Clinical Trial Protocol

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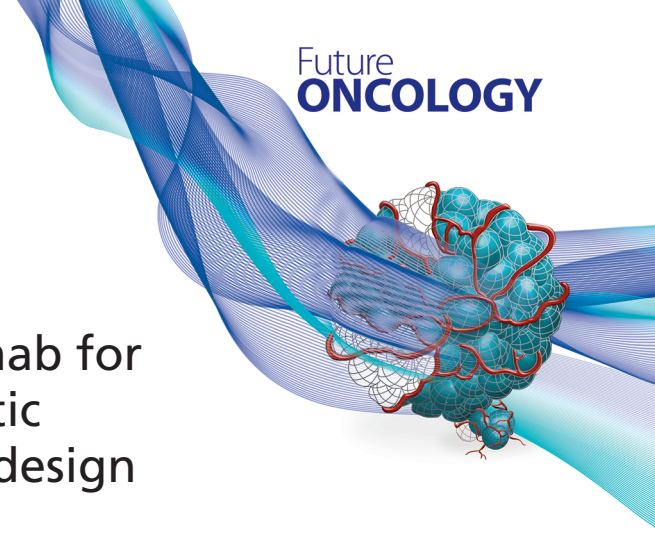

Trifluridine/tipiracil plus bevacizumab for third-line management of metastatic colorectal cancer: SUNLIGHT study design

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Trifluridine/tipiracil (FTD/TPI) is an orally active formulation of trifluridine, a thymidine-based nucleoside analog, and tipiracil hydrochloride, a thymidine phosphorylase inhibitor that increases the bioavailability of trifluridine. Preliminary studies of FTD/TPI plus bevacizumab have produced encouraging results in the treatment of refractory metastatic colorectal cancer. Here, we describe the design of the multinational Phase III SUNLIGHT, an open-label study of FTD/TPI plus bevacizumab as third-line treatment for patients with unresectable metastatic colorectal cancer. A total of 490 patients will be randomized 1:1 to receive either FTD/TPI plus bevacizumab, or FTD/TPI monotherapy. The primary objective is to significantly improve overall survival with FTD/TPI plus bevacizumab compared with FTD/TPI monotherapy. The first patient was enrolled in November 2020.

Lay abstract: Trifluridine/tipiracil is a cancer treatment used in patients with bowel cancer that has spread to other parts of the body (this is called 'metastatic bowel cancer'). This medicine is taken by mouth. Recently, a number of studies have suggested that better results might be obtained when trifluridine/tipiracil is used in combination with another cancer drug, bevacizumab. This article describes the design of a new clinical trial. The SUNLIGHT is being set up to confirm whether the combination of trifluridine/tipiracil plus bevacizumab is indeed better than trifluridine/tipiracil alone for patients who have already had two different treatments for metastatic bowel cancer. The trial began in late 2020.

Clinical trial registration: EudraCT no. 2020-001976-14 (www.ClinicalTrialsRegister.eu)

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Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the second leading cause of cancer-related mortality worldwide, accounting for 1,850,000 cases and 881,000 deaths worldwide in 2018 [1]. It accounts for approximately 10% of the global burden of cancer, in terms of incidence and mortality [1] and the increasing adoption of 'western' lifestyles appears to be driving an upsurge in CRC incidence in low- and middle-income countries [2]. Consequently, between 2018 and 2040, the global incidence of CRC is forecast to increase by >70%, to over 3 million cases annually, while the number of deaths is predicted to increase by >80%, to 1.6 million per year [3].

Stage of disease at diagnosis is a key prognostic indicator. In a study of >300,000 patients diagnosed with colon cancer between 2000 and 2007, localized disease was associated with 3-year age-standardized survival rates of 87.0–93.0%, whereas corresponding rates for metastatic CRC (mCRC) were 11.7–19.6% [4].

Patients with unresectable mCRC who are eligible to receive intensive standard first-line therapy can now achieve overall survival (OS) times of approximately 30 months, through the utilization of a 'continuum of care' that typically includes several sequential lines of therapy tailored to patient characteristics, disease characteristics and treatment history [5]. First-line intensive chemotherapy regimens usually include a fluoropyrimidine (capecitabine, or infusional 5-fluorouracil plus leucovorin) plus irinotecan and/or oxaliplatin [5]. An anti-VEGF (e.g., bevacizumab) or an anti-EGFR (e.g., cetuximab or panitumumab) agent for wild-type *RAS* tumors should be added. However, in such patients, recent published data suggest that the primary tumor location may have a predictive effect on anti-EGFR agent with a real benefit in left-sided CRC but is still debated in right-sided tumors [6]. Second-line therapy is individualized according to the prior treatment regimen and reason for failure (disease progression vs tolerability); a new combination of the same drugs recommended for first-line use is often feasible and appropriate [5].

In third-line setting, an anti-EGFR agent alone or in combination with an irinotecan-based chemotherapy may be appropriate in treatment-naive patients with *RAS* wild-type tumors [5]. Alternatively, chemotherapeutic agents or treatment combinations used in earlier therapy lines may be reintroduced, as long as there is no clear prior resistance to these agents, but there is limited evidence to support this approach [7]. Other agents for refractory mCRC have limited usefulness because they are approved only in certain territories, or only for specific tumor types. For example, fruquintinib is a selective VEGF receptor tyrosine kinase inhibitor that has shown a survival benefit in a randomized controlled trial [8,9], but is currently only marketed in China.

In recent years, two orally active agents, regorafenib and trifluridine/tipiracil (FTD/TPI; also known as TAS-102), have been approved as monotherapies for third-line use in refractory mCRC, without restrictions based on tumor biology [10,11]. Both drugs have been shown to significantly improve OS in randomized placebo-controlled trials [12,13], are supported by the findings of several real-world studies [6], and are recommended by current treatment guidelines [5,14]. The safety profiles of regorafenib and FTD/TPI are, however, distinct, as might be predicted from their mechanisms of action. Whereas regorafenib treatment is characterized by the development of fatigue and dermatologic toxicities (hand-foot syndrome, rash and desquamation) [12], FTD/TPI is associated with myelosuppression (albeit with low rates of febrile neutropenia) and gastrointestinal effects [13].

FTD/TPI & bevacizumab

Trifluridine is a thymidine-based nucleoside analog that undergoes intracellular, stepwise phosphorylation and subsequent incorporation into DNA [15], resulting in structural DNA damage and dysfunction. This is considered to be the primary anticancer mechanism of action of trifluridine, although inhibition of thymidylate synthase by trifluridine monophosphate may also contribute [15]. Following oral administration, trifluridine is rapidly inactivated by thymidine phosphorylase in the intestine and liver; consequently, its oral bioavailability is low. However, co-administration of tipiracil hydrochloride, an orally active thymidine phosphorylase inhibitor, reduces the first-pass degradation of trifluridine and increases its systemic exposure [15].

The efficacy and tolerability of FTD/TPI monotherapy (co-formulated at a molar ratio of 1:0.5) in the third-line treatment of mCRC was demonstrated in the Phase III, placebo-controlled RECOURSE trial [13]. In this trial, the starting dose of FTD/TPI was 35 mg/m^2, taken orally twice daily on days 1–5 and 8–12 of each 28-day cycle. FTD/TPI was associated with significantly greater median OS compared with placebo (7.1 vs 5.3 months; hazard ratio [HR]: 0.68; $p < 0.001$), a finding also confirmed for subgroups defined by sex, age (<65 vs ≥65 years), performance status (0 vs 1) and number of metastatic sites (1 or 2 vs ≥3). Of the 533 patients who received FTD/TPI and were evaluable for safety, 370 (69%) had grade ≥3 adverse events (AEs) [13]. No grade ≥3 nonhematologic toxicities occurred in >10% of FTD/TPI recipients; grade ≥3 neutropenia, anemia and thrombocytopenia occurred in 38, 18 and 5%, respectively, but only 4% experienced febrile neutropenia.

No head-to-head trials comparing regorafenib and FTD/TPI monotherapy in refractory mCRC have been conducted. However, a meta-analysis concluded that, while the two drugs were similarly efficacious in this setting, there were (as mentioned earlier) important differences in their safety profiles [16].

Thus, while the development of regorafenib and FTD/TPI is an important milestone in the treatment of refractory mCRC, the individual impact on median OS was modest [12,13]. Therefore, additional strategies are urgently needed to extend survival while maintaining quality of life (QoL).

Bevacizumab is an established anticancer agent that targets VEGF and, consequently, inhibits angiogenesis. In solid malignancies, this is thought to 'normalize' abnormal tumor vasculature and enhance the delivery of chemotherapeutic agents to neoplastic tissue [17]. Consistent with this theory, animal studies of CRC xenografts have shown that intracellular concentrations of phosphorylated trifluridine are increased when it is co-administered with bevacizumab [18], and, furthermore, that the incorporation of trifluridine into DNA is enhanced in the presence of the angiokinase inhibitor nintedanib [19].

The combination of FTD/TPI and bevacizumab has shown activity against CRC xenografts in mice, and in the treatment of refractory mCRC in two preliminary investigator-initiated clinical trials [18,20,21]. In both of the clinical trials [20,21], the dosage and administration schedule of FTD/TPI was the same as that used in the RECOURSE trial [13], and bevacizumab 5 mg/kg was given by intravenous infusion on days 1 and 15 of each 28-day cycle.

The first trial, C-TASK FORCE [20], was conducted in Japan in 2014, and was a noncomparative study of FTD/TPI plus bevacizumab in 25 patients with mCRC refractory to all standard therapies. At 16 weeks, the progression-free survival (PFS) rate was 42.9% (80% CI: 27.8–59.0%), while median PFS and OS were 3.7 (95% CI: 2.0–5.4) months and 11.4 (95% CI: 7.6–13.9) months, respectively. Grade ≥3 neutropenia occurred in 18 patients (72%), but rates of febrile neutropenia were low (n = 4 [16%]), and there were no discontinuations due to treatment-related AEs.

In the second trial, which was undertaken in Denmark in 2017 and 2018, 93 patients with refractory mCRC were randomized 1:1 to FTD/TPI plus bevacizumab or FTD/TPI monotherapy [21]. In a survival analysis with a cut-off date of February 2019, FTD/TPI plus bevacizumab was associated with significantly longer median PFS and OS than FTD/TPI monotherapy (PFS: 4.6 vs 2.6 months; p = 0.0015; OS: 9.4 vs 6.7 months; p = 0.028). The difference in OS was still evident after nearly 12 months of additional follow-up (9.9 vs 6.0 months; p = 0.03) [22]. Although grade ≥3 neutropenia was more frequent among patients who received FTD/TPI plus bevacizumab, treatment-related serious AEs were uncommon in both study arms [21]. Furthermore, the effectiveness of FTD/TPI plus bevacizumab in refractory mCRC does not appear to be affected by the inclusion of bevacizumab as part of front-line treatment [23].

Collectively, these data provide a strong foundation for further research into the clinical effects of FTD/TPI plus bevacizumab in the management of mCRC. Given the established benefits of bevacizumab in the first- and second-line treatment of mCRC, and the positive efficacy and good tolerability profile of FTP/TPI plus bevacizumab seen in the Phase II randomized trial of this combination therapy, the use of FTD/TPI with bevacizumab may prove to be an effective post progression treatment option in patients with mCRC. In this article, we describe the design of the Phase III Study of trifluridine/tipiracil in combination with bevacizumab versus trifluridine/tipiracil single agent in patients with refractory metastatic colorectal cancer (SUNLIGHT) trial of FTD/TPI plus bevacizumab versus FTD/TPI in the third-line treatment of mCRC.

SUNLIGHT trial

The purpose of the Phase III SUNLIGHT trial (EudraCT: 2020-001976-14) is to further investigate the efficacy and safety of FTD/TPI plus bevacizumab, compared with FTD/TPI alone, in patients with refractory mCRC following two chemotherapy regimens.

Objectives

The primary objective of the trial is to demonstrate the superiority of FTD/TPI plus bevacizumab over FTD/TPI monotherapy, in terms of OS (primary end point). Key secondary objectives are to compare the treatments in terms of PFS, overall response rate (ORR) and disease control rate (DCR). The trial will also explore the safety, tolerability and impact on QoL of FTD/TPI plus bevacizumab therapy in comparison with FTD/TPI monotherapy.

Key eligibility criteria

Key inclusion and exclusion criteria are listed in Table 1. Briefly, the trial will enroll adults with unresectable, refractory mCRC who have received two prior chemotherapy regimens containing fluoropyrimidines, irinotecan, oxaliplatin and anti-VEGF and/or (in patients with *RAS* wild-type tumors) anti-EGFR antibody therapy. To be eligible for inclusion, patients must have disease progression or have been unable to tolerate their most recent line of chemotherapy, a performance status of 0 or 1, and known *RAS* mutation status. In patients who have received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of

Table 1. Key inclusion and exclusion criteria in the SUNLIGHT.

Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior treatment with >2 chemotherapy regimens for mCRC, or with FTD/TPI
Histologically confirmed unresectable mCRC	Unresolved grade ≥3 nonhematologic toxicity related to previous chemotherapy regimen (excluding alopecia and skin pigmentation)
Prior treatment with ≤2 chemotherapy regimens for mCRC,† and disease progression or intolerance to the last regimen	CNS metastases that are unstable or require increasing doses of steroids for control
Prior regimens must have included a fluoropyrimidine, irinotecan, oxaliplatin and an anti-VEGF monoclonal antibody; and/or (in patients with *RAS* wild-type tumors) an anti-EGFR monoclonal antibody	Major surgery within 4 weeks before randomization
Known *RAS* mutation status	Gastrointestinal disease that could potentially interfere with study drug absorption
Ability to swallow oral tablets	Severe or uncontrolled active acute or chronic infection
Estimated life expectancy ≥12 weeks	Evidence of infection with HIV, hepatitis B virus or hepatitis C virus
ECOG performance status ≤1	Uncontrolled diabetes mellitus, hypertension or cardiac arrhythmia
Adequate bone marrow, renal, hepatic and coagulation function‡	Active (or history of) interstitial lung disease or pulmonary hypertension
If applicable, negative pregnancy test and agreement to use highly effective contraception§	Major adverse cardiovascular event within 6 months before randomization, severe/unstable angina, or NYHA class III or IV heart failure
	Malignant disease other than mCRC
	Systemic immunosuppressive therapy, except steroids given prophylactically or at chronic low dosage (≤20 mg/day prednisone equivalent)
	Radiotherapy within 4 weeks before randomization, except for palliation
	Serious nonhealing wound, ulcer or bone fracture
	Deep vein thromboembolic event within 4 weeks before randomization
	Known clinically relevant coagulopathy, bleeding diathesis or bleeding event within 4 weeks before randomization

†Including adjuvant/neoadjuvant chemotherapy, if cancer recurred either during treatment or within 6 months of its completion.
‡Absolute neutrophil count ≥1.5 × 10^9/l; hemoglobin >9 g/dl; platelet count ≥100 × 10^9/l; creatinine clearance ≥50 ml/min; total serum bilirubin <1.5 × ULN; alanine and aspartate aminotransferase levels ≤2.5 × ULN (≤5 × ULN in patients with liver metastases).
§Contraception criterion applies to women of childbearing potential and men with partners of childbearing potential.
ECOG: Eastern Cooperative Oncology Group; HIV: Human immunodeficiency virus; mCRC: Metastatic colorectal cancer; NYHA: New York Heart Association; ULN: Upper limit of normal.

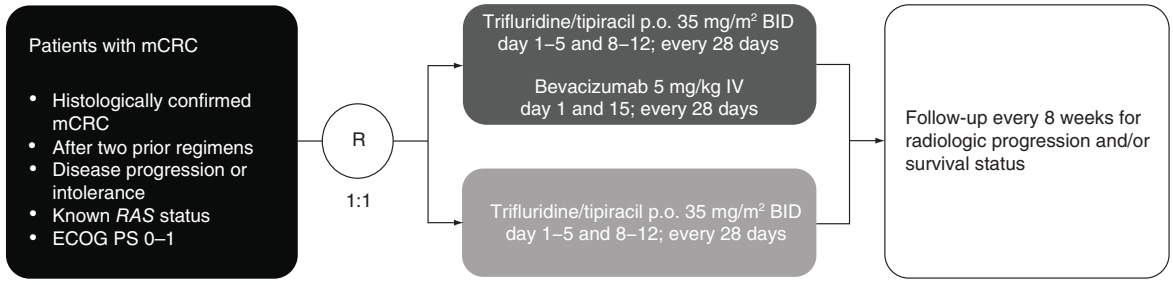

Figure 1. SUNLIGHT trial design.
BID: Twice daily; DCR: Disease control rate; ECOG PS: Eastern Cooperative Oncology Group performance status; IV: Intravenous; mCRC: Metastatic colorectal cancer; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; p.o.: Per orem (orally); QoL: Quality of life; R: Randomization.

the treatment, this adjuvant/neoadjuvant chemotherapy will count as one regimen of chemotherapy for advanced disease.

Study design

SUNLIGHT is an international, open-label, active-controlled, two-arm, Phase III trial. Enrollment began in mid-November 2020, and is ongoing. Patients are being recruited at approximately 120 sites in 13 countries: Austria, Belgium, Brazil, Denmark, France, Germany, Hungary, Italy, Poland, Russia, Spain, Ukraine and the USA.

The study design is shown in Figure 1. Patients will be randomly allocated (in a 1:1 ratio) to receive FTD/TPI plus bevacizumab or FTD/TPI monotherapy. To minimize bias, randomization will be stratified by geographic region (North America vs European Union vs the rest of the world), time since diagnosis of metastatic disease

(<18 months vs ≥18 months), and *RAS* status (wild type vs mutant). Randomized treatment with FTD/TPI plus bevacizumab or FTD/TPI monotherapy will continue until one or more criteria for withdrawal are met, namely radiologic or clinical disease progression, unacceptable toxicity or withdrawal of consent. Bevacizumab monotherapy is not permitted. After withdrawal, patients will be followed up every 8 weeks; patients without disease progression at withdrawal will continue to undergo tumor assessment until there is evidence of radiologic progression, and all patients will be followed up for survival status until death or the end of the study.

Evaluations

Tumor assessments will be performed, as per the Response Evaluation Criteria in Solid Tumors version 1.1 [24], by the investigator at baseline and then every two cycles from day 1 of cycle one until radiologic progression or the end of the study. ORR will be assessed (using 'best overall response' methodology) as the sum of complete response and partial response, while the DCR will be assessed as the sum of complete response, partial response and stable disease. QoL assessments will be performed at baseline, once per cycle, and at the withdrawal visit, using the patient-completed European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) [25] and the EuroQol EQ-5D-5L questionnaire [26]. Standard safety monitoring will be performed on an ongoing basis, and AEs will be graded using the Common Terminology Criteria for Adverse Events version 5.0 [27]. Other safety assessments, including hematology, biochemistry and coagulation monitoring, will be done at baseline, at least once per treatment cycle, and at the withdrawal visit.

Statistical analysis methods

Intent-to-treat analysis of all efficacy end points will be performed for the full analysis set, which includes all randomized patients according to the treatment group to which they were originally assigned. Safety will be assessed for the safety analysis set, which includes all randomized patients who have taken at least one dose of study medication, and will be analyzed according to the treatment received.

The primary variable is the effect of the randomized treatments on survival duration in all subjects, regardless of whether an intercurrent event (defined as the administration of additional anticancer therapy, treatment discontinuation or switching between treatment arms) occurred. OS and PFS will be summarized using Kaplan–Meier curves, and described in terms of medians and survival probabilities (at predetermined time points from 3 to 18 months). HRs will be estimated using a stratified Cox proportional hazard model. Depending on sample size, OS will be evaluated for subgroups defined by stratification variables, as well as sex, age, number of metastatic sites, performance status, prior exposure to bevacizumab and other variables. ORR and DCR will be compared between treatment groups using Fisher's exact test. Safety data will be summarized using descriptive statistics. QoL data will also be described in this way, but with the addition of survival modeling and repeated-measures mixed-effect models. The primary QoL variable of interest will be the change from baseline in the score for the global health status component of the EORTC QLQ-C30.

The study was designed to have 90% power to detect a HR of 0.70 (a 30% reduction in risk of death) in the FTD/TPI and bevacizumab group compared with the FTD/TPI monotherapy group, with a one-sided Type I error rate of 0.025. Given the treatment assignment ratio of 1:1, we calculated that 490 patients had to be enrolled in the study (245 per treatment arm), and at least 331 events (deaths from any cause) would be required for the primary analysis.

Ethical considerations

The SUNLIGHT trial is being conducted in accordance with the trial protocol, and with the ethical principles of the Declaration of Helsinki, good clinical practice and applicable regulatory requirements. All patients enrolled in the trial are required to provide written informed consent. The trial will not begin at a center until written approval has been obtained from the Institutional Review Board(s) and/or Independent Ethics Committee(s) at that center.

Discussion & future perspective

Despite therapeutic advances such as the approval of regorafenib and FTD/TPI, the prognosis for patients with refractory mCRC remains poor, with median OS times typically ranging from 4 to 8 months [6]. As the incidence and prevalence of CRC increase [3], so will the demand for well-tolerated treatment strategies that improve response rates and extend survival in patients with metastatic disease.

Preclinical and early clinical studies have indicated that FTD/TPI plus bevacizumab has the potential to extend survival in patients with refractory mCRC [18,20,21], and the purpose of the SUNLIGHT trial is to determine whether these preliminary findings can be confirmed in a large, international trial conducted across multiple study sites.

FTD/TPI plus bevacizumab is being investigated in other settings in mCRC. For example, a Phase III trial (SOLSTICE) is currently investigating the efficacy and safety of FTD/TPI plus bevacizumab (versus capecitabine plus bevacizumab) in the first-line treatment of mCRC in patients who are not eligible for intensive chemotherapy [28]. This trial follows on from the Phase II TASCO1 trial, in which FTD/TPI plus bevacizumab showed promising activity in this patient group (median PFS and OS: 9.2 and 18 months, respectively) [29]. Although the efficacy results of SOLSTICE will not inform the third-line treatment of mCRC, it will generate safety and tolerability data that may facilitate decision-making across the continuum of care.

Although clinical trial data underpin progress in all areas of medicine, it is generally considered essential to assess how well interventions perform in everyday clinical practice. In this context, it is encouraging that a real-world study has already shown FTD/TPI plus bevacizumab to be tolerable and more effective than FTD/TPI monotherapy in the treatment of refractory mCRC [30]. In this retrospective cohort analysis, which was undertaken by the C-TASK FORCE investigators [20], FTD/TPI plus bevacizumab (n = 60) was associated with a longer median PFS compared with FTD/TPI monotherapy (n = 66; 3.7 vs 2.2 months [HR: 0.69; 95% CI: 0.48–0.99]), as well as a higher 16-week PFS rate (46.6 vs 33.9%). Consistent with the findings of the Danish clinical trial [21], grade 3 or worse neutropenia was more common with FTD/TPI plus bevacizumab than monotherapy (50.0 vs 40.9%, respectively), but rates of febrile neutropenia were low.

In the future, further refinements to the FTD/TPI plus bevacizumab regimen may improve its safety and/or tolerability without compromising efficacy. Recently, a simplified regimen, in which FTD/TPI was administered every 2 weeks instead of in weeks 1 and 2 of each 4-week cycle, has been found to produce less grade $\geq$3 neutropenia than the 'standard' FTD/TPI plus bevacizumab regimen used in the C-TASK FORCE and Danish trials (15.9 vs 72 and 67%, respectively) [20,21], but with comparable median OS (10.9 vs 11.4 and 9.4 months, respectively) [31]. Although these results are preliminary, a simplified regimen could maintain outcomes with FTD/TPI plus bevacizumab while reducing hematologic toxicity, antibiotic use and the need for hematopoietic support.

Conclusion

The SUNLIGHT trial will confirm whether the combination of FTD/TPI with an anti-VEGF antibody, bevacizumab, offers additional benefits compared with FTD/TPI monotherapy. The trial is expected to be completed in May 2023.

Executive summary

- The international Phase III SUNLIGHT trial has been designed to more fully investigate the efficacy and safety of trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab, compared with FTD/TPI monotherapy, in patients with refractory metastatic colorectal cancer.
- The trial will enroll 490 patients who have disease progression or intolerance to their last line of chemotherapy, and have previously received all current standard therapies for metastatic colorectal cancer.
- Patients will be randomized 1:1 to receive either combination therapy or monotherapy, and will continue their assigned treatment until a discontinuation event (disease progression, unacceptable toxicity or withdrawal of consent) occurs.
- After withdrawal from the trial, patients will be followed up for disease progression (if applicable) and survival status every 8 weeks.
- The primary end point of the trial is overall survival. The secondary end points are progression-free survival, overall response rate, disease control rate, safety and quality of life.
- The trial is expected to end in May 2023.

Author contributions

J Tabernero, C Leger, N Amellal and R Fougeray were responsible for trial conception and design; J Tabernero is the principal investigator. All authors were responsible for reviewing and revising drafts of the manuscript, and all reviewed and approved the final version for submission.

Financial & competing interests disclosure

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Ethical conduct of research

The SUNLIGHT trial protocol, and with the ethical principles of the Declaration of Helsinki, good clinical practice and applicable regulatory requirements. All patients enrolled in the trial are required to provide written informed consent. The trial will not begin at a center until written approval has been obtained from the Institutional Review Board(s) and/or Independent Ethics Committee(s) at that center.

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