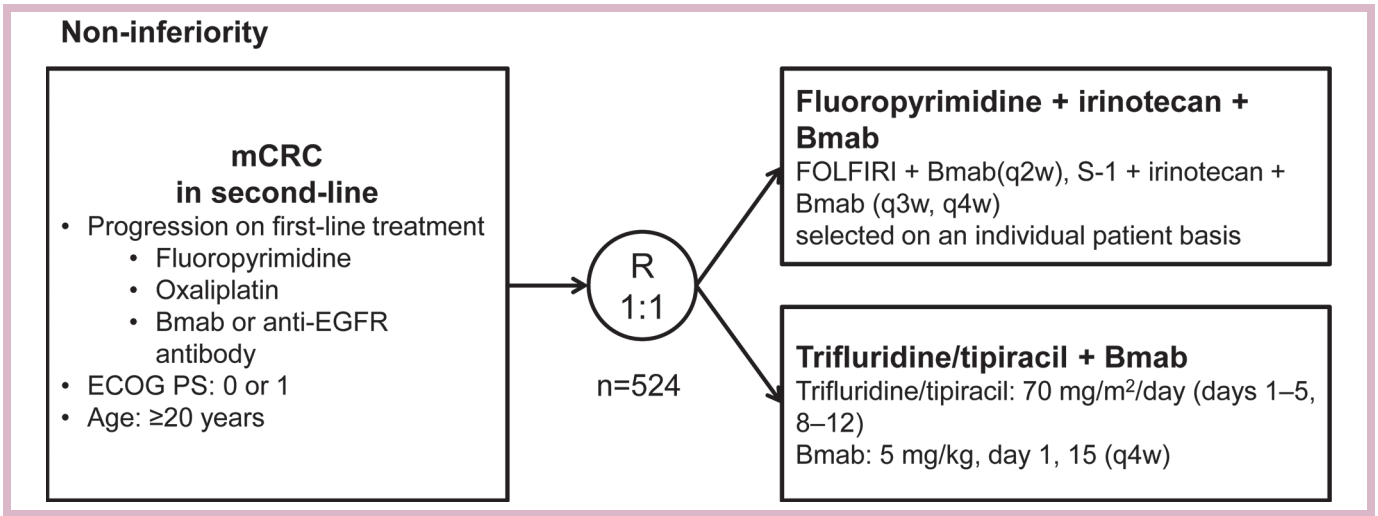

Figure 1 Study design. Bmab, bevacizumab; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; q(x)w, once every (x) weeks.

of S-1 40 mg/m^2 twice daily from day 1 to day 14 in a 21-day cycle) or (3) S-1 and irinotecan plus bevacizumab therapy with a 4-week cycle (bevacizumab 5 mg/kg and irinotecan 100 mg/m^2 by intravenous infusion on days 1 and 15, and oral administration of S-1 40 mg/m^2 twice daily from day 1 to day 14 in a 28-day cycle). Eligible patients are subsequently randomised at a ratio of 1:1 to either Group A or to the trifluridine/tipiracil plus bevacizumab (Group B) treatment arm (bevacizumab 5 mg/kg by intravenous infusion on days 1 and 15, plus oral administration of trifluridine/tipiracil 35 mg/m^2 twice daily on days 1–5 and 8–12 in a 28-day cycle). For all regimens, administration of chemotherapy is repeated until any study discontinuation criterion is met. For randomisation, a minimisation method is used after patient stratification according to *RAS* status (wild type vs mutant). The primary lesion (left sided vs right sided) and, for patients with wild-type *RAS* status, first-line treatment with a molecular-targeted drug (bevacizumab vs antiepidermal growth factor receptor antibody) are used as stratification factors. The phase II part of the study will analyse safety and efficacy data in the first 50 patients in Group B who become evaluable for tumour response based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. These data will be assessed by an independent data monitoring committee who will establish the criteria for the progression of patients to phase III.

This study is being conducted in accordance with the guidelines for Good Clinical Practice of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, as well as the ethical guidelines for medical and health research involving human subjects. Patients will provide written informed consent prior to participation. This study is registered with the Japan Pharmaceutical Information Center (registration number JapicCTI-173618).

Patients

Patients with confirmed, unresectable, advanced or recurrent colorectal adenocarcinoma and known *RAS* gene mutation status by a validated testing method, who have failed first-line oxaliplatin-based chemotherapy, are eligible for inclusion. Additional eligibility criteria are listed in box 1. Discontinuation criteria include progressive disease based on RECIST, clinical progression, patient decision or ineligibility or investigator judgement based on AEs or other reason.

Endpoints and assessments

The primary endpoint of the phase II study is disease control rate (DCR) with trifluridine/tipiracil plus bevacizumab therapy. The secondary endpoints are response rate (RR) and safety with trifluridine/tipiracil plus bevacizumab therapy. In the phase III study, the primary endpoint is OS, and secondary endpoints include QOL, PFS, RR, DCR, safety, time to treatment failure, time to post-study treatment failure (defined as the period from the date of enrolment to the date of discontinuation of

Box 1 TRiflUridine/tipiracil in Second-line sTudY key inclusion and exclusion criteria

Inclusion criteria

1. Metastatic colorectal adenocarcinoma (excluding appendix cancer and anal canal cancer) regardless of *RAS* mutational status.
2. In regard to the first-line chemotherapy with fluoropyrimidine (fluorouracil (5-FU)/L-leucovorin (LV), capecitabine or S-1) plus oxaliplatin combined with bevacizumab or antiepidermal growth factor receptor (EGFR) antibody (cetuximab or panitumumab):
   a. Patients who have received at least the following treatment as the first-line chemotherapy:
      – At least two doses of 5-FU/L-LV or 15 day or longer treatment with oral fluoropyrimidine (S-1, capecitabine).
      – At least 1 dose of oxaliplatin.
      – At least 2 doses of bevacizumab or anti-EGFR antibody.
   b. Patients in whom progression has been detected in less than 90 days of the first-line chemotherapy start day are excluded.
   c. Progression has been detected on imaging in less than 90 days after the first-line chemotherapy.
3. Age ≥20 years at the time of enrolment.
4. Eastern Cooperative Oncology Group performance status 0 or 1.
5. Oral medication can be administered.
6. Patients with evaluable lesions by imaging within 28 days before enrolment.
7. Adequate organ function tested within 7 days before enrolment:
   a. Neutrophil count: ≥1.5 10^9/L.
   b. Platelet count: ≥100 10^9/L.
   c. Haemoglobin: ≥9.0 g/dL.
   d. Total bilirubin: ≤1.5 mg/dL.
   e. Aspartate aminotransferase: ≤100 IU/L (≤150 IU/L if liver metastasis present).
   f. Alanine aminotransferase: ≤100 IU/L (≤150 IU/L if liver metastasis present).
   g. Urine protein: ≤1+.
   h. Serum creatinine: ≤1.2 mg/dL.
8. Written informed consent provided.

Exclusion criteria

1. Patients with serious comorbidities or a history (not limited to the following):
   a. A history of serious hypersensitivity to the study drug.
   b. Active multiple malignancies with less than 5 years disease free.
   c. Brain or leptomeningeal metastasis.
   d. Infections requiring systemic therapy (eg, a fever of ≥38°C).
   e. Intestinal obstruction, intestinal paralysis, renal failure or liver failure.
   f. Comorbid or a history of thromboembolism (history of thromboembolism of ≤Grade 2 are eligible), cerebral infarction (asymptomatic lacunar infarction is eligible), pulmonary infarction and interstitial pneumonia (including pulmonary fibrosis).
   g. Poorly controlled diabetes mellitus.
   h. Poorly controlled hypertension.
   i. Haemoptysis (expectoration of ≥2.5 mL of fresh blood).
   j. Congenital haemorrhagic diathesis or coagulation system abnormalities.
   k. Gastrointestinal ulcer or bleeding.
   l. History of gastrointestinal perforation within 180 days before enrolment (patients with gastrointestinal perforation caused by obstructive colorectal cancer are eligible.).
   m. History of myocardial infarction, severe or unstable angina pectoris or symptomatic congestive heart failure within 180 days

Continued

Box 1 Continued

before enrolment (New York Health Association class III or IV (Appendix 3)).
   n. Diarrhoea of ≥Grade 2.
   o. Positive for any of HIV antibody, hepatitis B surface antigen and hepatitis C virus antibody.
   p. Psychiatric disorders that are judged to make participation in this study difficult.
2. Patients who have received any of the following treatments or interventions before enrolment in this study:
   a. Anticancer therapy within 14 days before enrolment.
   b. Interventions, such as blood transfusion, administration of blood components, plasma derivatives, granulocyte-colony stimulating factor products, within 14 days before enrolment.
   c. Extensive surgery within 28 days before enrolment.
   d. Drainage of ascites or pleural effusions by abdominocentesis or thoracentesis within 28 days before enrolment.
   e. Extended-field radiotherapy within 28 days before enrolment or limited-field radiotherapy within 14 days before enrolment.
   f. Treatment with irinotecan or trifluridine/tipiracil.
   g. Current treatment with flucytosine or atazanavir sulfate.
   h. Current treatment with anticoagulants.
   i. Continuous systemic treatment with steroids or other immunosuppressants.
3. Women who are pregnant, breast feeding, tested positive for pregnancy or do not want to use contraception or men who wish to have children.
4. Patients determined as ineligible for participating in this study by the investigator or subinvestigator.

post-study treatment) and proportion of patients receiving post-study treatment. Efficacy is evaluated according to RECIST V.1.1. AEs are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03. QOL is assessed according to the The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30[13] and EuroQol5D–5L[14] questionnaires.

Statistical analysis

Based on previous studies[5 15] and improved treatment options for patients with mCRC, the MST is assumed to be 19 months for both groups. The lower point estimate of MST with Group B therapy is considered acceptable for maintaining QOL, and the acceptable non-inferiority margin for the HR is specified as 1.33 based on the value for Group A therapy. Consequently, with a one-sided significance level of 2.5% and a power of 80%, and with a 24-month enrolment period and a 30-month follow-up period after last patient enrolment, a sample size of at least 499 patients was deemed necessary. Assuming a discontinuation rate of approximately 5%, the target number of patients was set at 524. If non-inferiority with a margin of 1.33 (as HR) is demonstrated, superiority and the non-inferiority hypothesis with a margin of 1.25 (as HR) will be evaluated.

Primary analysis in the phase III study will be performed in the full-analysis set, defined as all randomised patients except those with serious protocol violations or who have withdrawn consent to participate. The safety analysis set will comprise all patients in the full analysis set who receive at least one dose of study drug in their assigned treatment group. The Kaplan-Meier method will be used to describe OS, with Cox proportional hazard modelling used to calculate HRs and two-sided 95% CIs.

CONCLUSION

TRUSTY is the first phase II/III study to evaluate the efficacy and safety of trifluridine/tipiracil in combination with bevacizumab compared with irinotecan-based chemotherapy as second-line treatment in patients with mCRC. This study, to be conducted at 63 study sites in Japan, commenced in October 2017 and is expected to complete in March 2022. We anticipate that the findings will contribute to establishing the safety and efficacy of the study treatment in this patient population.

Author affiliations
[1]Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[3]Department of Surgical Oncology, University of Tokyo, Tokyo, Japan
[4]Department of Clinical Oncology, St. Marianna University School of Medicine, Kanagawa, Japan
[5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan
[6]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan
[7]Clinical Development and Medical Affairs Division, Taiho Pharmaceutical Co., Ltd, Tokyo, Japan
[8]Department of Medical Oncology and Hematology, Oita University Faculty of Medicine, Oita, Japan

Acknowledgements We thank Clare Cox, PhD, of Edanz Medical Writing for providing medical writing support, which was funded by Taiho Pharmaceutical Co., Ltd.

Contributors TY, EO, HN, TEN, HT, NT and DO designed and prepared the protocol. SM is the chief statistician and KS is the medical advisor. All authors will contribute to the collection and analysis of data in this study. All authors have approved the final version of the manuscript for submission and agree to be accountable for the contents.

Funding This study is funded by Taiho Pharmaceutical Co., Ltd.

Competing interests TY reports grants from MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., GlaxoSmithKline K.K., and Nippon Boehringer Ingelheim Co., Ltd.; grants and personal fees from Sanofi K.K. and Chugai Pharmaceutical Co., Ltd.; and personal fees from Eli Lilly Japan K.K. and Merck Serono Co., Ltd., outside the submitted work. EO reports personal fees from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Merck Serono Co., Ltd., Yakult Honsha Co., Ltd., Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Bayer, outside the submitted work; HN reports grants from Taiho Pharmaceutical Co. Ltd. and personal fees from Chugai Pharmaceutical Co. Ltd., during the conduct of the study. TEN reports grants from Daiichi Sankyo, Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., MSD , Eisai Co. Ltd., A straZeneca, Chugai Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Sanofi K.K., Merck, Takeda Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd.; and personal fees from Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., MSD K.K., Chugai Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Sanofi K.K., Bristol7Myers Squibb, Sawai Pharmaceutical Co., Ltd., Bayer, Merck, Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., and Kyowa Hakko Kirin Co., Ltd., outside the submitted work. HT reports personal fees (honoraria for lectures) from Takeda Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd. and grants from Takeda Pharmaceutical

Co., Ltd., outside the submitted work. SM reports personal fees from Taiho Pharmaceutical Co., Ltd., during the conduct of the study and personal fees from Chugai Pharmaceutical Co., Ltd. and Daiichi Sankyo, outside the submitted work. NT and DO report personal fees from Taiho Pharmaceutical Co., Ltd., during the conduct of the study and outside the submitted work, and are employees of Taiho Pharmaceutical Co., Ltd., the manufacturer of trifluridine/tipiracil. KS reports grants and personal fees from Taiho Pharmaceutical Co., Ltd., grants from Bristol7Myers Squibb, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Pfizer, Daiichi Sankyo, Sanofi K.K., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma, Shionogi & Co. Ltd., and Takeda Pharmaceutical Co., Ltd., outside the submitted work.

Patient consent Obtained.

Ethics approval The ethics committee and/or institutional review board at each participating institution approved the study protocol before enrolment commenced.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Tournigand C, André T, Achille E, *et al*. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37.
2. Watanabe T, Muro K, Ajioka Y, *et al*. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. *Int J Clin Oncol* 2018;23:1–34.
3. Yoshino T, Arnold D, Taniguchi H, *et al*. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. *Ann Oncol* 2018;29:44–70.
4. National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology: colon cancer. 2, 2018. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
5. Muro K, Boku N, Shimada Y, *et al*. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). *Lancet Oncol* 2010;11:853–60.
6. Yamada Y, Denda T, Gamoh M, *et al*. S-1 and irinotecan plus bevacizumab versus mFOLFOX6 or CapeOX plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer (TRICOLORE): a randomized, open-label, phase III, noninferiority trial. *Ann Oncol* 2018;29:624–31.
7. Bennouna J, Sastre J, Arnold D, *et al*. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29–37.
8. Douillard JY, Cunningham D, Roth AD, *et al*. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;355:1041–7.
9. Mayer RJ, Van Cutsem E, Falcone A, *et al*. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372:1909–19.
10. Xu J, Kim TW, Shen L, *et al*. Results of a randomized, double-blind, placebo-controlled, phase iii trial of trifluridine/tipiracil (tas-102) monotherapy in asian patients with previously treated metastatic colorectal cancer: The TERRA Study. *J Clin Oncol* 2018;36:350–8.
11. Tsukihara H, Nakagawa F, Sakamoto K, *et al*. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. *Oncol Rep* 2015;33:2135–42.
12. Kuboki Y, Nishina T, Shinozaki E, *et al*. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol* 2017;18:1172–81.
13. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
14. Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
15. Iwamoto S, Takahashi T, Tamagawa H, *et al*. FOLFIRI plus bevacizumab as second-line therapy in patients with metastatic colorectal cancer after first-line bevacizumab plus oxaliplatin-based therapy: the randomized phase III EAGLE study. *Ann Oncol* 2015;26:1427–33.