STANDARD COVER PAGE

Document title	**AMENDED CLINICAL STUDY PROTOCOL**
Study official title	A randomised, open-label, multi-centre, two-arm Phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a Safety Lead-In part in participants with KRAS/NRAS and BRAF wild type metastatic colorectal cancer previously treated with standard treatment and anti-EGFR therapy (COLSTAR)
Study brief title	Phase 3 study of futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil single agent in participants with previously treated metastatic colorectal cancer
Study public title	A study of futuximab/modotuximab in combination with trifluridine/tipiracil in participants with previously treated colorectal cancer that has spread (metastatic)
Study name	COLSTAR
Test drug code	Futuximab/modotuximab (also known as S95026 or Sym004)
Indication	Pre-treated metastatic colorectal cancer
Development phase	Phase 3 with Safety Lead-In part
Protocol code	CL3-95026-001
EudraCT Number	2021-003151-41
Universal Trial Number	Not applicable
Other register number CT. gov)	NCT05223673
Investigational New Drug Application Number	IND 105953
Sponsor	Institut de Recherches Internationales Servier (I.R.I.S.)
International coordinator	Prof. Fortunato Ciardiello University of Campania, Napoli Italy
Date of the document	26 July 2022
Version of the document	Final version
Version number	3.0
Substantial Amendment(s) integrated	

No	Final version date	Countries concerned
1	24 January 2022	All
2	26 July 2022	All

CCI [redacted]

VERSION LIST

Protocol No	Substantial amendment	Final version date	Countries concerned	Nature of key modifications
1.0	NA	28 July 2021	All	Original protocol
1.1	NA	5 January 2022	DNK	- See Appendix 13
2.0	1	24 January 2022	All	- Typos and formatting changes were made throughout the protocol. - Synopsis and investigational schedule were revised to reflect changes made in the protocol body. - Blood volume was revised in Section 4.1.2 (Investigation schedule) and Appendix 12; text was added "For men and post-menopausal women the total volume of blood collected will be slightly lower (since pregnancy tests don't apply)". - In Table (4.1.3.2) 1: Dose-limiting Toxicity Criteria, other adverse events was revised to specify that "Grade 3 nausea and/or vomiting controlled by anti-emetic therapy that lasts less than 72h" as stipulated by the FDA (incorporated non-substantial amendment 1). - Screening Criterion 5 was revised to specify that "patients with known MSI-H/dMMR tumours are eligible if they have received previous treatment with immune checkpoint inhibitors according to approved indication" to align with FDA requirements. - Screening Criteria 8, 9, 13, 14, 16-25, 29, 32, 33, 35, 36, 39, and 40 were revised to clarify that the inclusion visit "(Safety Lead-in part) or randomisation visit (Phase 3 part)". - Inclusion Criterion 17 was revised to specify that "Creatinine clearance ≥ 30 mL/min assessed using the Cockcroft & Gault formula" to align with FDA requirements. - Inclusion Criterion 21 was revised to specify that "In addition, highly effective contraception should be considered for their female partners." as stipulated by health authority request (Belgium). - Exclusion Criterion 26 was removed; patients with MSI-H tumours will be allowed in the study provided they have received previous treatment with immune check point inhibitors that are approved for this indication/population. - Exclusion Criterion 32 and corresponding text was revised to include "QTc interval >480 ms" per FDA feedback. - Exclusion Criterion 35 and corresponding text was revied to specify that participants with skin rash of Grade > 1 from prior anti-EGFR "at the time of inclusion (Safety Lead-in part) or randomisation (Phase 3 part)" for clarification.

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				- Exclusion Criterion 36 and corresponding text was revised to specify drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior "to inclusion (Safety Lead-in part) or randomisation (Phase 3 part)" for clarification. - Exclusion Criterion 39 and corresponding text was revised to specify that treatment with systemic immunosuppressive therapy would occur "within 4 weeks prior to inclusion (Safety Lead-in part) or randomisation (Phase 3 part)" for clarification. - The text describing futuximab/modotuximab administration in Section 6.1.1.2 was revised to remove "an indwelling" for consistency. - Text and references were added regarding the prophylactic use of antibiotics in Section 6.1.2.2. Text regarding the recommendation for medical management of EGFR-related skin toxicity was deleted, per FDA feedback. - Section 6.3.2 (Authorised treatments) was modified to specify that "Premedication for dermatologic AEs is allowed throughout the study" to align with FDA feedback. - Table (7.2.4.6) 1 was revised to clarify "Time point response for participants with target, or/and non-target"disease. - Section 8.1 (Specification of safety parameters) and corresponding text was revised to specify "total calcium" for clarification. - Section 8.2.5 (Only for futuximab/modotuximab participants (Safety Lead-In part and Arm A of Phase 3 part) was modified to remove text regarding "trifluridine/tipiracil intake in Arm B of Phase 3 part" as dermatologic examination does not apply to Arm B. - Regarding trifluridine/tipiracil intake in Sections 8.2.7.1 (Haematology) and 8.2.7.2 (Biochemistry) text was added: "only for CxD1" for clarification. - "Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1" and "(trifluridine/tipiracil intake in Arm B of Phase 3 part)" was removed in Section 8.2.7.3. - Text in Section 8.2.7.4 was revised to clarify that "PTT and/or activated PTT" can be included in the coagulation assessment. - "Pregnancy tests should be performed prior to randomisation, at the beginning of each cycle during the treatment period (treatment cycle is repeated every 28 days), upon treatment discontinuation and at the first follow-up visit, for all relevant patients." in Section 8.2.7.6 was added as stipulated by health authority request (Belgium). - The following text were added in Section 8.3 as a modification to the template: "Any **clinical finding or** clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the studied disease should not be considered as an AE unless judged by the investigator to

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				be more severe than expected for the participant's condition." And "A non-fatal studied "disease progression" **itself** should not be considered as an AE." - Footnote in Table (8.11.2.3) 1 was corrected to remove "except for management of skin toxicity where a third reduction to 1.5 mg/kg is permitted". - Codons for KRAS &NRAS mutational analysis were specified in Section 9.1.1.3. - Table (9.2.1) 1 and Table (9.5) 1 footnotes were revised to "5-60 minutes". - Blood volume was corrected in Section 9.2.2, 9.5, and in Appendix 12. - Text was corrected in Section 9.4: and corresponding table and text: "Peripheral whole blood (20 mL) will be collected pre-dose on C1D1 C2D1, C3D1 and then every 2 cycles along with tumour assessment **and at withdrawal visit**, and analysed centrally for ctDNA monitoring." To align with the investigational schedule. - Footnote in Table (9.5) 1 was added: "**The frequency of futuximab/modotuximab immunogenicity assessments will be reduced to every 2 months after the first 6 months in the first year and every 4 months after the first year." per FDA request. - Text was added in Section 9.5 (Immunogenicity): ". ADA Backup samples will be stored, for a maximum of 3 years after the end of the study, to allow additional analyses related to immunogenicity assessment to be performed in case of agencies' request during their review process. All samples will be destroyed at the latest at the end of the storage period or at any time on participant's or sponsor's request" because storage of back-up ADA samples is needed as agencies could request additional analysis until the time of filing. - Text in Section 10.1.1.1 (Analysis sets) was removed: "Must have measurable or non-measurable lesion according to RECIST v1.1 [Screening criterion #4]." Because no deviation from this criterion is possible. - Text in Section 10.1.2.4.2 (Phase 3 part) was added: "and anti-EGFR mAb therapy for ≥ 4 months)" to align with the Study Plan (Section 4.1.1). - Text was added in Section 10.1.2.4.2.1 under the subheading Subgroup analyses: response to previous treatment with anti-EGFR (CR/PR, SD), last previous regimen (anti-EGFR, no anti-EGFR), skin toxicity with previous anti-EGFR (yes, no), skin toxicity with previous anti-EGFR (Grade 1-2, Grade 3-4, no toxicity), duration of previous anti-EGFR (< 8, ≥ 8 months), Race (White, American Indian/Alaska native, Asian, Black/African American, Native Hawaiian/Other pacific islander)" due to the additional subgroup analysis. - Text regarding statistical analyses were revised in Section 10.1.2.4.2.4 under the subheading (Secondary estimands based on ORR and DCR) per FDA feedback. - Text in Section 17.2 (Concerning the sponsor) regarding supplying the investigator with the Product Information and Investigator Brochure was corrected. - Appendix 9 under the subheading B. Grading of Infusion-Related Reactions, table rows (Allergic reaction, Cytokine release syndrome) wording was revised to align with CTCAE version 5. Similar change was

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				made in Appendix 10 (Futuximab/modotuximab Management of Management of Rash, Paronychia, Xerosis, and Pruritus) and Appendix 11 (Management of Hypomagnesemia). - Appendix 10 under the subheading A. Prophylaxis for futuximab/modotuximab-Related Dermatologic AEs, the title of the table was revised to "Options for Premedication for Dermatologic AEs", per FDA feedback. - PK and ADA sample collection at predose was extended from 5-30 min before start of infusion to 5-60 min before start of infusion
2.1	NA	10 February 2022	CHN	- See Appendix 14
3.0	2	26 July 2022	All	- Typographical errors were corrected globally. - Revised number of participating centres and countries, and updated study initiation and completion dates. - "Phase 3 part" was changed to "Randomised part" for clarity throughout the protocol. - Replaced BICR with Investigator assessment; BICR will be performed only if needed, retrospectively, and will not be provided to investigators for decisions regarding patient treatment. - Revised text regarding management of skin toxicity globally per FDA feedback. - Molecular weight of futuximab and modotuximab was corrected in Section 2.2. - Addition in Section 2.3.2 of the description and results of study WJOG8916G. - Correction of DC definition in Table (3.4) 1 and Table (3.4) 2, and in Sections 10.1.2.4.1 and 10.1.2.4.2: suppression of "24 weeks" for SD since it corresponds to a different endpoint (clinical benefit) not evaluated in this study. - Changed naming of "Inclusion" period to "Screening" period to align with study plan Figure (4.1.1) 2 Figure (4.1.1) 3 and added wording regarding televisits in Section 4.1.1. Added QoL to C2D1 in Figure (4.1.1) 3 to align with the investigation schedule. - Changed 'futuximab/modotuximab' to study treatments in footnote #7 in Table (4.1.2) 1 and throughout the protocol where applicable for clarity. - Footnote #9 in Table (4.1.2) 1 and Footnote #12 in Table (4.1.2) 2 was revised to align with criterion #32a. - Footnote #13 in Table (4.1.2) 1 was revised to align with modifications in Section 9.1.1.3. - Footnote #13 in Table (4.1.2) 2 was revised to align with modifications in Section 9.6. - Footnote #17 in Table (4.1.2) 2 was revised to align with modifications in Section 9.1.1.3. - Text in Section 4.1.3.2 was revised to better specify DLT period. - Figure (4.1.3.4) 1 was revised to specify 'evaluable' for 6, 12, and 25 participants. - Section 4.1.4, criterion #6a and corresponding text regarding previous treatment with anti-EGFR mAb therapy was revised to for ≥16 weeks. - Criterion #5a was revised to remove "based on clinical evaluation" for clarity.

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				- Criterion #32b was revised to add “per the investigator’s discretion” for consistency. - Text was revised in Section 6.1 regarding COVID-19, as with the advanced knowledge on the COVID-19 infection, the period to re-start study treatment can be reduced, to increase at the same time the chances to respond to treatment. - Text revised regarding size of in-filter in Section 6.1.1.2. - Text was corrected to remove “at C1D1 only” in Section 6.1.1.6. - Text in Section 6.1.5 was revised for clarity, following modifications regarding dose delays in Section 8. - Text in Section 6.3.1.1 was revised to align with wording of criterion# 40a. - Text in Section 8.2.6 was revised to align with wording of criterion# 32a. - Text regarding “Any events of COVID-19” was removed in Section 8.7 since there is no longer a reason to consider COVID-19 events as ERINs because only serious adverse events should be integrated in the PV database. - Text was revised in Sections 8.11, 8.11.1, and 8.11.2, to provide more information about dose delay and specify maximum delay periods to allow initiation of both IMPs at the same time in the next cycle or, when that is not possible, to have the next cycle started with only one of the IMPs; and to allow treatment re-start with the re-administration of a loading dose of 9 mg/kg after 2 consecutive doses of S95026 have been omitted, in order to re-achieve steady state and target saturation after treatment interruption, in line with the rationale for the initial loading dose at C1D1. - Revised text in Section 9.1.1.3 to align with amended main ICF. - Added timepoint in Section 9.6 and investigation schedule. - Revised subgroup analyses and exploratory analyses in Section10.1.2.4.2.1. - Added text regarding the PK and PK/PD analysis in Section 10.3.2. - Revised text regarding composition of SC members in Section 12.4.1. - Text regarding ICF availability in electronic format added in Section 13.3. - Added text regarding confirming the authenticity of the data in the e-CRF in Section 14.1. - Updated Appendix 5 with current version of the EQ-5D-5L scale. - Added footnote in Appendix 9 regarding use or H1 antagonists. - Removed Part A in Appendix 10 due to FDA feedback. - Revised and added footnotes in Appendix 12.

SYNOPSIS

Name of the sponsor: I.R.I.S.
Name of Finished Product: Futuximab/modotuximab (also known as S95026 or Sym004)
Name of Active Ingredient: futuximab and modotuximab
Title of study: A randomised, open-label, multi-centre, two-arm Phase 3 study comparing futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil single agent with a Safety Lead-In part in participants with KRAS/NRAS and BRAF wild type metastatic colorectal cancer previously treated with standard treatment and anti-EGFR therapy (COLSTAR) **Study Brief Title**: Phase 3 study of futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil single agent in participants with previously treated metastatic colorectal cancer. **Study Public Title:** A study of futuximab/modotuximab in combination with trifluridine/tipiracil in participants with previously treated colorectal cancer that has spread (metastatic). **Protocol No.:** CL3-95026-001 **Study name:** COLSTAR
International Coordinator and Steering Committee Chairman: Prof. Fortunato Ciardiello National coordinators and investigators: listed in a separate document
Study centre(s): **Safety Lead-In part** Total number of centres: approximately 25 centres. Total number of countries: approximately 8 countries. **Randomised part** Total number of centres: approximately 200 centres. Total number of countries: approximately 20 countries.
Study period: - Study duration for the participant: approximately 6.5 months of treatment + follow-up period for survival. - Study initiation date (planned date of first visit first participant (FVFP)): • Safety Lead-In part: Q2 2022. • Randomised part: Q3 2023. - Study completion date (planned date of last visit last participant (LVLP)): Approximately Q4 2026. **Study development phase:** Phase 3 with Safety Lead-In part
Objectives / Endpoints: **Safety Lead-In part** **Primary** - To assess safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil according to National Cancer Institute Comment Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. **Secondary** - To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil per investigator assessment using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in terms of: • Objective Response Rate (ORR). • Best Overall Response (BOR). • Disease Control Rate (DCR). • Progression Free Survival (PFS). - To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil in terms of: • Overall Survival (OS). - To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination of futuximab/modotuximab with trifluridine/tipiracil. - To evaluate the immunogenicity of futuximab/modotuximab (*i.e.* occurrence of anti-drug antibody [ADA]).

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Exploratory - To explore biomarkers as potential predictors of response and to track the emergence of resistance. **Randomised part** **Primary** - To compare OS of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in participants with tumours that are KRAS/NRAS and BRAF wild-type (WT) (Double negative [DN]). **Key Secondary** - To compare OS of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in participants with tumours that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]). **Secondary** - To compare anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy per investigator's assessment using RECIST v1.1 in terms of: • PFS. • ORR. • DCR. • Duration of response (DoR). • Time to Response (TTR). - To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in terms of: • Time to Next Treatment (TTNT). • Time to Eastern Cooperative Oncology Group (ECOG) Performance Status ≥ 2 (TtPS2). - To further evaluate and to compare the safety profile of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy. - To compare Quality of life (QoL) of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy Appendix 5 and Appendix 6. - To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination futuximab/modotuximab with trifluridine/tipiracil. - To further evaluate the immunogenicity of futuximab/modotuximab (*i.e.* occurrence of ADAs). **Exploratory** - To explore the PK/pharmacodynamic (PD) relationship for safety and/or efficacy of the combination futuximab/modotuximab with trifluridine/tipiracil. - To explore biomarkers as potential predictors of response and to track the emergence of resistance.
Methodology: This is a Phase 3 study, with a Safety Lead-In part. The Safety Lead-In is an international, open-label, single-arm, non-randomised part, with the aim to evaluate the safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil in participants previously treated by chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and by anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) therapy for ≥ 16 weeks, KRAS/NRAS and BRAF WT metastatic colorectal cancer (mCRC). The Randomised part is an international, open-label, randomised, multi-centre, parallel-group, 2-arm part. The participants previously treated by chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and with anti-EGFR mAb therapy for ≥ 16 weeks with KRAS/NRAS and BRAF WT mCRC will be randomised in a 1:1 ratio, to either futuximab/modotuximab in combination with trifluridine/tipiracil (Arm A) or trifluridine/tipiracil (Arm B).

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The participants will be stratified according to:

- Performance Status (PS) (0 *vs* 1).
- Extracellular domain EGFR mutations (ECD) (presence *vs* absence).
- Previous regimens of treatment (2 *vs* ≥ 3).

Number of included participants:
Planned: Approximately 25 participants with a minimum of 3 Japanese participants in Safety Lead-In part and approximately 500 participants in Randomised part.
Number of primary events: For Randomised part 383 OS events.

Diagnosis and main criteria for inclusion (Section 5)
Screening criteria
Demographic characteristics

- Male or female participant aged ≥ 18 years old.

Medical and therapeutic criteria

- Participants must have histologically or cytologically confirmed adenocarcinoma of mCRC (all other histological types are excluded), not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumour.
- Based on circulating tumour DNA (ctDNA) screening blood test analysis participants should be:
  - Without RAS (KRAS and NRAS) mutations in any of the following codons:
    - CCI [redacted]
    - CCI [redacted]
    - CCI [redacted]
  - Without BRAF CCI [redacted].
- Participants must have measurable or non-measurable lesion according to RECIST v1.1.
- Participants must have received at least 2 prior regimens of standard chemotherapy for mCRC and had demonstrated progressive disease or intolerance to their last regimen. The following characteristics apply:
  - Prior standard chemotherapy must not have included trifluridine/tipiracil but must have included all of the following agents approved and available in each country:
    - Fluoropyrimidines, irinotecan and oxaliplatin.
    - At least one anti-vascular endothelial growth factor (VEGF) pathway inhibitor (bevacizumab and/or aflibercept and/or ramucirumab and/or regorafenib).
    - At least one anti-EGFR mAb (cetuximab or panitumumab).
    - Patients with known MSI-H/dMMR tumours are eligible if they have received previous treatment with immune checkpoint inhibitors according to approved indication.
  - Participants must have progressed during or within 6 months of the last administration of last standard chemotherapy regimen. Participants who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will be eligible to enter the study.
  - Participants who received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy are permitted to count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy.
- Participants should have received previous treatment with commercially available anti-EGFR mAbs for ≥ 16 weeks.
- Ability to swallow oral medication.
- Estimated life expectancy ≥ 12 weeks. This criterion should be rechecked at inclusion visit (Safety Lead-in part) or randomisation visit.
- ECOG performance status 0 or 1 (or equivalent Karnofsky PS of 70% to 100%). This criterion should be rechecked at inclusion visit (Safety Lead-in part) or randomisation visit (Appendix 2).

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Informed consent ❖ Written informed consent obtained prior any study-specific procedure as described in Section 13.3.

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Non-screening criteria

General criteria

- Pregnancy, possibility of becoming pregnant during the study and breast-feeding woman.
- Unlikely to cooperate in the study.
- Participation in another interventional study at the same time or within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit. Participation in study follow-up part without IMP administration non-interventional registry or epidemiological study is allowed.
- Patients currently receiving or having received anticancer therapies within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit.
- Participant already enrolled in the study (informed consent form [ICF] signed).

Inclusion criteria

Medical and therapeutic criteria

- Adequate haematological function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit, defined as:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
  - Haemoglobin ≥ 90 g/L. In case of blood transfusion, the haemoglobin assessment must be performed 2 weeks or more after the transfusion.
  - Platelet count ≥ 100 x 10^9/L.
  - Adequate coagulation function for all participants. For participants receiving anti-coagulant therapy (except platelet anti-aggregates) the adequate therapeutic levels of international normalized ratio (INR) should be confirmed.
- Adequate renal function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit defined as:
  - Creatinine clearance ≥ 30 mL/min assessed using the Cockcroft & Gault formula (Appendix 3).
- Adequate hepatic function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit, defined as:
  - Total serum bilirubin < 1.5 x upper limit of normal (ULN) (unless Gilbert disease confirmed).
  - Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 x ULN (if liver function abnormalities are due to underlying liver metastasis, AST [SGOT] and ALT [SGPT] ≤ 5 x ULN).
- Serum potassium, serum phosphates, serum magnesium within normal limits with or without supplementation based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit.
- Women of childbearing potential (WOCBP) must use a highly effective method of birth control (Section 5.5) during study treatment beginning within 2 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit and continuing at least 6 months after the last IMP administration. In case of oral contraception, women should have been stable on the same contraceptive drug (*i.e.* same active principle) for at least 3 months prior to the inclusion visit (Safety Lead-in part) or randomisation visit.
- Male participants with WOCBP partners must use a condom during the study and until at least 6 months after the last IMP administration. In addition, highly effective contraception should be considered for their female partners. Contraceptive measures do not apply if the participant is sterile, vasectomised or sexually abstinent. Sperm donation will not be allowed during the study and for 6 months after the last IMP administration.

Exclusion criteria

Medical and therapeutic criteria

- Major surgery within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit or participants who have not recovered from side effects of the surgery.
- Participants with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit.

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❖ Known clinically significant cardiovascular disease or condition, including: - Any uncontrolled arrhythmia (per the investigator's discretion). - Severe conduction disturbance (*e.g.* 3rd degree heart block) (per the investigator's discretion). - Uncontrolled hypertension (per the investigator's discretion). - Class III or IV cardiovascular disease according to the New York Heart Association (NYHA) Functional Classification (Appendix 4). - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, stenting or bypass grafting within 6 months prior to inclusion (Safety Lead-in part) or randomisation. - QTc interval > 480 ms ❖ Participants with a significant gastrointestinal abnormality, including: - Diarrhoea of Grade > 1 at the time of inclusion. - Requirement for IV alimentation. - In the investigator's opinion, that might significantly interfere with proper absorption of the study treatments. ❖ Participants with skin rash of Grade > 1 from prior anti-EGFR at the time of inclusion (Safety Lead-in part) or randomisation, or any other skin toxicity precluding participation in the study according to investigator's discretion. ❖ Other malignancies including those which were radically treated and for which the remission period at the time of screening is less than five years. Exemptions for this minimally required duration of remission period may be applied for carcinoma in situ of the cervix, basal cell skin cancer and carcinoma in situ of gastric and oesophageal cancer that are deemed to be cured by adequate treatment. ❖ Treatment with systemic immunosuppressive therapy within 4 weeks prior to inclusion (Safety Lead-in part) or randomisation (except steroids given in prophylactic setting or at a chronic low dose [≤ 20 mg/day prednisone equivalent]). ❖ Prior radiotherapy if completed less than 4 weeks before the inclusion visit (Safety Lead-in part) or randomisation visit, except if provided as a short course for symptoms palliation only. Tumour lesions if previously irradiated cannot be chosen as target lesions for response evaluation.
Test drug: **IMPs:** Safety Lead-In part: futuximab/modotuximab + trifluridine/tipiracil Randomised part: futuximab/modotuximab (Arm A) + trifluridine/tipiracil *vs* trifluridine/tipiracil (Arm B) **Futuximab/modotuximab** Premedication: - Premedication for Infusion-Related Reactions (IRR): There is an inherent risk for IRRs with the administration of mAbs, therefore premedication for prophylaxis of IRRs will be mandatory prior to each dose of futuximab/modotuximab. All participants will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen (Section 6.1.2.1). - Premedication for skin toxicity: Management of skin toxicity will be done throughout the study according to the investigator's discretion. Para-aminobenzoic acid (PABA)-free sun protection factor (SPF) ≥ 15 ultraviolet (UV) A and UVB sunscreen protection is recommended to be applied to exposed skin areas before going outdoors. (Section 6.1.2.2). - Premedication for other toxicities: In the event of other futuximab/modotuximab associated AEs, participants may be pre-medicated with standard therapies at the investigator's discretion, to reduce the potential for such reactions in the future. The sponsor may implement additional mandatory premedication for all participants treated in this study if a pattern emerges of other mild-to-moderate futuximab/modotuximab -related AEs

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Name of Finished Product: Futuximab/modotuximab (also known as S95026 or Sym004)
Name of Active Ingredient: futuximab and modotuximab
(*e.g.*, mucositis, diarrhoea) that are amenable to prophylaxis with standard agents (Section 6.1.2.3). Such action will occur following discussions between the investigator(s) and the sponsor. Administration schedule: futuximab/modotuximab will be administered at a dose 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly (± 2 days) beginning on C1D8 (maintenance doses) for all subsequent administrations, by IV infusion, after trifluridine/tipiracil intake. Infusion duration: The first infusion on C1D1 (9 mg/kg in 500 mL) is to be administered over 1 hour. The maximum rate of infusion of 500 mL/hour should not be exceeded throughout the administration. Subsequent infusions (6 mg/kg in 250 mL) may be delivered over 30 minutes, maintaining the maximum infusion rate of 500 mL/hour. Observation requirements: The participants will be observed for a minimum of 2 hours following completion of the first administration of futuximab/modotuximab on C1D1 and a minimum of 1 hour following completion of subsequent infusions of futuximab/modotuximab (C1D8, onward). Participants could be hospitalized for 24 hours after the administration of futuximab/modotuximab per the investigator's discretion and/or local practice per country, to enable a close in-patient safety monitoring. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary. Futuximab/modotuximab infusions will take place under the close supervision of physician or other study personnel experienced in administration of IV agents and in an environment where full resuscitation facilities are immediately available. **Trifluridine/tipiracil** Premedication: Anti-emetic therapy is recommended to prevent nausea and vomiting (Section 6.1.4). Administration schedule: Trifluridine/tipiracil will be administered, before futuximab/modotuximab administration, at a dose 35 mg/m²/dose, orally twice a day (BID), within 1 hour after completion of morning and evening meals (or in accordance with the local SmPC [Summary of Product Characteristics] of trifluridine/tipiracil), 5 days on/2 days off, over 14 days (2 weeks), followed by a 14-day (2 weeks) rest. This treatment cycle will be repeated every 28-days (4 weeks).
Comparator (Only for Randomised part): The comparator agent (control) is trifluridine/tipiracil. Trifluridine/tipiracil will be administered at a dose 35 mg/m²/dose, orally BID, within 1 hour after completion of morning and evening meals (or in accordance with the local SmPC of trifluridine/tipiracil), 5 days on/2 days off, over 14 days (2 weeks), followed by a 14-day (2 weeks) rest. This treatment cycle will be repeated every 28-days (4 weeks).
Duration of treatment: **Active treatment period:** Participants will be treated until they meet a discontinuation criterion (Section 5.8.1). Administration will be at the same dose level (unless dose reduction is necessary) and infusion duration established for the participant during Cycle 1, and on the same weekly schedule provided retreatment criteria are met. **Follow-up period:** After the withdrawal visit, all treated participants will be followed every 8 weeks (±10 calendar days): - For tumour assessment (unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy - For survival status until death or until end of the study is reached (whichever occur first) If a participant is still receiving IMPs at the end of the study, please see Section 6.5 for procedures to be followed.
Criteria for evaluation: Efficacy measurements: Tumour assessments will be performed as per RECIST version 1.1 (Eisenhauer, 2009) at baseline and then every 8 weeks (± 7 calendar days) from C1D1 until radiologic progression, death or end of study, whichever occurs first.
Safety measurements: AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. AEs will be reported up to 30 calendar days after the last IMPs intake and the serious AEs

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related to the research product will be reported without any time delay. Information of any change or addition of a new concomitant treatment at each visit must be obtained.
Safety assessments will include:

- Concomitant medication/procedure surveys.
- ECOG PS assessment.
- Vital sign assessment (including temperature, pulse, respiratory rate, and blood pressure).
- Physical examination (with weight, body surface area [BSA] calculation, and dermatologic examination).
- Dermatologic examination (additional for futuximab/modotuximab participants in Safety Lead-In part and ARM A in Randomised part).
- Haematology panel.
- Biochemistry panel.
- Serum magnesium (Mg), total calcium (Ca), potassium (K) monitoring (additional for futuximab/modotuximab participants in Safety Lead-In part and ARM A in Randomised part).
- Coagulation panel.
- Urinalysis.
- Pregnancy testing (if applicable).
- Electrocardiogram (ECG), 12-lead.

For each participant, DLT assessment will be performed during Safety Lead in part. Assessments include all toxicities observed during the initial 28-day treatment period (Cycle 1). A DLT is defined as:

- A clinically significant AE graded according to the NCI-CTCAE version 5.0, observed during the initial 28-day treatment period following the first IMP administration.
- Assessed as unrelated to underlying disease, disease progression, intercurrent illness, or concomitant medications.
- At least possibly related to the IMPs (futuximab/modotuximab or trifluridine/tipiracil or both) by the investigator and meeting any of the following criteria:
  - Anaemia ≥ Grade 3.
  - Febrile neutropenia.
  - Uncomplicated Grade 4 neutropenia that lasts ≥ 1 week.
  - Uncomplicated Grade 4 thrombocytopenia (less than 25,000 per mm^3) that lasts ≥ 1 week or any Grade ≥ 3 thrombocytopenia with bleeding episodes or thrombocytopenia requiring platelet transfusion.
  - Grade 3 diarrhoea for >2 days despite adequate treatment or with fever and/or dehydration.
  - Any Grade 3 skin toxicity lasting for more than 2 weeks, or Grade 4 skin toxicity regardless of the duration[1].
  - Grade ≥ 3 infusion-related reaction.
  - AST or ALT ≥ 3 x ULN along with a total bilirubin > 2.0 x ULN and confirmed Hy's law cases according to FDA guidance.
  - Grade ≥ 3 isolated AST or ALT.
  - Any laboratory value Grade ≥ 3 with a duration ≥ 3 days, considered unrelated to underlying disease, disease progression, intercurrent illness or concomitant medications/therapies.
  - Any other Grade 3 or Grade 4 non-haematologic AE (except for Grade 3 nausea and/or vomiting controlled by anti-emetic therapy that last less than 72 h, or Grade 3 diarrhoea responsive to anti-diarrheal medication).

[1]acne, cellulitis, dermatitis acneiform, dry skin, erysipelas, erythema, folliculitis, hypertrichosis, paronychia, pruritus, rash, rash maculopapular, rash vesicular, skin exfoliation, skin hyperpigmentation and xerosis

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Pharmacokinetic measurements: - Individual PK parameters such as area under the plasma concentration-time curve (AUC) or maximum plasma concentration (C_{max}) will be derived using a population PK modelling approach, which is described in a separate data analysis plan (DAP). - Exploratory assessment of the relationship between individual PK parameters and PD endpoints for efficacy or safety may be performed; a separate DAP will be written. *Other measurements* *Genomic Analysis* Genomic analysis for defining patient eligibility and stratification will be based on assessment of ctDNA in plasma with an oncogene panel. The genomic analysis includes a series of genes frequently mutated in cancer, but will be focused on the following genes: - BRAF CCI CCI - KRAS / NRAS CCI CCI - EGFR-ECD CCI *Futuximab/modotuximab Immunogenicity* ADA in serum will be measured *Quality of life assessments (QoL)* QoL assessments will be performed at baseline, after the end of cycle 1 (C2D1), then from cycle 3 (C3D1) every 2 cycles during the treatment period, at the withdrawal visit, and every 8 weeks (2 months) during the follow-up period until death or until end of the study is reached (whichever occur first), using EORTC QLQ-C30 and EQ-5D-5L questionnaires Appendix 5 and Appendix 6.
Data Monitoring Committee: Safety data collected during the Safety Lead-In part will be reviewed by a Data Monitoring Committee (DMC) to assess whether 1) the drug combination is tolerable, 2) if the maximum tolerated dose (MTD) has been exceeded, and 3) if the randomised portion of the study may proceed. During the Safety Lead-In part, the DMC will initially assess tolerability after 6 evaluable participants, then after 12 evaluable participants treated and finally when all 25 participants will have been treated. During the Randomised part the DMC will meet approximately every 4 months in the first year and approximately twice a year thereafter and at the planned interim analysis as well. For more details see Section 4.1.3.4. The composition and role of the DMC will be described in a charter finalised before the trial is initiated.
Specific COVID-19 situation In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted. The study treatment(s) could be restarted if participant is asymptomatic and a period of at least 7 days after the diagnosis has been respected, and with a negative test (if the testing is required by the institutional site). Vaccination against COVID-19 is highly encouraged for all patients, preferably before study inclusion or whenever possible for patients included in the study. In this case, it is recommended to avoid vaccination 48 hours before or after futuximab/modotuximab administration if possible, for all cycles.

Contractual signatories	
I, the undersigned, have read the foregoing protocol and the "Participant information and consent form" document attached to the protocol and agree to conduct the study in compliance with such documents, Good Clinical Practice and the applicable regulatory requirements. **INVESTIGATOR:**	
NAME	
CENTER NUMBER	
DATE	
SIGNATURE	
HEAD OF GLOBAL DEVELOPMENT GI INDICATIONS	
NAME	PPD
DATE	Digitally signed by PPD Date: 2022.07.26 18:23:45 +02'00'
SIGNATURE	

Other signatories	
BIOSTATISTICS HEAD ONCOLOGY OR DESIGNEE:	
NAME	PPD
DATE	27 July 2022
SIGNATURE	DocuSigned by: PPD

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List of abbreviations

ABPM	:	Ambulatory Blood Pressure Monitoring
ADA	:	Anti-Drug Antibody
ADL	:	Activities of Daily Living
ADME	:	Absorption Distribution Metabolism Excretion
AE	:	Adverse Event
ALT	:	Alanine Aminotransferase
ANC	:	Absolute Neutrophil Count
AST	:	Aspartate Aminotransferase
AUC	:	Area Under the Plasma Concentration-Time Curve
BICR	:	Blinded Independent Central Review
BID	:	Twice Daily
BOR	:	Best Overall Response
BSA	:	Body Surface Area
BSC		Best Supportive Care
BPM	:	beats per minute
BUN	:	Blood Urea Nitrogen
CFR	:	Code of Federal Regulations
CISO	:	Chief Information Security Officer
C_{max}	:	Maximum Plasma Concentration
CMH	:	Cochran-Mantel-Haenszel
CMP	:	Clinical Monitoring Plan
CNS	:	Central Nervous System
CR	:	Complete Response
CRC	:	Colorectal Cancer
ctDNA	:	Circulating tumour DNA
CT	:	Computerized Tomography
CV	:	Curriculum Vitae
DAP	:	Data Analysis Plan
DCR	:	Disease Control Rate
DDI	:	Drug-Drug Interaction
DLT	:	Dose-Limiting Toxicity
DMC	:	Data Monitoring Committee
DN	:	Double-Negative
DoR	:	Duration Of Response
DPO	:	Data Protection Officer
ECD	:	Extracellular Domain
ECG	:	Electrocardiogram
e-COA	:	Electronic Clinical Outcome Assessment
ECOG	:	Eastern Cooperative Oncology Group
e-CRF	:	Electronic Case Report Form
EEA	:	European Economic Area
EGFR	:	Epidermal Growth Factor Receptor
EMA	:	European Medicines Agency
EoI	:	End of Infusion
EORTC	:	European Organization For Research And Treatment Of Cancer
e-PRO	:	Electronic Participant-Reported Outcomes
ERIN	:	Event Requiring Immediate Notification

ESMO	:	European Society for Medical Oncology
FAS	:	Full Analysis Set
FDA	:	Food and Drug Administration
FDG	:	Fluorodeoxyglucose
GCP	:	Good Clinical Practice
GDPR	:	General Data Protection Regulation
GGT	:	Gamma-Glutamyl Transferase (Gamma-Glutamyl Transpeptidase)
GHS	:	Global Health Status
HER	:	Human Epidermal Growth Factor Receptor
HIPAA		Health Insurance Portability and Accountability Act
HIV	:	Human Immunodeficiency Virus
HR	:	Hazard Ratio
HRT	:	Hormone Replacement Therapy
I.R.I.S.	:	Institut De Recherches Internationales Servier
IB	:	Investigator's Brochure
IC	:	Investigator's Choice
ICF	:	Informed Consent Form
ICH	:	International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use
IE	:	Intercurrent Event
IEC	:	Independent Ethics Committee
IMP	:	Investigational Medicinal Product
INR	:	International Normalized Ratio
IRB	:	Institutional Review Board
IRR	:	Infusion-Related Reaction
ITT	:	Intention-To-Treat
IV	:	Intravenous (Route)
IWRS	:	Interactive Web Response System
JSCCR	:	Japanese Society for Cancer of The Colon And Rectum
LDH	:	Lactate Dehydrogenase
LLN	:	Lower Limit of Normal
MA	:	Marketing Authorisation
LVEF	:	Left Ventricular Ejection Fraction
MAF	:	Mutant Allele Frequency
MASCC	:	Multinational Association of Supportive Care In Cancer
MedDRA	:	Medical Dictionary f or Regulatory Activities
MMR	:	Mismatch Repair
MoA	:	Mechanism of Action
MRI	:	Magnetic Resonance Imaging
MSI	:	Microsatellite Instability
MTD	:	Maximum Tolerated Dose
NCI-CTCAE	:	National Cancer Institute - Common Terminology Criteria For Adverse Events
NE	:	Not Evaluable
NIMP	:	Non-Investigational Medicinal Product
NYHA	:	New York Heart Association
OR	:	Objective Response
ORR	:	Objective Response Rate
OS	:	Overall Survival
PABA	:	Para-Aminobenzoic Acid

PD	:	Progressive Disease
PFS	:	Progression Free Survival
PK	:	Pharmacokinetics
PMDA	:	Pharmaceuticals and Medical Devices Agency
PO	:	Orally
PPS	:	Per Protocol Set
PR	:	Partial Response
PRO	:	Participant-Reported Outcome
PS	:	Performance Status
PTT	:	Partial Thromboplastin Time
QoL	:	Quality of Life
QTc	:	Corrected QT Interval
RBC	:	Red Blood Cells
RECIST	:	Response Evaluation Criteria In Solid Tumours
SAE	:	Serious Adverse Event
SAP	:	Statistical Analysis Plan
SARS	:	Severe Acute Respiratory Syndrome
SC	:	Steering Committee
SD	:	Stable Disease
SOC	:	System Organ Class
SmPC	:	Summary of Product Characteristics
SPF	:	Sun Protection Factor
STEAEs		Serious Treatment Emergent Adverse Events
TdP	:	Torsade De Pointes
TEAE	:	Treatment Emergent Adverse Event
TK	:	Thymidine Kinase
TMDD	:	Target-Mediated Drug Disposition
TtPS2	:	Time to ECOG Performance Status ≥ 2
TTNT	:	Time To Next Treatment
TTR	:	Time To Response
ULN	:	Upper Limit of Normal
US	:	United States
VEGF	:	Vascular Endothelial Growth Factor
WBC	:	White Blood Cells
WHO	:	World Health Organization
WHO-Drug	:	World Health Organization, Drug Dictionary
WMA	:	World Medical Association
WNL	:	Within Normal Limits
WOCBP	:	Woman Of Child Bearing Potential
WT	:	Wild Type
WV	:	Withdrawal Visit

1. ADMINISTRATIVE STRUCTURE OF THE STUDY

Non-sponsor parties, sponsor parties and contract research organizations responsible for local management of the study are described in a separate document entitled: "Administrative part of clinical study protocol."

The list of investigators is given in a separate document attached to the protocol and entitled "Investigators list."

The composition and role of the supervisory committees are described in Sections 8.10 and 12.4.

2. BACKGROUND INFORMATION

2.1. Metastatic Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer type in the world in terms of incidence and the second one in terms of mortality, with an estimated 1,800,000 new cases and 881,000 deaths in 2018.[1]

Approximately 25% of patients present with metastases at initial diagnosis and approximately 50% of patients with early-stage disease will develop metastases, which contribute to the high mortality rates reported for CRC [2]

Therapy for patients with metastatic CRC (mCRC) has mostly palliative intention, except for patients with limited metastatic disease in the liver for whom a surgical approach with curative intent may be used. Systemic therapy for mCRC typically pairs a chemotherapy backbone regimen with a biologic agent. Oxaliplatin, irinotecan and 5-fluorouracil commonly form the chemotherapy backbone in various regimens of two-drug or three-drug regimens. A biologic agent such as anti-vascular endothelial cell growth factor (VEGF) or anti-epidermal growth factor receptor (EGFR) antibody is added to the chemotherapy regimen depending on tumour-specific and patient-specific factors. Molecular testing of the tumour is required before considering treatment with anti-EGFR antibodies such as cetuximab and panitumumab. Mutations in hot spot regions of CCI of KRAS or of NRAS genes (occurring in approximately 55% of mCRC patients) and the BRAF-CCI (occurring in approximately 5-15% of mCRC patients) have been associated with lack of benefit from anti-EGFR treatment.[3-5] Additionally, "sidedness" of the tumour has a key role in the metastatic setting and is increasingly recognised as a predictive marker of response to anti-EGFR drugs, with left sided tumours demonstrating better outcome.[2]

Participants with mCRC typically receive several lines of therapy. In clinical practice, of all mCRC patients receiving first-line chemotherapy, approximately 50% go on to receive second line chemotherapy, and of these patients, approximately 25% go on to receive third-line chemotherapy.[6] This "continuum of treatment" with several subsequent lines of therapy has led to an improvement of the clinical outcome for patients with mCRC, in the last decade. Today, the median overall survival (OS) for patients with mCRC is approximately 30 months; more than double that of 20 years ago [7]

Most patients with mCRC will eventually become insensitive or unresponsive to first- and second-line chemotherapy (chemo-refractory) or will not tolerate multiple cycles of chemotherapy (chemo-intolerant). The treatment options available in chemo-refractory mCRC in the third-line setting are limited. Regorafenib (STIVARGA®) received United States (US) Food and Drug Administration (FDA) approval in 2012, and European Medicines Agency (EMA) approval in 2013; trifluridine/tipiracil (TAS-102, LONSURF®)[8] received Pharmaceuticals and Medical Devices Agency (PMDA) approval in 2014, FDA approval in 2015 and EMA approval in 2016. Both treatments are approved in Europe for patients with mCRC "who have been previously treated with, or are not considered candidates for, available therapies" including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents and, anti-EGFR agents. Regorafenib and trifluridine/tipiracil represent the standard of care options for patients with mCRC in the third-line setting,[7,9] producing an expected median OS of 6.4 months and 7.1 for regorafenib[10] and trifluridine/tipiracil,[11] respectively. For patients with wild-type (WT) RAS not previously treated with anti-EGFR antibodies in the third-line/salvage therapy setting, cetuximab in combination with irinotecan or panitumumab monotherapy can also be considered.[12]

2.2. Futuximab/modotuximab

Futuximab/modotuximab (also known as S95026 or Sym004) is a biological compound composed of a 1:1 mixture (by concentration) of two monoclonal antibodies, futuximab and modotuximab, both of which bind to non-overlapping epitopes on the extracellular domain (ECD) of the EGFR. The two drug substances (futuximab and modotuximab) have the same formulation and protein concentration in futuximab/modotuximab and the drug product is released as a mixture of the antibodies.

Futuximab is a chimeric IgG1 mAb that contains two light chains of 214 amino acid residues each and two heavy chains of 452 amino acid residues each, and a theoretical molecular weight of 149180 Da. Modotuximab is a chimeric IgG1 mAb that contains two light chains of 219 amino acid residues each and two heavy chains of 448 amino acid residues each, and a theoretical molecular weight of 149325 Da.

The dosage form of futuximab/modotuximab is a sterile, liquid product, it is further diluted at the participant level into a specific total volume using 0.9% sodium chloride for injection.

The route of administration is an intravenous infusion (IV) with a maximum infusion rate of 500 mL/hour. This maximum infusion rate should not be exceeded throughout the administration. Futuximab/modotuximab is administered on a weekly basis at a recommended dose of 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly beginning on C1D8 (maintenance doses).

2.2.1. Non-clinical development

Futuximab/modotuximab was identified through a phenotypic screen of hundreds of anti-EGFR antibody mixtures searching for a synergistic mixture with superior growth inhibitory activity compared to individual monoclonal antibodies.[13] The mixture of modotuximab and futuximab was discovered to be the most synergistic antibody mixture tested. The two antibodies had little inhibitory activity on their own and thus are highly synergistic when combined.[14]

Mechanistic studies of futuximab/modotuximab demonstrated that the superior activity of futuximab/modotuximab was achieved by induction of effective internalisation and subsequent degradation of EGFR as shown in a range of cancer cell lines of different tissue origin.[14,15] The effective internalisation and degradation were only obtained when both full-length antibodies were present and the superior activity of futuximab/modotuximab was lost when either of the two antibodies were replaced with a Fab fragment.[14] Efficient removal of the receptor from the cancer cell has the advantage of eliminating all interactions of EGFR with other proteins such as EGFR ligands, other members of the human epidermal growth factor receptor (HER) family (HER2 and HER3) and other cell surface receptors. This mechanism of action (MoA) is critical to the therapeutic potential of futuximab/modotuximab as compensatory upregulation of EGFR ligands and cross-talk with HER2 and HER3 are common mechanisms of primary and acquired resistance to anti-EGFR antibodies in clinical use.[16] In line with this, futuximab/modotuximab, but not the individual mAbs futuximab or modotuximab, has the ability to inhibit cancer cells in settings of cetuximab/panitumumab resistance where clinically, other anti-EGFR antibodies have failed.[16-18]

The efficient removal of EGFR from cancer cells in vitro translated into a superior futuximab/modotuximab anti-tumour response in vivo in preclinical models, compared to individual antibodies and reference antibodies[13,14]. The efficacy of futuximab/modotuximab was tested in several xenograft models and found to be superior in many of these models as compared to approved monoclonal antibody therapies, such as cetuximab and panitumumab. Futuximab/modotuximab was clearly superior to both futuximab and modotuximab monotherapy in vivo, indicating that the futuximab/modotuximab synergy observed in vitro also translated to in vivo studies [14]

The nonclinical safety profile of futuximab/modotuximab was extensively characterised in cynomolgus monkeys and included a side-by-side comparison with cetuximab in dose-range finding studies and a side-by-side comparison with futuximab and modotuximab in the Good Laboratory Practice 8-week toxicology study. Futuximab and modotuximab, bind to EGFR from human and cynomolgus monkeys with similar affinity. Futuximab/modotuximab is cleared faster than the individual antibodies in the monkeys, reflecting a more efficient target-mediated drug disposition in the presence of both antibodies, which again reflects the synergestic MoA described in vitro and in vivo.

The general higher incidence and severity of skin and gastrointestinal toxicity in the toxicology studies suggest that futuximab/modotuximab exerts a greater pharmacological effect than the individual antibodies, futuximab and modotuximab, at the same dose level. As compared to cetuximab, futuximab/modotuximab induced a more rapid onset of expected anti-EGFR-mediated pharmacological effects (toxicity). Importantly, futuximab/modotuximab did not demonstrate any novel safety findings not previously observed with cetuximab in cynomolgus monkeys.

In conclusion, non-clinical studies support extensive EGFR down-modulation as a novel MoA for futuximab/modotuximab that is different from that of approved anti-EGFR monoclonal antibodies. The EGFR down-regulation by futuximab/modotuximab is only achieved when both antibodies (futuximab and modotuximab) are present as shown both in vitro and in vivo and these consistent findings provide a clear rationale for evaluating futuximab/modotuximab as a fixed mixture in clinical trials with human EGFR-positive cancers.

2.2.2. Clinical development

Phase 1 study

The futuximab/modotuximab Sym004-01 was a Phase 1 dose escalation study that included a total of 111 patients (20 patients with refractory or recurrent advanced solid tumours in the Phase 1a dose escalation part and 91 patients with heavily pre-treated mCRC and acquired resistance to previous anti-EGFR therapy into five Phase 2 dose expansion cohorts). The recommended Phase 2 dose (R2PD) levels of two regimens of futuximab/modotuximab were defined based on safety and tolerability and were identified as 12 mg/kg when administered weekly and 18 mg/kg when administered on a every two weeks schedule. The adverse effect profile was similar to that observed with previously studied anti-EGFR mAbs with no novel safety findings identified, although cutaneous toxicity and hypomagnesemia were observed more frequently and were more severe in patients treated with futuximab/modotuximab at the R2PD on each of these schedules. This apparent difference in the AE profile may be due to differences in the doses or schedule of futuximab/modotuximab utilised, differences due to its unique MoA, or to the potential enrichment for patients likely to manifest these specific AEs. As it has been documented in other studies, cutaneous AEs and hypomagnesemia have been shown to be associated with responsiveness to anti-EGFR therapies,[19,20] nd the patients studied in cohorts B-F were selected based on documented development of refractoriness following prior response to or prolonged disease stabilisation (> 16 weeks) while receiving one or more of the available anti-EGFR mAbs (cetuximab, panitumumab) approved for the treatment of mCRC.

Two dosage regimens cohorts (Parts B: 12 mg/kg weekly and F: 9 mg/kg loading dose followed by 6 mg/kg weekly) were chosen for further evaluation in subsequent trials. Confirmed objective response rate was 6.9% (2/29 patients) and 0% (0/20 patients) with 12 mg/kg and 9/6 mg/kg dose regimens, respectively.

Phase 2 study

The futuximab/modotuximab Sym004-05 is an open-label, randomised, controlled, multicentre, Phase 2 trial that enrolled 254 patients with mCRC cancer refractory or intolerant to chemotherapy (5-FU, irinotecan and oxaliplatin), who had responded to and progressed on prior anti-EGFR mAb therapy (*i.e.* acquired resistance to anti-EGFR mAbs).

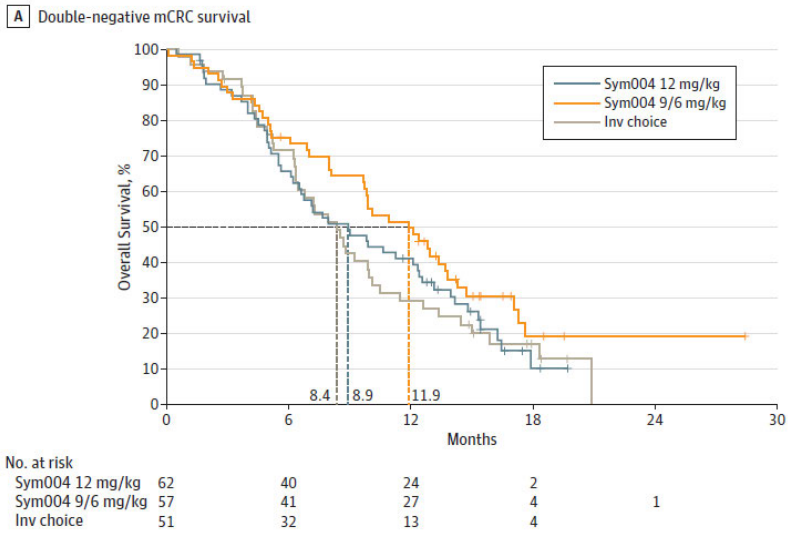
Patients were randomly assigned in a 1:1:1 ratio to either of two dose regimens of futuximab/modotuximab, 12 mg/kg weekly (Arm A; 83 patients, 83 treated), loading dose of 9 mg/kg on Day 1 followed by maintenance dose of 6 mg/kg weekly beginning on Day 8 (Arm B; 86 patients, 84 treated), or to a control group treated with the investigator`s choice (IC) therapy of capecitabine (61 patients), 5-FU (13 patients), or Best Supportive Care (BSC) (4 patients) (Arm C; 85 patients, 78 treated). The primary endpoint of the study was OS.

The primary endpoint was not met. Median OS in the intention-to-treat (ITT) population was 7.9 months (95% CI, 6.5-9.9), 10.3 months (95% CI, 9.0-12.9), and 9.6 months (95% CI, 8.3-12.2) for arms A, B and C, respectively (HR, 1.31; 95% CI, 0.92-1.87 for A *vs* C; and HR, 0.97; 95% CI, 0.68-1.4 for B *vs* C). Median PFS in the ITT population was 2.8 months (95% CI, 1.8-3.2), 2.7 months (95% CI, 2.6-3.3), and 2.6 months (95% CI, 1.4-3.1) for arms A, B, and C, respectively.

Response rates for evaluable patients in the ITT population were 11 PRs (14.1%), 8 PRs (9.6%), and 1 complete response (CR) and 1 PR (2.9%) in arms A, B and C, respectively. A per protocol analysis excluded patients from Russia as these patients were less refractory to standard EGFR mAb and considered more sensitive to therapy. For these reasons, this population was excluded from further analysis.

Baseline ctDNA mutation profiles of 70 genes (Guardant Health360 V2.9) were obtained from blood samples collected from 193 patients in the trial. An exploratory analysis of efficacy was carried out in a genomically defined subpopulation, which excluded patients with clonal RAS (KRAS/NRAS) and BRAF CCI (named double-negative [DN] mCRC; n = 170). This exploratory biomarker defined analysis showed an increase in median OS of 3.5 months in the DN mCRC population of patients treated with futuximab/modotuximab 9/6 (arm B; 11.9 months) compared with patients randomised to IC (Arm C; 8.4 months) (Figure (2.2.2) 1).

Figure (2.2.2) 1 - Kaplan-Meier curve of OS for the futuximab/modotuximab Sym004-05 patients with DN disease



The futuximab/modotuximab AE profile was consistent with other anti-EGFR mAbs, although the frequency and severity of both dermatologic AEs (94.0% and 92.9% for arms A and B, respectively, compared with 10.3% in the IC arm) and hypomagnesemia (68.7% and 56.0%f or arms A and B, respectively, compared with 7.7% in the IC arm) were higher than those found with other approved anti-EGFR mAb therapies. In contrast, the frequency of gastrointestinal AEs appeared to be lower than has been reported for other anti-EGFR mAbs (51.8% and 48.8% for arms A and B, respectively, compared with 47.4% in IC arm). Treatment with both regimens of futuximab/modotuximab was less well tolerated than the heterogeneous standard treatments administered to patients on the IC arm. Treatment Emerging AEs (TEAEs), related TEAEs, serious TEAEs, > Grade 3 related TEAEs, and treatment-related Serious AEs (SAEs) were more frequent in patients receiving either dose of futuximab/modotuximab compared to patients in the IC treatment group. The futuximab/modotuximab regimen of 12 mg/kg (12) weekly was less well tolerated than the 9 mg/kg loading dose followed by a 6 mg kg (9/6) weekly dosing schedule.

Compared to patients on the 9/6 arm (Arm B), patients receiving 12 mg/kg of futuximab/modotuximab had more serious TEAEs (32.5% *vs* 27.4%), TEAEs leading to dose reduction (34.9% *vs* 20.2%), TEAEs leading to treatment discontinuation (14.5% *vs* 6%), and > Grade 3 related TEAEs (69.9% *vs* 48.8%).

2.2.3. Clinical pharmacokinetic properties

The noncompartmental analysis and the population PK model found that the PK of futuximab/modotuximab was non-linear which is typical for mAb where target-mediated drug disposition (TMDD) impacts the elimination. Indeed, the observed half-life increased with the dose which was less than 2 days for dose levels of 3 mg/kg and below, whereas for dose levels of 6 mg/kg and above the half-life was 3-6 days. At dose levels of 6 mg/kg and above, the dose-normalised AUC_{tau} was constant, suggesting that the TMDD was close to saturation. For weekly dosing of 6 mg/kg and higher, futuximab/modotuximab accumulated approximately 2-fold from the first to the 3rd/4th dose. But, a lower accumulation (<= 1.3-fold) for the 9/6 mg/kg regimen was observed, indicating that steady state was reached after the first doses, which is expected with a loading dose followed by a maintenance dose.

Drug-drug interaction

As PK-related drug-drug interaction (DDI) between trifluridine/tipiracil and futuximab/modotuximab are unlikely to occur, no dose adjustment is required when co-administered.

Trifluridine is metabolized by Thymidine Phosphorylase (TPase) and transported by the nucleoside transporters CNT1, ENT1 and ENT2; while Tipiracil is not metabolized (neither in human liver S9 nor cryopreserved hepatocytes) and is a substrate for OCT2 and MATE1 transporters. As a mixture of the two monoclonal antibodies futuximab and modotuximab, futuximab/modotuximab is not expected to interact with TPase, OCT2, MATE1 or nucleoside transporters. Therefore, futuximab/modotuximab is unlikely to have a significant effect on Trifluridine and Tipiracil metabolic clearance or transport.

The clearance of the monoclonal antibodies futuximab and modotuximab is mainly driven by TMDD as a consequence of their binding to the target EGFR and subsequent internalisation and degradation into small peptides and amino acids. Therefore, trifluridine/tipiracil is unlikely to have a significant impact on futuximab/modotuximab PK.

2.2.4. Rationale for selected dose

From the Phase 2b Sym004-05 study, the futuximab/modotuximab regimen of 12 mg/kg (12) weekly was less well tolerated than the 9/6 mg/kg regimen. Compared to patients on the 9/6 arm, patients receiving 12 mg/kg of futuximab/modotuximab had more serious Treatment Emerging AEs (TEAEs) (32.5% *vs* 27.4%), TEAEs leading to dose reduction (34.9% *vs* 20.2%), TEAEs leading to treatment discontinuation (14.5% *vs* 6.0%), and > Grade 3 related TEAEs (69.9% *vs* 48.8%). Efficacy results from Sym004-05 were consistent with results of the study Sym004-01 for these 2 dose regimens (12 mg/kg and 9/6 mg/kg). The proportion of patients achieving objective responses (OR) on the 12 mg/kg weekly regimen in both the Sym004-01 expansion part (29 patients, 6.9% ORR) and in Sym004-05 (83 patients, 14.1% ORR) was higher than in patients treated on the 9/6 regimen (20 patients, 0% ORR in Sym004-01 and 86 patients, 9.6% ORR in Sym004-05). In contrast OS was longer for the 9/6 mg/kg regimen than the 12 mg/kg regimen in primary analysis sets in both studies (9.6 *vs* 6.9 months in Sym004-01 and 10.3 *vs* 7.9 months in Sym004-05).

The results of both trials document that the 9/6 regimen was better tolerated and resulted in more robust evidence of anti-tumour efficacy than observed in patients treated with the higher weekly doses of 12 mg/kg.

The proposed futuximab/modotuximab dose regimen for the study CL3-95026-001 (9 mg/kg followed by 6 mg/kg weekly dosing) was selected as the optimal dose regimen based on a benefit-risk assessment of available clinical data. In addition, the PK evaluation indicates that the target is saturated within the one-week dosing interval with this dose regimen.

2.3. Trifluridine/tipiracil in third-line mCRC

2.3.1. Trifluridine/tipiracil as single-agent in third treatment of mCRC

Trifluridine/tipiracil is approved by EMA, FDA and the Pharmaceuticals and Medical Devices Agency for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents and, anti-EGFR agents [7,9,21]

The approved indication in European Union was supported by the results of the global Phase 3 study (RECOURSE). TPU-TAS-102-301 (RECOURSE) study was a multinational, double-blind, two-arm, parallel-group, randomised, Phase 3 study evaluating the efficacy and safety of trifluridine/tipiracil plus BSC *vs* placebo plus BSC in Western (EU, USA and Australia) and Japanese patients with refractory mCRC who had failed previous treatment with standard chemotherapies.[11] The study randomly assigned 800 patients, in a 2:1 ratio, to receive trifluridine/tipiracil or placebo with OS as primary endpoint. The median OS improved from 5.3 months with placebo to 7.1 months with trifluridine/tipiracil, and the HR for death in the trifluridine/tipiracil group *versus* the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; $P < 0.001$).

2.3.2. Trifluridine/tipiracil in combination with anti-EGFR mAbs for the treatment of mCRC

APOLLON was an investigator-sponsored, open-label, single-arm Phase 1/2 study that evaluated the efficacy and safety of panitumumab in combination with trifluridine/tipiracil in patients with KRAS/NRAS WT mCRC, EGFR-naïve and refractory to standard therapy (fluoropyrimidines, irinotecan, oxaliplatin or anti-angiogenesis therapy).[22] Fifty-six patients were treated with panitumumab 6 mg/kg on Days 1 and 15, every 4 weeks (Q4W) and trifluridine/tipiracil at 35 mg/m² twice daily (BID) on Days 1–5 and 8–12, Q4W. No dose-limiting toxicities (DLT) occurred in Phase 1 and the recommended dose was determined to be 6 mg/kg for panitumumab and 35 mg/m^2 for trifluridine/tipiracil. In Phase 2 part, the PFS rate at 6 months (n = 54) was 33.3% (90% CI: 22.8–45.3; p = 0.24), and median PFS and OS were 5.8 months (95% CI: 4.5–6.5) and 14.1 months (95% CI: 12.2–19.3), respectively. The response rate and disease control rate were 37.0% and 81.4%, respectively. The most common Grade 3 or higher AEs (n = 55) were neutropenia (10.9%), febrile neutropenia (9.1%), stomatitis (9.1%), and dermatitis acneiform (9.1%). There were no treatment-related deaths or unexpected safety signals.

The WJOG8916G trial evaluated the efficacy and safety of concomitant administration of cetuximab (anti-EGFR antibody) and trifluridine/tipiracil in patients with mCRC who had been previously treated with irinotecan, oxaliplatin, fluoropyrimidine, and anti-angiogenic therapy and were refractory to anti-EGFR antibody (re-challenge strategy) [23] The study did not

demonstrate any new safety signal with the combination and AEs observed were the AEs of each single agent. The study had only one dose level tested (full dose of trifluridine/tipiracil and full dose of cetuximab, as per the EMA summary of product characteristics[8,24,25]) in the safety cohort of 6 patients and according to the protocol no observation period was imposed between enrolment of each patient. According to the protocol in the safety part of the initial 6 patients, if a DLT was observed in > 3/6 patients, the initial doses would be reconsidered. Out of 6 patients, only 1 DLT was observed, so the trial continued as planned. Overall, 56 patients were included and treated at the planned dose. The most frequently reported AEs were anaemia, dermatitis acneiform, hypomagnesemia, neutropenia, dry skin, platelet count decreased, fatigue, and decreased appetite. The most frequent Grade 3 or higher AEs were neutropenia (55%), anaemia (30%) and hypomagnesemia (16%). No new safety signals were observed with the combination treatment, and the observed AEs were similar to those observed with each single agent.

2.4. Rationale for the Study

Acquired resistance to anti-EGFR antibodies in mCRC is caused by both genomic and non-genomic mechanisms. Emergence of clones with mutations in KRAS, NRAS or BRAF are common and confer resistance to anti-EGFR therapies as in the primary resistance setting [26] However, a significant portion of patient tumours will remain dependent on the EGFR pathway and second-generation EGFR targeting agents such as futuximab/modotuximab has been designed to address these resistance mechanisms. The Sym004-05 study has evaluated the potential of futuximab/modotuximab to overcome acquired resistance to approved anti-EGFR mAbs in mCRC and has demonstrated encouraging results in a subgroup of molecularly selected patients with KRAS/NRAS and BRAF WT mCRC. To further improve the anti-tumour activity in this patient population the strategy is to combine futuximab/modotuximab with trifluridine/tipiracil. The combination of anti-EGFR antibodies and trifluridine/tipiracil has been explored in several pre-clinical CRC models and demonstrated synergistic or additive activity.[27,28] Moreover, trifluridine/tipiracil can be safely combined with anti-EGFR therapies with encouraging efficacy, as demonstrated by the APOLLON and the WJOG8916G studies.[22,23]

Servier plans to develop futuximab/modotuximab (investigational medicinal product [IMP]) in combination with trifluridine/tipiracil to provide a new third-line or later treatment option for patients with KRAS/NRAS and BRAF WT mCRC previously treated with chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and with anti-EGFR mAb therapy for ≥ 16 weeks, or not considered candidates for available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies and anti-VEGF agents. Trifluridine/tipiracil is a standard of care option in that setting and is an approved agent in the EU, US, and Japan.[7,9,21]

2.5. Design of the trial

CL3-95026-001 is an international, randomised, open label, multi-centre, two-arm Phase 3 study to evaluate futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil monotherapy in participants ≥ 18 years of age with KRAS/NRAS and BRAF WT mCRC who were previously treated with chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and with anti-EGFR mAb therapy for ≥ 16 weeks. The study will comprise two parts- a Safety Lead-In part with approximately 25 participants and a Randomised part with approximately 500 participants.

The safety of trifluridine/tipiracil in combination with anti-EGFR antibody (panitumumab and cetuximab) was judged as acceptable in previous trials[22,23]; however, the safety of the combination of trifluridine/tipiracil and futuximab/modotuximab has not been evaluated. Study CL3-95026-001 will therefore begin with a safety and tolerability assessment prior to dosing in the Randomised part of the study. A similar approach with a Safety Lead-In part for safety evaluation was incorporated into the design of other Phase 3 studies recently in patients with mCRC.[29]

CL3-95026-001 is an open label study. Given the immediately identifiable differences in the toxicity profiles of trifluridine-tipiracil and futuximab/modotuximab, it is not possible to conduct a blinded study. The high incidence of dermatological AEs in the futuximab/modotuximab plus trifluridine-tipiracil arm compared with the lack of dermatological events in the trifluridine-tipiracil single-agent arm, will allow the differentiation of the two treatment arms even in the case a blinded design is used.

Another important issue is related to the differences in the route of administration in both study arms. The experimental arm includes an oral drug and an IV administered drug, while the control arm includes only an oral drug. Given the type of population included, *i.e.*, patients with metastatic colorectal cancer, we consider unethical to subject patients to additional risk of harm or even to uncomfortable conditions such as administration of a dummy IV drug, at this stage of life.

2.6. Expected overlapping toxicities

Considering the safety profile of futuximab/modotuximab (skin toxicities, hypomagnesemia, infusion-related reactions and gastro-intestinal disorders) and the one of trifluridine/tipiracil (bone marrow suppression especially neutropenia, gastro-intestinal disorders such as diarrhoea, nausea and vomiting), the potential risks of the combination could be an increased risk of skin infections and of gastro-intestinal disorders.

2.7. Clinical pharmacokinetic properties and selected dose rationale

Trifluridine is metabolized by Thymidine Phosphorylase (TPase) and transported by the nucleoside transporters CNT1, ENT1 and ENT2 while tipiracil is not metabolized (neither in human liver S9 nor in cryopreserved hepatocytes) and is a substrate for OCT2 and MATE1 transporters.[8] As described for other monoclonal antibodies, the clearance of futuximab and modotuximab is expected to be mainly driven by TMDD as a consequence of their binding to the target EGFR and subsequent internalisation and degradation into small peptides and amino acids

Based on their non-overlapping PK properties, PK-related DDI between trifluridine/tipiracil and futuximab/modotuximab (futuximab and modotuximab) are unlikely to occur. Therefore, no dose adjustment is required when co-administered.

Overall, the proposed futuximab/modotuximab dose regimen for the study CL3-95026-001 (9 mg/kg followed by 6 mg/kg weekly dosing) was selected as the optimal dose regimen based on a benefit-risk assessment of available clinical data. In addition, the PK evaluation indicates that the target is saturated within the one-week dosing interval with this dose regimen.

2.8. Known Risks of the Therapeutic Regimen

In the dose-expansion part of the Phase 1 Sym004-01 study, 20 patients with heavily pre-treated mCRC were treated with the 9/6 regimen of futuximab/modotuximab. All 20 patients experienced an AE of "skin and subcutaneous disorders" (58 AEs in 20 patients, 100.0%). The most frequently experienced AEs in this system organ class (SOC) were rash (18 patients, 90.0%) and skin fissures (10 patients, 50.0%). Additionally, 18 events of hypomagnesemia (11 patients, 55.0%), were reported.

In the randomised Phase 2 Sym004-05 study, a total of 84 pre-treated mCRC patients were included in the 9/6 arm. A total of 78 patients (93%) experienced an AE of "dermatological toxicity", while 47 patients (56%) were reported with any Grade of hypomagnesemia AE. Additional details are provided in the futuximab/modotuximab Investigator's Brochure.

Neither dermatological toxicity, nor hypomagnesemia are reported as common toxicities of single-agent trifluridine/tipiracil; the most frequently observed adverse drug reactions (≥ 30%) in patients receiving trifluridine/tipiracil are neutropenia (53% [34% ≥ Grade 3]), nausea (34% [1% ≥ Grade 3]), fatigue (32% [4% ≥ Grade 3]) and anaemia (32% [12% ≥ Grade 3]).[8]

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki Appendix 1 and the applicable regulatory requirements.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Primary objective

Please refer to Table (3.4) 1 and Table (3.4) 2.

3.2. Secondary objectives

Please refer to Table (3.4) 1 and Table (3.4) 2.

3.3. Exploratory objectives

Please refer to Table (3.4) 1 and Table (3.4) 2.

3.4. Endpoints

The study endpoints for the Safety Lead-In and Randomised parts are listed in Table (3.4) 1 and Table (3.4) 2 respectively.

Table (3.4) 1 - Endpoints for the Safety Lead-In Part

	Objectives	Endpoints
Primary	To assess safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil according to National Cancer Institute Comment Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0	- Incidence of dose-limiting toxicities (DLTs) - Incidence, severity and relationship of Treatment Emergent Adverse Events (TEAEs) and Serious Treatment Emergent Adverse Events (STEAEs) - AEs leading to dose interruption, modification, delays and permanent treatment stop - Changes from baseline in key laboratory safety assessments, and vital signs
Secondary	To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil per investigator assessment using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in terms of: - Objective Response Rate (ORR) - Best Overall Response (BOR) - Disease Control Rate (DCR) - Progression Free Survival (PFS)	- Objective Response (OR): achievement of complete response (CR) or partial response (PR) - BOR: the best response recorded from screening through disease progression/recurrence - Disease Control (DC): achievement of best response: • CR: disappearance of all target lesions • PR: ≥ 30% decrease in the sum of the longest diameter of target lesions, or • Stable Disease (SD) - PFS: the time from the first administration of first IMP date until the date of the investigator-assessed radiological disease progression or death, whichever occurs first
	To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil in terms of: - Overall Survival (OS) To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination of futuximab/modotuximab with trifluridine/tipiracil To evaluate the immunogenicity of futuximab/modotuximab (*i.e.* occurrence of anti-drug antibody [ADA])	- OS: the time from the first administration of first IMP date to death from any cause - Derived PK parameters (*e.g.* Cmax, AUC) for futuximab/modotuximab, trifluridine and tipiracil - ADA development for futuximab/modotuximab
Exploratory	To explore biomarkers as potential predictors of response and to track the emergence of resistance	- Circulating tumour DNA (ctDNA) monitoring

Table (3.4) 2 - Endpoints for the Randomised part

	Objectives	Endpoints
Primary	To compare OS of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in participants with tumours that are KRAS/NRAS and BRAF WT (Double negative [DN])	- OS (in DN) is defined as the time from date of randomisation into the study to death from any cause
Key secondary	To compare OS of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in participants with tumours that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN])	- OS (in TN) is defined as the time from date of randomisation into the study to death from any cause
Secondary	To compare anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy per investigator's assessment using RECIST v1.1 in terms of: - Progression Free Survival (PFS) - Objective Response Rate (ORR) - Disease Control Rate (DCR) - Duration of response (DoR) - Time to Response (TTR) To assess anti-tumour activity of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy in terms of: - Time to Next Treatment (TTNT) - Time to ECOG Performance Status ≥ 2 (TtPS2)	- PFS: the time from date of randomisation until the date of the investigator-assessed radiological disease progression or death, whichever occurs first - OR: achievement of confirmed, complete response (CR) or partial response (PR) - DC: achievement of best response: • CR: disappearance of all target lesions • PR: ≥ 30% decrease in the sum of the longest diameter of target lesions, or • Stable Disease (SD) - DoR: the time from the first documentation of confirmed tumour response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause - TTR: the time from randomisation until first radiologically confirmed tumour response (CR or PR) - TTNT: the time from the randomisation to initiation of the next systemic anti-cancer therapy - TtPS2: the time from the date of randomisation to the date when ECOG PS score of ≥ 2 is observed for the first time

Table (3.4) 2 (Cont'd) - Endpoints for the Randomised part

	Objectives	Endpoints
	To further evaluate and to compare the safety profile of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy	- Incidence, severity and relationship of TEAEs and STEAEs collected from administration of the first dose of IMPs - AEs leading to dose interruption, dose delays and permanent treatment stop - Changes from baseline in key laboratory safety assessments, and vital signs
	To compare Quality of life (QoL) of futuximab/modotuximab in combination with trifluridine/tipiracil *vs* trifluridine/tipiracil monotherapy	- QoL is assessed by 2 questionnaires European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L
	To characterise the pharmacokinetic (PK) profile of futuximab/modotuximab, trifluridine and tipiracil in the combination futuximab/modotuximab with trifluridine/tipiracil	- Derived PK parameters (*e.g.* Cmax, AUC) for futuximab/modotuximab, trifluridine and tipiracil
	To further evaluate the immunogenicity of futuximab/modotuximab (*i.e.* occurrence of antidrug antibody [ADA])	ADA development for futuximab/modotuximab
Exploratory	To explore the PK/pharmacodynamic (PD) relationship for safety and/or efficacy of the combination futuximab/modotuximab with trifluridine/tipiracil	- Relationship between exposure and PD (as safety and efficacy)
	To explore biomarkers as potential predictors of response and to track the emergence of resistance	- Circulating tumour DNA (CtDNA) monitoring

4. STUDY DESIGN

4.1. Investigational Plan

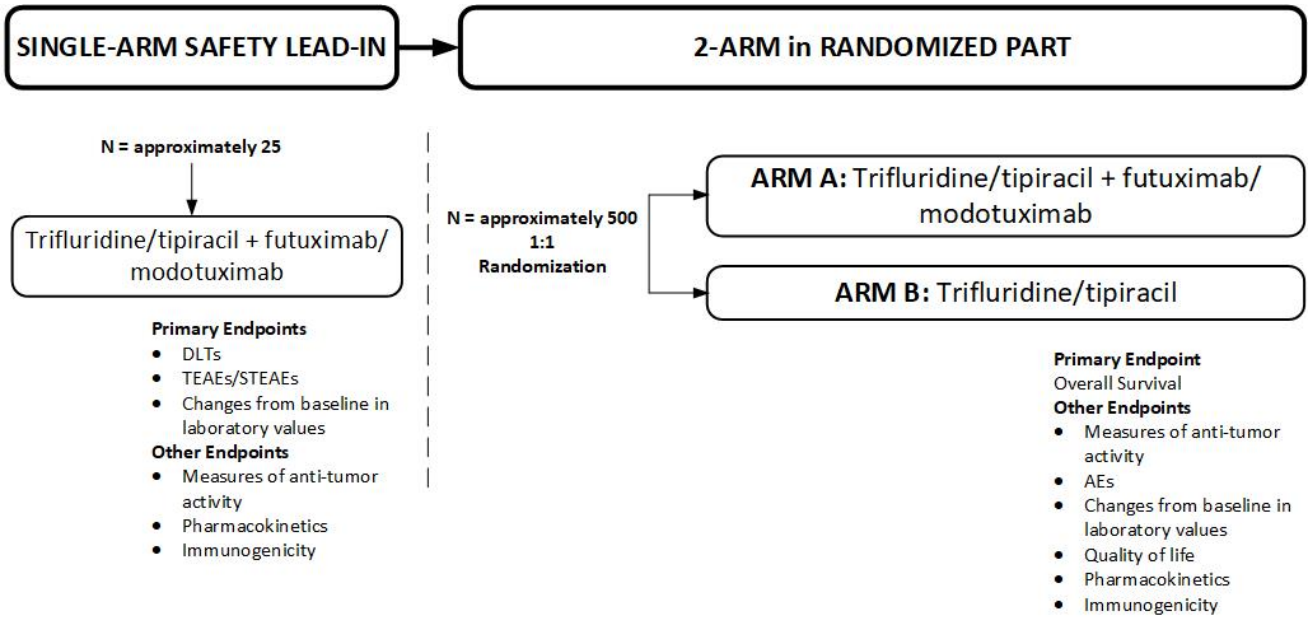
4.1.1. Study plan

This is a randomised, open label, multi-centre, two-arm Phase 3 study to evaluate futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil monotherapy in participants ≥ 18 years of age with KRAS/NRAS and BRAF WT mCRC who were previously treated with chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and with anti-EGFR mAb therapy for ≥ 16 weeks.

The study will comprise two parts a Safety Lead-In part in approximately 25 participants and a Randomised part in approximately 500 participants.

The study design is depicted in Figure (4.1.1) 1.

Figure (4.1.1) 1 - CL3-95026-001 Study Design



AE = adverse event; DLT = dose-limiting toxicity; ECD = extracellular domain; EGFR = epidermal growth factor receptor; mCRC = metastatic colorectal cancer; TEAE = treatment-emergent adverse event; STEAE = serious treatment emergent adverse events

Figure (4.1.1) 2 - Study plan for the Safety Lead-In Part

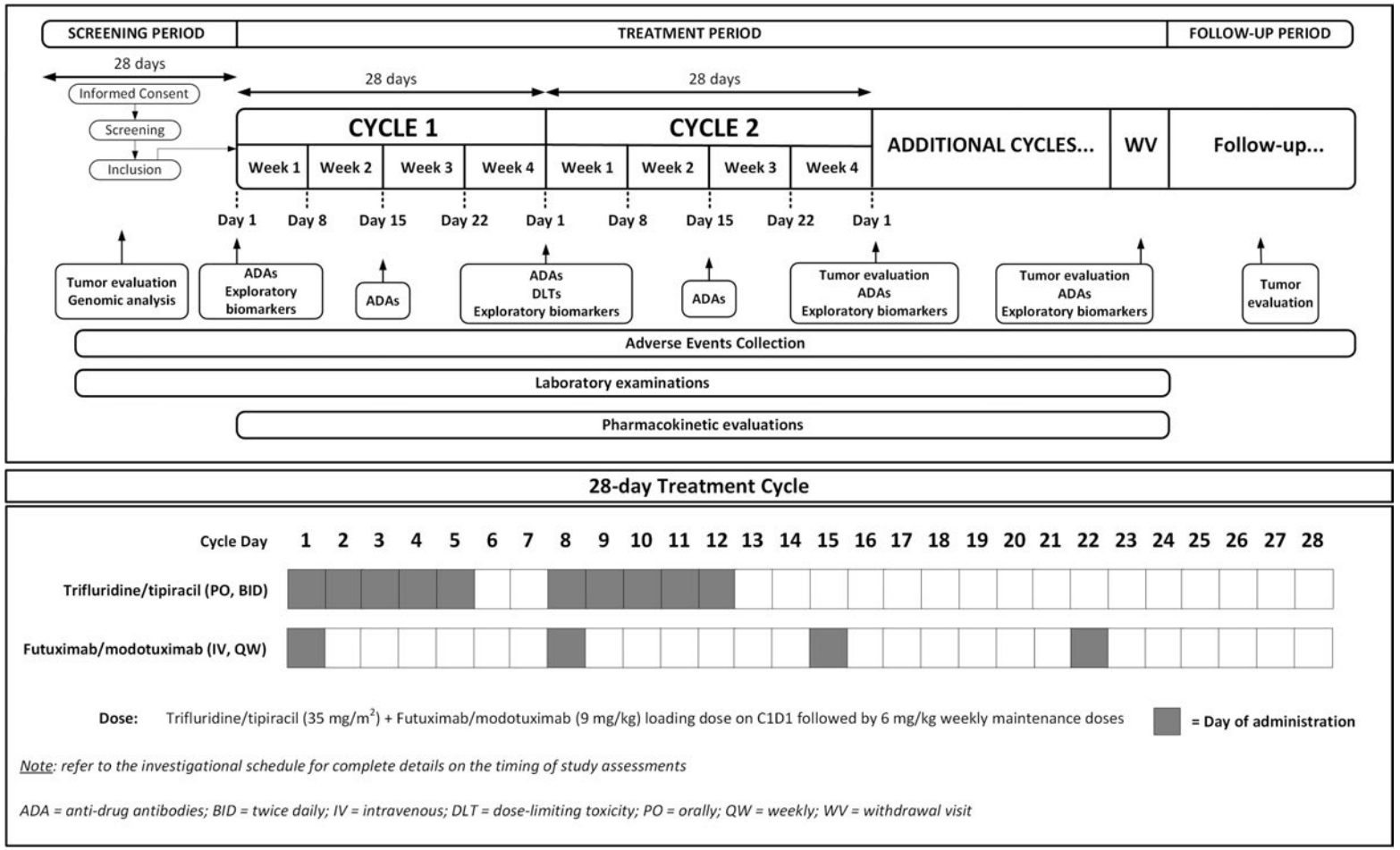
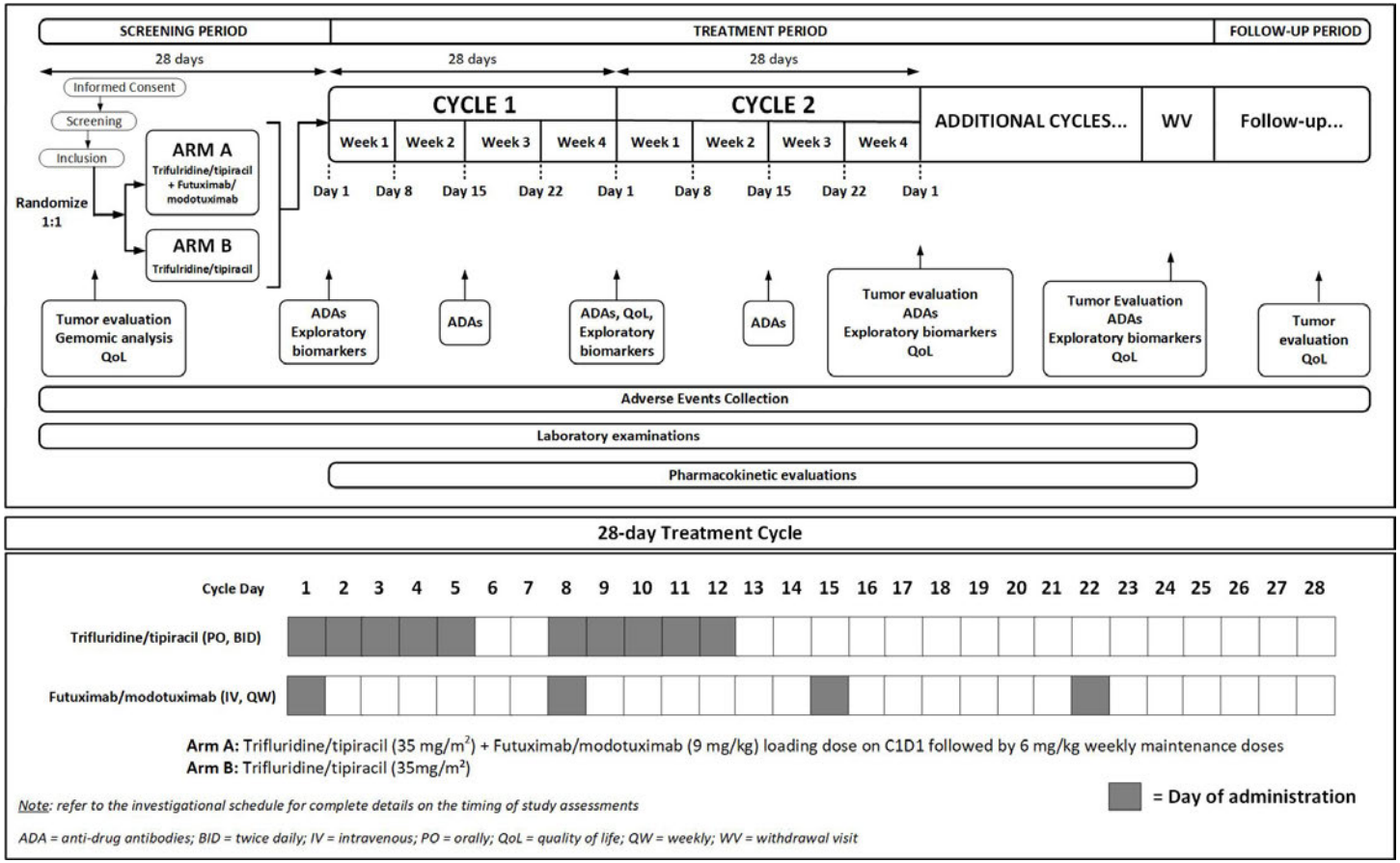


Figure (4.1.1) 3 - Study plan for the Randomised part



The study start is defined as the date of the first visit of the first participant.

The study will be divided into the following periods for each participant:

- Screening visit/Screening period (maximum 28 days):
  - Screening visit: after signature of the Informed Consent Form(s) (ICF) to check screening criteria and decide if participant can be screened for the study.
  - Screening period: if the participant is screened in the study, check the inclusion and exclusion criteria and decide if participant can be included in the study.
  - Randomisation: included participants will be randomly assigned to one of the two treatment groups:
    - Arm A: trifluridine/tipiracil + futuximab/modotuximab.
    - Arm B: trifluridine/tipiracil.
- Treatment period: participants will be treated until they meet a discontinuation criterion as described in Section 5.8.1. The participants should receive the first dose of first IMP (Day 1 of Cycle 1) within 3 days after inclusion (in the Safety Lead-in part) or after randomisation.
- Withdrawal visit (WV): should be conducted within approximately 4 weeks following the date of study treatment withdrawal and before the start of a new anticancer therapy.
- Follow-up period: after the WV the participant will be followed every 8 weeks (± 10 calendar days):
  - For survival status until the end of the study. This follow-up can be done remotely by using various telecommunication technologies including but not limited to phone, internet, and shared electronic medical records.
  - For tumour assessment (if the patient was withdrawn from the study for another reason than radiologic disease progression) (compared to the last assessment) until radiologic progression regardless of initiation of new anticancer therapy.

This study will deploy Televisits as part of the study schedule in the randomised part only. This means that some study visits could be conducted using a telehealth video remote visit platform. The system used is HIPAA, 21 CFR part 11 and GDPR compliant, and provides easy to use, on-demand Televisits to provide a remote environment for the investigator and his/her site team and study participants to remain closely connected throughout the life of the study. These visits can be utilised to address changes in patient activities, healthcare or health status in order to make timely decisions around ongoing clinical care and adverse event management. Options to convert non-critical study visits to a televisit will also help ease the study burden for participants and hence minimise drop-out. Televisits will be available to the participants and site on an ad-hoc basis in addition to the regular schedule should the need arise.

End of Trial is defined as the date of the last follow-up of the last participant (including a contact phone), or the date of last contact attempt if the last participant is declared lost to follow-up, or when the target number of OS events is reached, whichever occurs first.

Any participants still receiving IMPs at the end of the study will be allowed to continue at the discretion of the investigator and as long as none of the treatment discontinuation criteria are met.

If some participants are still receiving study treatments when the end of study is met, please see Section 6.5 for procedures to be followed.

Due to the exceptional circumstances in relation to the coronavirus disease pandemic, the sponsor, in accordance with competent regulatory authority's guidelines, could decide to

implement precautionary measures during the study to ensure participants safety, while maintaining compliance with GCP and study data integrity. These precautionary measures will remain in effect only for the duration of national public health emergency.

4.1.2. Investigation schedule

Table (4.1.2) 1 and Table (4.1.2) 2 describe the efficacy, safety and other assessments performed during the Safety Lead-In and Randomised parts of the study, respectively.

Table (4.1.2) 1 - CL3-95026-001 Investigation schedule for the Safety Lead-In part

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
Informed consent[1]	X																13.3
Screening criteria	X																5.1
Demography	X																9.1.2.7
Inclusion/exclusion criteria		X															5
Current medical condition		X															8.2.1
Medical/surgical history		X															5 / 8 / 6.3
Previous treatments		X															
Concomitant treatments		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	6.3
STUDY TREATMENT																	
Futuximab/modotuximab[2]			X	X	X	X	X	X	X	X	X	X	X	X			6.1.1
Trifluridine/tipiracil[3]			D1-5	D8-12			D1-5	D8-12			D1-5	D8-12					6.1.3
EFFICACY																	
Radiological and clinical tumour measurement[4]		X[4a]									X[4b]				X[4c]	X[4d]	7.2
SAFETY																	
Vital signs[5]		X	X pre-dose[6]; EoI (± 5 min)	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X pre-dose[7]	X		8.2.1
ECOG		X	X pre-dose[6]				X pre-dose[7]				X pre-dose[7]				X		8.2.2
Physical examination		X	X pre-dose[6]				X pre-dose[7]				X pre-dose[7]				X		8.2.3
Height		X															8.2.4
Body weight		X	X pre-dose[6]				X pre-dose[7]				X pre-dose[7]				X		
Pregnancy testing[8]		X[8a]	X[8b]				X[8b]				X[8b]				X[8b]	X[8b]	8.2.7.6
ECG[9]		X	X pre-dose[6]				X pre-dose[7]										8.2.6
Adverse events		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	8.3
Dermatologic examination		X		X pre-dose[7]	X pre-dose[7]	X pre-dose[7]		X pre-dose[7]	X pre-dose[7]	X pre-dose[7]		X pre-dose[7]	X pre-dose[7]	X pre-dose[7]			8.2.5
LABORATORY EXAMINATIONS																	
Blood hematology[10]		X	X pre-dose[6]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X		8.2.7.1
Blood biochemistry		X	X pre-dose[6]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X		8.2.7.2
Serum Mg, Ca, K				X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]		X pre-dose[7]			8.2.7.3
Blood coagulation		X	X pre-dose[6]				X pre-dose[7]				X pre-dose[7]				X		8.2.7.4
Urinary biochemistry[11]		X	X pre-dose[6]				X pre-dose[7]				X pre-dose[7]				X		8.2.7.5

Table (4.1.2) 1 (Cont'd) - CL3-95026-001 Investigation schedule for the Safety Lead-In part

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
PHARMACOKINETICS																	
Blood sample for futuximab/modotuximab[12]			X pre-dose*; EoI**; 1-2h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*				X		9.2
Blood sample for trifluridine/tipiracil[12]			X pre-dose*; EoI**; 1-2h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI			X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI							X		
Anti-futuximab/ modotuximab antibodies[12]			X pre-dose*		X pre-dose*		X pre-dose*		X pre-dose*		X pre-dose* ***				X		9.5
GENOMIC ANALYSIS																	
Blood sample for ctDNA[13]	X																9.1.1.3
BIOMARKERS																	
Blood exploratory biomarkers[14]			X pre-dose				X pre-dose				X pre-dose				X		9.4

1. Sign Informed Consent Form (ICF): written informed consent must be obtained during the screening visit, prior to the performance of any study procedure
2. Futuximab/modotuximab administration: futuximab/modotuximab will be administered at a dose 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly (± 2 days) beginning on C1D8 (maintenance doses), by IV infusion
3. Trifluridine/tipiracil administration: Trifluridine/tipiracil will be administered at a dose 35 mg/m²/dose, orally twice a day, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest (or in accordance with the local SmPC (Summary of Product Characteristics) of trifluridine/tipiracil)
4. Tumour measurements: tumour assessments should be performed according to RECIST version 1.1. The same method of assessment and the same technique must be used for all evaluations. To include diagnostic imaging by CT or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis, and other sites as indicated based on tumour location and clinical judgment in order to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the investigator, as medically indicated. At each time point, obtain imaging-based evaluation of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated).
   a. Baseline: tumour assessment will be done within 28 days prior to the first administration of first IMP. Images obtained prior to participant signed informed consent form (ICF) may be used if the date of the images is within 28 days of randomisation (first administration of first IMP for Safety Lead-In part) and if in line with methods and techniques that will be used during study
   b. Treatment period: tumour assessments will be done every 8 weeks from C1D1 (± 7 calendar days) until radiologic progression is documented
   c. Withdrawal visit: tumour assessments will be performed only if not performed within previous 8 weeks. Every effort should be made to perform the WV tumour assessments prior to the start of new anti-cancer therapy
   d. Follow-up period: unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent, obtain tumour assessments within 8 weeks after the last previous tumour assessment and then every 8 weeks (± 10 calendar days) until documentation of radiologic disease progression, regardless of initiation of a new anticancer therapy
5. Vital signs: Vital signs including body temperature, pulse rate, respiratory rate, blood pressure, oxygen saturation by pulse oximetry
6. Study procedures prior to the first IMP administration: to be done at C1D1 prior to the first IMP administration only if baseline procedures have been done more than 7 days prior to C1D1
7. Study procedures obtained within 48 hours prior to study treatments administration
8. Pregnancy testing
   a. Pregnancy testing at screening period: with serum βHCG test only (Within 7 days prior to first administration of first IMP)
   b. Pregnancy tests should be performed at the beginning of each cycle during the treatment period, upon treatment discontinuation, at the first follow-up visit, and additionally if clinically indicated, for all relevant patients. More frequent pregnancy tests should be performed if required by local law or as clinically indicated.
9. ECG assessment: To include standard 12-lead ECG with measurement of PR interval, QRS duration, time from the beginning of the QRS complex, representing ventricular depolarization, to the end of the T wave, resulting from ventricular repolarization (QT) interval, and QTc interval [ms], as well as heart rate [beats per minute (BPM)]).
   To be evaluated locally; ECGs should be performed using the calibrated instrument at each study centre and should be conducted after the participant has been supine (or semirecumbent) for > 10 minutes.
   Participants with a QTc interval >480 ms at baseline are excluded. Participants with a QTc interval > 480 ms during the treatment period should not be treated; dosing to be delayed.
   In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.
   An ECG should be performed in the event of ≥ Grade 3 hypomagnesemia
10. Blood haematology: In the event of haematologic toxicity, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated
11. Urinary biochemistry: Collect urine samples
12. PK/ADA assessment
    **i.e.* 5-60 minutes before infusion of futuximab/modotuximab
    **i.e. within 10 minutes before to the end of infusion of futuximab/modotuximab
    ***The frequency of futuximab/modotuximab immunogenicity assessments will be reduced to every 2 months after the first 6 months in the first year and every 4 months after the first year.
13. Genomic analysis from peripheral whole blood sample for defining patient eligibility and stratification will be based on assessment of ctDNA in plasma with an oncogene panel. After isolation of the plasma, the sample will be submitted for mutation analysis prior to first administration of first IMP. The genomic analysis includes a series of genes frequently mutated in cancer, but will be focused on the following genes:
    - BRAF [redacted]
    - KRAS & NRAS [redacted]
    - EGFR-ECD [redacted]
14. Exploratory biomarkers from peripheral whole blood sample collected pre-dose at C1D1, C2D1, C3D1, then every 2 cycles along with tumour assessment and at withdrawal, for ctDNA monitoring

ctDNA = circulating tumour DNA; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INCL = inclusion; EoI = end of infusion; IV = intravenous; SCR = screening.

Table (4.1.2) 2 - CL3-95026-001 Investigation schedule for the Randomised part

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
Informed consent[1]	X																13.3
Screening criteria	X																5.1
Demography	X																9.1.2.7
Inclusion/exclusion criteria		X															5
Current medical condition		X															8.2.1
Medical/surgical history		X															5 / 8 / 6.3
Previous treatments		X															6.3
Concomitant treatments		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Randomisation[2]			X														4.2
IWRS[3]		X	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X	X[10]	X		
STUDY TREATMENT																	
Futuximab/ modotuximab[4, 10]			X	X	X	X	X	X	X	X	X	X	X	X			6.1.1
Trifluridine/tipiracil[5]			D1-5	D8-12			D1-5	D8-12			D1-5	D8-12					6.1.3
EFFICACY																	
Radiological and clinical tumour measurement[6]		X[6a]									X[6b]				X[6c]	X[6d]	7.2
SAFETY																	
Vital signs[7]		X	X pre-dose; EoI (± 5 min)[8]	X pre-dose[9,10]	X pre-dose[9]	X pre-dose[9,10]	X pre-dose[9]	X pre-dose[9,10]	X pre-dose[9]	X pre-dose[9,10]	X pre-dose[9]	X pre-dose[9,10]	X pre-dose[9]	X pre-dose[9,10]	X		8.2.1
ECOG		X	X pre-dose[8]				X pre-dose[9]				X pre-dose[9]				X		8.2.2
Physical examination		X	X pre-dose[8]				X pre-dose[9]				X pre-dose[9]				X		8.2.3
Height		X															8.2.4
Body weight		X	X pre-dose[8]				X pre-dose[9]				X pre-dose[9]				X		
Pregnancy testing[11]		X[11a]	X[11b]				X[11b]				X[11b]				X[11b]	X[11b]	8.2.7.6
ECG[12]		X	X pre-dose[8]				X pre-dose[9]										8.2.6
Adverse events		X	→	→[10]	→	→[10]	→	→[10]	→	→[10]	→	→[10]	→	→[10]	→	→	8.3
Dermatologic examination[10]		X		X pre-dose[9]	X pre-dose[9]	X pre-dose[9]		X pre-dose[9]	X pre-dose[9]	X pre-dose[9]		X pre-dose[9]	X pre-dose[9]	X pre-dose[9]			8.2.5

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
QUALITY OF LIFE ASSESSMENT																	
Quality of life assessment[13]		X					X				X				X	X	9.6

Table (4.1.2) 2 (Cont'd) - CL3-95026-001 Investigation schedule for the Randomised part

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
LABORATORY EXAMINATIONS																	
Blood hematology[14]		X	X pre-dose[8]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X		8.2.7.1
Blood biochemistry		X	X pre-dose[8]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X		8.2.7.2
Serum Mg, Ca, K[10]				X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]		X pre-dose[9]			8.2.7.3
Blood coagulation		X	X pre-dose[8]				X pre-dose[9]				X pre-dose[9]				X		8.2.7.4
Urinary biochemistry[15]		X	X pre-dose[8]				X pre-dose[9]				X pre-dose[9]				X		8.2.7.5
PHARMACOKINETICS																	
Blood sample for futuximab/ modotuximab (Arm A)[16]			X pre-dose*; EoI**; 1-2h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*				X		9.2
Blood sample for trifluridine/tipiracil (Arm A)[16]			X pre-dose*; EoI**; 1-2h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI			X pre-dose*; EoI**; 0.5-1h after EoI	X pre-dose*; EoI**; 0.5-1h after EoI							X		
Blood sample for trifluridine and tipiracil (Arm B) [16]			X beginning, end of visit		X during visit		X during visit		X during visit						X		
Anti-futuximab/ modotuximab antibodies[10; 16]			X pre-dose*		X pre-dose*		X pre-dose*		X pre-dose*		X pre-dose* ***				X		9.5
GENOMIC ANALYSIS																	
Blood sample for ctDNA[17]	X																9.1.1.3

	SCR	INCL	Cycle 1				Cycle 2				Cycles 3 and after				WV within 4 weeks after treatment withdrawal and before new anticancer treatment	Follow-up period Every 8 weeks, until death or end of study	Protocol section
			D1	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days	D1 ± 2 days	D8 ± 2 days	D15 ± 2 days	D22 ± 2 days			
BIOMARKERS																	
Blood exploratory biomarkers[18]			X pre-dose				X pre-dose				X pre-dose				X		9.4

1. Sign Informed Consent Form (ICF): written informed consent must be obtained during the screening visit, prior to the performance of any study procedure
2. Randomisation must be done ≤ 3 days prior C1D1
3. IWRS: to obtain participant's number at screening, randomisation of participant, allocation and re-allocation of therapeutic units (other visits) and to register the end of treatment for a participant at withdrawal visit
4. Futuximab/modotuximab administration: futuximab/modotuximab will be administered at a dose 9 mg/kg on Cycle 1 Day 1 (C1D1) (loading dose) and then at a 6 mg/kg weekly (± 2 days) beginning on C1D8 (maintenance doses), by IV infusion
5. Trifluridine/tipiracil administration: Trifluridine/tipiracil will be administered at a dose 35 mg/m²/dose, orally twice a day, within 1 hour after completion of morning and evening meals, 5 days on/2 days off, over 2 weeks, followed by a 14-day rest (or in accordance with the local SmPC of trifluridine/tipiracil)
6. Tumour measurements: tumour assessments should be performed according to RECIST version 1.1. The same method of assessment and the same technique must be used for all evaluations. To include diagnostic imaging by CT or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis, and other sites as indicated based on tumour location and clinical judgment in order to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the investigator, as medically indicated. At each time point, obtain imaging-based evaluation of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated).
   a. Baseline: tumour assessment will be done within 28 days prior to the first administration of first IMP. Images obtained prior to participant signed informed consent form (ICF) may be used if the date of the images is within 28 days of randomisation (first administration of first IMP for Safety Lead-In part) and if in line with methods and techniques that will be used during study
   b. Treatment period: tumour assessments will be done every 8 weeks from C1D1 (± 7 calendar days) until radiologic progression is documented
   c. Withdrawal visit: tumour assessments will be performed only if not performed within previous 8 weeks. Every effort should be made to perform the WV tumour assessments prior to the start of new anti-cancer therapy.
   d. Follow-up period: unless patient had discontinued study treatments for radiologic disease progression or withdrawal of consent, obtain tumour assessments within 8 weeks after the last previous tumour assessment and then every 8 weeks (± 10 calendar days) until documentation of radiologic disease progression, regardless of initiation of a new anticancer therapy
7. Vital signs, including body temperature, pulse rate, respiratory rate, blood pressure, oxygen saturation by pulse oximetry
8. Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1
9. Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part on CXD1)
10. To be performed only for futuximab/modotuximab participants (Arm A)
11. Pregnancy testing
    a. Pregnancy testing at screening period: with serum βHCG test only (Within 7 days prior to first administration of first IMP)
    b. Pregnancy tests should be performed at the beginning of each cycle during the treatment period, upon treatment discontinuation, at the first follow-up visit, and additionally if clinically indicated, for all relevant patients. More frequent pregnancy tests should be performed if required by local law or as clinically indicated.
12. ECG assessment: To include standard 12-lead ECG with measurement of PR interval, QRS duration, time from the beginning of the QRS complex, representing ventricular depolarization, to the end of the T wave, resulting from ventricular repolarization (QT) interval, and QTc interval [ms], as well as heart rate [beats per minute (BPM)])
    To be evaluated locally; ECGs should be performed using the calibrated instrument at each study centre and should be conducted after the participant has been supine (or semi recumbent) for > 10 minutes.
    Participants with a QTc interval >480 ms at baseline are excluded. Participants with a QTc interval > 480 ms during the treatment period should not be treated; dosing to be delayed.
    In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. For futuximab/modotuximab participant, an ECG should be performed in the event of ≥ Grade 3 hypomagnesemia
13. QoL Assessment: QoL Assessment will be done at baseline, after the end of cycle 1 (C2D1), then from cycle 3 (C3D1) every 2 cycles during the treatment period, at the withdrawal visit and every 8 weeks (2 months) during the follow-up period, until death or until end of the study is reached (whichever occur first). Evaluation by participant reporting questionnaires including: EORTC QLQ-C30 (v3) and EQ-5D-5L
14. Blood haematology: In the event of haematologic toxicity, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated
15. Urinary biochemistry: Collect urine samples
16. PK/ADA assessment
    **i.e.* 5-60 minutes before infusion of futuximab/modotuximab
    ***i.e.* within 10 minutes before to the end of infusion of futuximab/modotuximab
    ***The frequency of futuximab/modotuximab immunogenicity assessments will be reduced to every 2 months after the first 6 months in the first year and every 4 months after the first year.
17. Genomic analysis from peripheral whole blood sample for defining patient eligibility and stratification will be based on assessment of ctDNA in plasma with an oncogene panel. After isolation of the plasma, the samples will be submitted for mutation analysis prior to randomisation. The genomic analysis includes a series of genes frequently mutated in cancer, but will be focused on the following genes:
    - BRAF CCI [redacted]
    - KRAS & NRAS CCI [redacted] CCI [redacted]
    - EGFR-ECD CCI [redacted] CCI [redacted]
18. Exploratory biomarkers from peripheral whole blood sample collected pre-dose at C1D1, C2D1, C3D1, then every 2 cycles along with tumour assessment and at withdrawal, for ctDNA monitoring

ctDNA = circulating tumour DNA; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; INCL = inclusion; EoI = end of infusion; IV = intravenous; SCR = screening.

For further practical details, methods of measurement are provided in Sections 7 and 8.

The approximate total volume of blood collected per participant will be 45 mL for the screening period, < 130 mL **per cycle** for the Cycle 1 and Cycle 2, < 80 mL **per cycle** for the further cycles and <55 mL for WV (Appendix 12). For men and post-menopausal women, the total volume of blood collected will be slightly lower (since pregnancy tests do not apply).

4.1.3. Safety Lead-In Part

The Safety Lead-In part is an open-label, single-arm and non-randomised study phase in approximately 25 participants. A minimum of 3 Japanese participants will be enrolled. During this part, the safety and tolerability of futuximab/modotuximab in combination with trifluridine/tipiracil will be evaluated prior to the start of the Randomised part. Efficacy parameters, futuximab/modotuximab and trifluridine/tipiracil PK and futuximab/modotuximab immunogenicity will also be evaluated as secondary endpoints.

The Study plan of Safety Lead-In part is depicted in Figure (4.1.1) 2. The schedule of study assessments is provided in Table (4.1.2) 1.

4.1.3.1. Dose administration schedule

The therapeutic regimen for the Safety Lead-In part Figure (4.1.1) 2 is as follows:

- Trifluridine/tipiracil (35 mg/m^2 BID) 5 days on/2 days off over 2 weeks followed by 14 days off, before futuximab/modotuximab administration.
- Futuximab/modotuximab (9 mg/kg) loading dose on C1D1 followed by (6 mg/kg) weekly maintenance doses.

4.1.3.2. DLT definition

For each participant, DLT assessment will be performed during Safety Lead in part. Assessments include all toxicities observed during the initial 28-day treatment period (Cycle 1).A DLT is defined as:

- A clinically significant adverse event (AE) graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 observed during the initial 28-day treatment period following the first IMP administration.
- Assessed as unrelated to underlying disease, disease progression, intercurrent illness, or concomitant medications.
- At least possibly related to the IMPs (Futuximab/modotuximab or Trifluridine/tipiracil or both) by the investigator and meeting any of the criteria included in Table (4.1.3.2) 1.

Table (4.1.3.2) 1 - Dose-limiting toxicity criteria

Toxicity Class	Dose-limiting Toxicity Criteria
Haematological abnormalities	Anaemia ≥ Grade 3
	Febrile neutropenia
	Uncomplicated Grade 4 neutropenia that lasts ≥ 1 week
	Uncomplicated Grade 4 thrombocytopenia (less than 25 10^9/L) that lasts ≥ 1 week or any Grade ≥ 3 thrombocytopenia (between 25 and 50 10^9/L) with bleeding episodes or thrombocytopenia requiring platelet transfusion
Gastrointestinal disorders	Grade 3 diarrhoea for > 2 days despite adequate treatment or with fever and/or dehydration
Skin disorders	Any Grade 3 skin toxicity lasting for more than 2 weeks, or Grade 4 skin toxicity regardless of duration[1]
Infusion-related reactions	Grade ≥ 3 infusion related reaction
Hepatic abnormalities	AST or ALT ≥ 3 x ULN along with a total bilirubin > 2.0 x ULN and confirmed Hy's law cases according to FDA guidance
	Isolated AST or ALT ≥ CTCAE Grade 3
Other adverse events	Any laboratory value Grade ≥ 3 with a duration ≥ 3 days, considered unrelated to underlying disease, disease progression, intercurrent illness or concomitant medications/therapies
	Any Grade 3 or Grade 4 non-haematologic adverse event (except for Grade 3 nausea and/or vomiting controlled by anti-emetic therapy that last less than 72h, or Grade 3 diarrhoea responsive to anti-diarrheal medication)

[1] *acne, cellulitis, dermatitis acneiform, dry skin, erysipelas, erythema, folliculitis, hypertrichosis, paronychia, pruritus, rash, rash maculopapular, rash vesicular, skin exfoliation, skin hyperpigmentation and xerosis*

Participants who meet any following criteria will not be evaluable for DLT and therefore will be replaced during the Safety Lead-In part of the study.

- Permanently discontinued treatment during DLTs assessment period for reasons other than DLT.
- Did not undergo a DLT assessment at the end of Cycle 1.
- Participants must complete at least the first cycle of treatment with a dose intensity [(administered dose in mg/planned dose in mg) x 100] higher than 75% with a minimum follow-up duration of 28 days. The dose intensity for single-agent trifluridine/tipiracil in Phase 3 studies is approximately 89%; therefore, for the combination a value of 75% is considered appropriate. Participants who require a dose interruption or reduction during the initial 28-day treatment period (Cycle 1) will remain evaluable for tolerability decisions if the reason for the reduction and/or interruption is a DLT. Participants will be replaced if they have received fewer than 75% dose intensity of trifluridine/tipiracil or futuximab/modotuximab for any reason other than an AE or abnormal laboratory value that is not related to their disease, disease progression, intercurrent illness or concomitant medications/therapies.

4.1.3.3. DLT management

Study treatments must be delayed for any participant who experienced a DLT. Conditions to resume treatment are described in Section 8.11.

All DLT will be reported to I.R.I.S. within 24 hours via DLT form in the e-CRF. After having filled in the DLT form, fill in the "Adverse Event" page of the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data of the DLT form are submitted, an e-mail will be immediately and automatically sent to the sponsor.

If the e-CRF is unavailable when the investigator is informed of the DLT, he/she should:

- Report the DLT on a paper "DLT form".
- Send the form immediately to I.R.I.S. at the following e-mail address CL3-95026-001@servier.com, with local project manager and monitor in copy

As soon as the e-CRF becomes available, the investigator must enter the data in the e-CRF.

4.1.3.4. Safety Lead-In and Tolerability Evaluation Procedure

The safety and tolerability data obtained from the safety lead-in period will be reviewed by a data monitoring committee (DMC) to assess whether:

- The drug regimen is tolerable.
- The maximum tolerated dose (MTD) has been exceeded.
- The Randomised part of the study may proceed.

The safety evaluation will be conducted as follows:

- After the 6th patient has signed the ICF and eligibility for inclusion has been confirmed, recruitment will be halted. After the 6th patient has been treated and followed for at least one 28-day cycle of treatment, a DMC meeting will be organized to assess safety and tolerability. If the 6th patient is not evaluable (see Section 4.1.3.2) then recruitment will re-start to allow enrolment of a new patient to ensure that a cohort of 6 evaluable patients will be available for the DMC first evaluation meeting. Available data beyond the first cycle collected from the first 5 participants will also be reviewed and used for decisions regarding tolerability of the regimen. If ≤ 2 participants out of the first 6 evaluable participants experience a DLT, and the DMC assesses the doses as tolerable based on the totality of safety data, the Safety Lead-In will be expanded by an additional cohort of 6 participants. If ≥ 3 of the 6 experience a DLT, or the DMC considers the doses to be non-tolerable based on the totality of safety data, enrolment will remain halted pending DMC recommendation on study continuation, modification or discontinuation.
- The DMC will again review all available data when a total of 12 evaluable participants have been treated and followed for at least one 28-day cycle of treatment. The DMC will again evaluate the totality of safety data and will provide a recommendation regarding tolerability of the doses. The enrolment will continue unless ≥ 4 participants experience a DLT. If DMC considers the doses to be intolerable, then enrolment will be halted, until DMC recommendation on study continuation, modification or discontinuation.
- The DMC will meet again at the completion of Safety Lead-In when approximately 25 participants will have been treated and followed for at least one 28-day cycle of treatment. When the 25th patient is enrolled in the study and completes the first 28-day cycle of treatment, patients previously enrolled in the study will have received more treatment cycles. Safety data from all treatment cycles will be collected for these patients. The overall safety profile of the evaluable participants, including data from all cycles of treatment beyond the first cycle of treatment, will be used for the safety evaluation. The DMC will review all accumulated safety data from all treatment cycles to judge whether the doses are acceptable for use in the randomised part of the study.

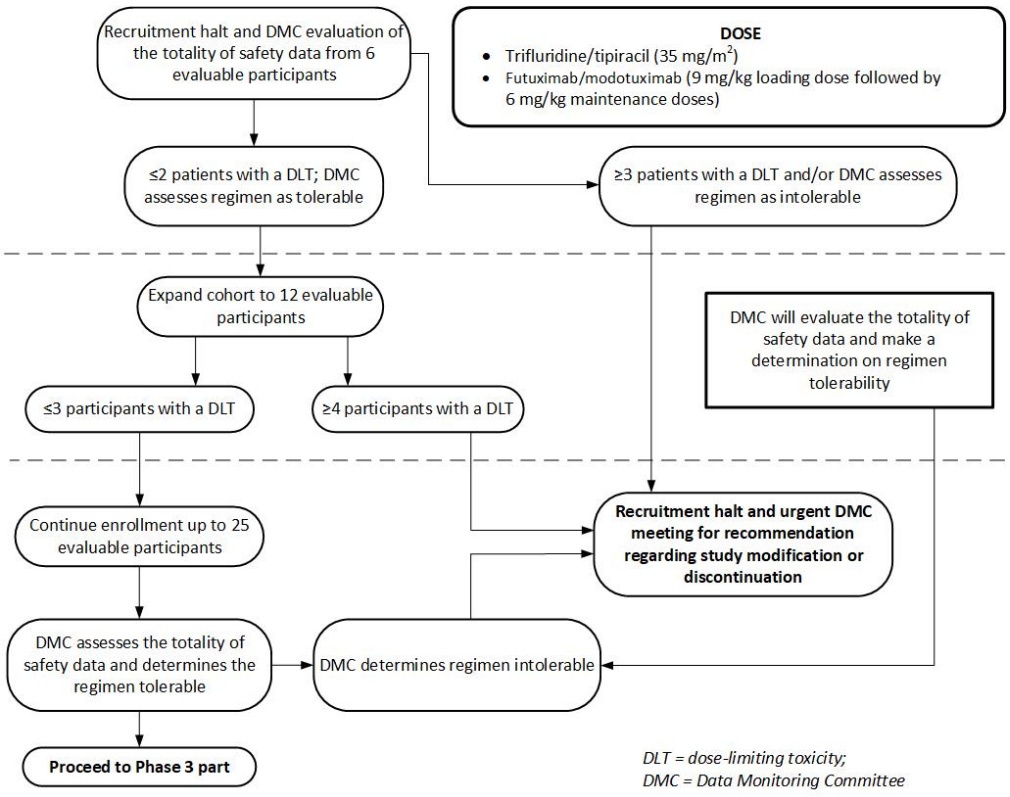
The Randomised part will start if < 8/25 evaluable participants experienced DLTs, the DMC recommends starting Phase 3 without any modification and no identification of any other new important safety risk during Safety Lead-In part. In addition, serum/plasma concentrations from the participants included in the Safety Lead-In part will be assessed and compared to the

expected PK profiles using the available population PK models for futuximab/modotuximab and trifluridine/tipiracil (Visual Predictive Check).

Throughout the Safety Lead-In part, DLT occurrence will be followed on a continuous basis and if the number of participants who experienced at least one DLT in each cohort exceeds the maximum number of DLTs that is considered safe (≥ 3/6 evaluable participants, ≥ 4/12 evaluable participants, ≥ 6/18 evaluable participants and ≥ 8/25 evaluable participants), at any time during the Safety Lead-In part the enrolment will be halted, an urgent DMC meeting will be organized and DMC will provide recommendations on study continuation, modification or discontinuation (Figure (4.13.4) 1).

DMC can decide at any moment of the study to discontinue the enrolment of new participants. At that time participants already treated in the study may continue the treatment if they have not experienced any clinically significant toxicity and are benefiting from the treatment according to the investigator's discretion.

Figure (4.1.3.4) 1 - Safety and tolerability evaluation procedure for dose evaluation in the Safety Lead-In part



4.1.3.5. Communication plan between the sponsor and centres

The following communication plan between the sponsor and centres is in place in order to manage recruitment from multiple centres. A registration form will be completed by the investigator for each new patient included in the Safety Lead-In part. The sponsor will immediately (within 24/48 hours on working days) send back to the investigator the form completed. More details will be provided in the Registration and Prescription guide. The sponsor will also ensure a continuous communication with the centres related to the study progress, including the enrolment status, and safety observations

4.1.4. Randomised Part

The Randomised part has an open-label, multi-centre, parallel-group, 2-arm, randomised design. Approximately 500 participants previously treated with chemotherapy (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents) and who have received previous treatment with anti-EGFR mAb therapy for ≥ 16 weeks, KRAS/NRAS and BRAF WT mCRC will be randomised in a 1:1 ratio to either futuximab/modotuximab in combination with trifluridine/tipiracil (Arm A) or trifluridine/tipiracil (Arm B), and stratified according to performance status (PS) (0 *versus* 1), previous regimens of treatment (2 *versus* ≥ 3) and by the presence or absence of EGFR ECD mutations. The Study plan of Randomised part is depicted in Figure (4.1.1) 3. The schedule of study assessments is provided in Table (4.1.2) 2.

4.2. Measures to minimise bias

The following measures will be taken in order to minimise bias:

- Stratification by PS (0 *versus* 1), previous regimens of treatment (2 *versus* ≥ 3) and by the presence or absence of EGFR ECD mutations.
- Analysis of samples for PK and ADAs will be performed in a specific central laboratory to minimise the variability of measurements.
- Randomisation, allocation, reallocation and dose adjustments will be centralised by Interactive Web Response System (IWRS) in the Randomised part.
- Screening for participants with mCRC with KRAS/NRAS and BRAF WT will be performed based on a central evaluation by using a ctDNA-based analytically and clinically validated diagnostic test.
- Treatment arms blinding process set-up for OS and PFS related data to preserve the trial from dissemination of aggregated efficacy results in order to minimise the potential operational bias.
- QoL questionnaires (EORTC QLQ-C30 and EQ-5D-5L) will be completed by the patient (only for the Randomised part), independently of the study personnel, at the beginning of visit and prior to any study procedure. These questionnaires will be completed in the local language using an electronic device (electronic participant-reported outcome [e-PRO]). In case the patient is not able to use the e-PRO, a caregiver (not a medical/investigator staff) will be allowed to read the questions to the patient and to collect the answer without any interpretation of the questions and the answers. The objective is to enhance the validity of QoL data by reducing missing data and improving the completion rate. Completion of paper versions of the QoL questionnaires is not allowed by the protocol.

4.3. Study products and blinding systems

This is an open-label study. No blinding to study medication is required.

4.3.1. Products administered

Futuximab/modotuximab and trifluridine/tipiracil are the IMPs. Both will be manufactured by Les LABORATOIRES Servier Industrie (Gidy France). Futuximab/modotuximab is not licenced in any country. Trifluridine/tipiracil is licenced for use in the EU, USA, and Japan.

The labelling of packages complies with the regulatory requirements of each country involved in the study.

Table (4.3.1) 1 provides a description of the IMPs. Additional details on the characteristics of futuximab/modotuximab are provided in the futuximab/modotuximab Investigator Brochure. Additional details on the characteristics of trifluridine/tipiracil are provided in the SmPC.[8]

Table (4.3.1) 1 - Description of the investigational medicinal products

Futuximab/ modotuximab	Pharmaceutical form	Solution for infusion
	Unit dosage	20 mL vial
	Appearance, colour	Clear to opalescent, colourless to slightly yellow solution
	Composition	25 mg/mL active ingredient formulated with histidine as a buffer component, trehalose for tonicity adjustment, polysorbate 20 as stabilizer, and Water for Injection as a solvent, contained within a 20 mL USP Type 1 glass vial with a FluroTec® coated halobutyl/ butyl rubber stopper, secured with a cap and flip-off seal.
Trifluridine/ tipiracil 15 mg	Pharmaceutical form	Film-coated tablet
	Unit dosage	15 mg
	Appearance, colour	White round tablet printed with “15” on one side and “102” on the other side
	Composition	15 mg trifluridine and 7.065 mg tipiracil hydrochloride, lactose monohydrate
Trifluridine/ tipiracil 20 mg	Pharmaceutical form	Film coated table
	Unit dosage	20 mg
	Appearance colour	Pale-red round tablet printed with “20” on one side and “102” on the other side
	Composition	20 mg trifluridine and 9.42 mg tipiracil hydrochloride, lactose monohydrate

USP = United States Pharmacopeia

Table (4.3.1) 2 provides a description of the IMP packaging.

Table (4.3.1) 2 - Investigational medicinal product packaging

Futuximab/ modotuximab	Number of units of the pharmaceutical form per primary packaging	1 vial of 500 mg
	Number of primary packaging per secondary packaging	1 vial per small box
Trifluridine/ tipiracil	Number of units of the pharmaceutical form per primary packaging	10 tablets by blister
	Number of primary packaging per secondary packaging	2 blisters

The labelling of packages complies with the regulatory requirements of the country involved in the study.

The non-investigational medicinal products (NIMPs) are the drugs linked to futuximab/modotuximab premedication for IRR (glucocorticoid therapy, antihistamine (H1 antagonist).

4.3.2. IMPs management

The IMPs will be sent by Les Laboratoires Servier Industrie (Gidy, France) either directly to the study sites or to sub-distribution centres or to local pharmacies depending on the geographic areas and the local regulatory requirements.

The investigator and/or the pharmacist of the study site should only use the IMPs provided for the participants involved in the study.

The investigator and/or pharmacist of the study site is responsible for:
- IMPs receipt and storage according to the local procedures and requirements.
- IMPs temperature monitoring.
- IMPs dispensing according to treatment arm assigned by the IWRS for Randomised part.
- Maintaining records of IMPs inventory at study site.
- IMPs collection for destruction.

Storage
The IMPs should be stored in a secure area with restricted access. For specific storage conditions, please refer to the SmPC for trifluridine/tipiracil and to the Pharmacy manual for futuximab/modotuximab.

The investigator and/or pharmacist of the study site will record temperature storage daily, using FONT-CIRT-FORM-311 "Therapeutic Unit temperature log sheet - centre" (recording Min-Max temperature every working day) or an equivalent document.

In case of temperature deviation, the investigator and/or pharmacist should immediately:
- Block the IWRS for the concerned IMPs and place them in quarantine (for Randomised part only).
- Alert the sponsor monitor and forward all required information.
- Put in place an adequate corrective/preventive action after the first temperature deviation occurs, in order to avoid recurrence.

IMPs management will be verified on a regular basis by the study monitor.

The investigator and/or the pharmacist of the study site and/or a designated person from their study team must complete in real time all the documents provided by the sponsor concerning IMPs management (therapeutic unit tracking form or an equivalent document…). Therapeutic unit tracking form, or an equivalent document, is the source document to fulfil.

All defects or deterioration of IMPs or of their packaging, including complaints set out by a participant (change of taste, appearance…) are to be reported to the sponsor monitor, or to the IWRS if applicable.

Destruction of the IMPs
Destruction of the IMPs is the responsibility of the sponsor and/or the investigator and/or the pharmacist of the study site.

Remaining treatments (used and unused IMPs except for used vials of futuximab/modotuximab) will subsequently be collected and stored according to the local procedures and requirements, by the person responsible for the IMPs management.

A certificated destruction will be performed according to standard modalities for that class of product and the attestation must be sent to the sponsor. The practical procedures for destruction of unused IMPs will be defined by the sponsor and adapted to the study site. IMPs collection and destruction form will be completed before the shipment of IMPs to destruction. Destruction of IMPs may be possible (after drug accountability and sponsor authorisation) when the product has been used, has expired or after at least the last visit of the last treated participant.

For futuximab/modotuximab, used vials will be collected and destroyed according to local procedure by the study site at the time of preparation/administration along with other wastes. Thus, accountability and recovery by monitor are not applicable for used vials of futuximab/modotuximab.

In case of batch recall
In the event of anticipated return of IMPs to the sponsor (*i.e.*, batch recall), the sponsor will prepare a notification letter for the investigator and/or pharmacist of the study site. On letter receipt, the investigator and/or the pharmacist will have to identify the participants in possession of the IMPs at the moment the incident becomes known, by using, among other tools, the therapeutic unit tracking form, or an equivalent document, and will contact them immediately.

4.3.2.1. Futuximab/modotuximab

Futuximab/modotuximab vials must be stored in a refrigerator at 2-8 °C protected from direct sunlight at all times and must not be frozen. For handling conditions and cleaning procedures instructions, please refer to the Pharmacy manual.

4.3.2.2. Trifluridine/tipiracil

Trifluridine/tipiracil tablets should not be sucked, chewed, crushed or kept in mouth. Direct contact of the powder from tablets containing trifluridine/tipiracil with the skin or mucous membranes should be avoided. If such contact occurs, immediately begin wash with soap and running water for minimum 15 minutes.

The participant must be instructed in the handling of trifluridine/tipiracil as follows:
- To store at room temperature.
- To keep in a safe place and out of reach of children.
- To take within 1 hour after completing a meal (morning and evening meals) with a glass of water (or in accordance with the local SmPC of trifluridine/tipiracil).
- To make every effort to take doses on schedule.
- To remove from the study medication kit, only the number of tablets needed at the time of dosing and not to remove doses in advance of the next scheduled dosing.
- To wash their hands after handling.
- To report any missed doses to the investigator. If doses are missed or held, the participant should not make up for missed doses.
- If the participant vomits after taking trifluridine/tipiracil, the participant should not take another dose.
- To bring all used and unused kits to the study site at each CxD1.

4.3.3. Management of blinding systems

Not applicable.

4.4. Discontinuation of the study or temporary halt

4.4.1. Premature discontinuation of the study or temporary halt

After having informed the coordinator(s), this study may be temporarily halted or prematurely discontinued at any time for any sufficient reasonable cause by the sponsor (or by the sponsor further to a request from the DMC) or by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or by the Competent Authorities or if the study meets the criteria for futility at the planned interim analyses.

Two copies of the written confirmation will be dated and signed by the coordinator(s). The IRB/IECs and Competent Authorities will be informed according to local regulations.

If the study is prematurely discontinued, the on-going participants should be seen as soon as possible, and the same assessments as described in Section 5.8 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participant's interests.

In case of study temporary halt, the study may resume once concerns about safety, protocol compliance and data quality are addressed and satisfy the sponsor and the DMC and following approval from the IRB/IEC and/or Competent Authorities, according to local regulations.

4.4.2. Premature discontinuation of the study in an investigator site (early site closure)

The sponsor reserves the right to close a study site at any time for any sufficient reasonable cause at the sole discretion of the sponsor.

The investigator may also initiate study site closure at any time, provided there is reasonable cause(s) and sufficient notice is given in advance of the intended termination.

Reason for early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Competent Authorities, the sponsor procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

The IRB/IEC(s) and competent Authorities will be informed according to local regulations.

4.4.3. Discontinuation of the study in the event of objective reached

An efficacy interim analysis is planned for the study when approximately 66% of the targeted total number of OS events have been reached. In case statistical significance is achieved at this planned interim analysis, the study will be stopped early for efficacy. Otherwise, the study will proceed to final analysis.

After having informed the International Coordinator, the sponsor or the DMC or the Institutional Review Board (IRB)/IEC or the Competent Authorities may terminate the study before its scheduled term. The IRB/IECs and competent authorities will be informed according to local regulations.

If the study is prematurely discontinued due to objective reached, the ongoing participants should be seen as soon as possible, and the assessments described in Section 5.8 should be performed.

Under some circumstances, the investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests.

4.5. Source data

Source data and source documents of the centre should be clearly identified in a specific, detailed and signed document before the beginning of the study

- Participant's medical file (*e.g.*, ECG report, clinical laboratory examinations reports, tumour assessment reports, paper diary (Safety lead in part) and e-Diary (Randomised part) and all other participant's examinations results), requisition forms and registration forms, oncogene panel report will be considered as source document.
- Therapeutic unit tracking form, or an equivalent document.
- e-PRO service provider's database (Randomised part) will be considered as source data.

5. SCREENING AND WITHDRAWAL OF PARTICIPANTS

5.1. Screening criteria

5.1.1. Demographic characteristics

1. Male or female participant ≥ 18 years old.

5.1.2. Medical and therapeutic criteria

2. Participants must have histologically or cytologically confirmed adenocarcinoma of mCRC (all other histological types are excluded), not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumour.
3. Based on ctDNA screening blood test analysis participants should be:
   - Without RAS (KRAS and NRAS) mutations in any of the following codons:
     - CCI
     - CCI
     - CCI
   - Without BRAF CCI .
4. Participants must have measurable or non-measurable lesion according to RECIST v1.1.

5b. Participants must have received at least 2 prior regimens of standard chemotherapy for mCRC and had demonstrated progressive disease or intolerance to their last regimen. The following characteristics apply:
- Prior standard chemotherapy must not have included trifluridine/tipiracil but must have included all of the following agents approved and available in each country:
  - Fluoropyrimidines, irinotecan and oxaliplatin.
  - At least one anti-VEGF pathway inhibitor (bevacizumab and/or aflibercept and/or ramucirumab and/or regorafenib).
  - At least one anti-EGFR mAb (cetuximab or panitumumab).
  - Patients with known MSI-H/dMMR tumours are eligible if they have received previous treatment with immune checkpoint inhibitors according to approved indication.
- Participants must have progressed during or within 6 months of the last administration of the last standard chemotherapy regimen. Participants who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will be eligible to enter the study.
- Participants who received adjuvant/neoadjuvant chemotherapy and had recurrence during or within 6 months of completion of the adjuvant/neoadjuvant chemotherapy are permitted to count the adjuvant/neoadjuvant therapy as one regimen of chemotherapy.

6a Participants should have received previous treatment with commercially available anti-EGFR mAbs for ≥ 16 weeks.

7. Ability to swallow oral medication.

8a. Estimated life expectancy ≥ 12 weeks. This criterion should be rechecked at inclusion visit (Safety Lead-in part) or randomisation visit.

9a. ECOG performance status 0 or 1 (or equivalent Karnofsky PS of 70% to 100%). This criterion should be rechecked at inclusion visit (Safety Lead-in part) or randomisation visit. (Appendix 2).

5.1.3. Informed consent

10. Written informed consent obtained prior any study-specific procedure as described in Section 13.3.

5.2. Non-screening criteria

5.2.1. General criteria

11. Pregnancy, possibility of becoming pregnant during the study and breast-feeding women.

12. Unlikely to cooperate in the study.

13a. Participation in another interventional study at the same time or within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit. Participation in study follow-up part without IMP administration, non-interventional registry or epidemiological study is allowed.

14a. Patients currently receiving or having received anticancer therapies within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit.

15. Participant already enrolled in the study (informed consent signed).

5.3. Inclusion criteria

5.3.1. Medical and therapeutic criteria

16a. Adequate haematological function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit, defined as:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
- Haemoglobin ≥ 90 g/L. In case of blood transfusion, the haemoglobin assessment must be performed 2 weeks or more after the transfusion.
- Platelet count ≥ 100 x 10^9/L.
- Adequate coagulation function for all participants. For participants receiving anti-coagulant therapy (except platelet anti-aggregates) the adequate therapeutic levels of INR should be confirmed.

17a. Adequate renal function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit defined as:

- Creatinine clearance ≥ 30 mL/min assessed using the Cockcroft & Gault formula (Appendix 3).

18a. Adequate hepatic function based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit, defined as:

- Total serum bilirubin < 1.5 x upper limit of normal (ULN) (unless Gilbert disease confirmed).
- Aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 x ULN (if liver function abnormalities are due to underlying liver metastasis, AST [SGOT] and ALT [SGPT] ≤ 5 x ULN).

19a. Serum potassium, serum phosphates, serum magnesium within normal limits with or without supplementation based on the last assessment performed within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit

20a. Women of childbearing potential (WOCBP) must use a highly effective method of birth control (Section 5.5) during study treatment beginning within 2 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit and continuing at least 6 months after the last dose of IMP. In case of oral contraception, women should have been stable on the same contraceptive drug (*i.e.* same active principle) for at least 3 months prior to the inclusion visit (Safety Lead-in part) or randomisation visit.

21a. Male participants with WOCBP partners must use a condom during the study and until at least 6 months after the last dose of IMP. In addition, highly effective contraception should be considered for their female partners. Contraceptive measures do not apply if the participant is sterile, vasectomised or sexually abstinent. Sperm donation will not be allowed during the study and for 6 months after the last dose of IMP.

5.4. Exclusion criteria

5.4.1. Medical and therapeutic criteria

22a. WOCBP tested positive in a serum pregnancy test within 7 days prior to the inclusion visit (Safety Lead-in part) or randomisation visit (Section 5.5).

23a. Participants who have not recovered from toxicity of previous anticancer therapy, including grade ≥ 2 non-haematologic toxicity, prior to the inclusion visit (Safety Lead-in part) or randomisation visit. Certain toxicities will not be considered in this category (*e.g.* Grade 2 alopecia, peripheral neuropathy and/or endocrine end-organ failure being adequately managed by hormone replacement therapy).

24a. Major surgery within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit or participants who have not recovered from side effects of the surgery.

25a. Participants with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit.

27. Known Hepatitis B Virus infection determined as HBsAg positive and / or known Hepatitis C Virus infection determined as detection of HCV RNA in serum or plasma by a sensitive quantitative molecular method.

28. Known carriers of HIV antibodies.

29a. Participants with active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 4 weeks prior to the inclusion visit (Safety Lead-in part) or randomisation visit, unless adequately treated and considered by the investigator to be stable.

30. Participants with active uncontrolled bleeding or a known bleeding diathesis.

31. In the investigator's opinion, uncontrolled diabetes mellitus even under treatment.

32b. Known clinically significant cardiovascular disease or condition, including:

- Any uncontrolled arrhythmia (per the investigator's discretion).
- Severe conduction disturbance (*e.g.* 3rd degree heart block) (per the investigator's discretion).
- Uncontrolled hypertension (per the investigator's discretion).
- Class III or IV cardiovascular disease according to the New York Heart Association (NYHA) Functional Classification (Appendix 4).
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, stenting or bypass grafting within 6 months prior to inclusion (Safety Lead-in part) or randomisation.
- QTc interval >480 ms

33a. Participants with a significant gastrointestinal abnormality, including:

- Diarrhoea of Grade > 1 at the time of inclusion (Safety Lead-in part) or randomisation.
- Requirement for IV alimentation.
- In the investigator's opinion, that might significantly interfere with proper absorption of the study treatments.

34. Participants with non-healing wounds on any part of the body

35a. Participants with skin rash of Grade > 1 from prior anti-EGFR at the time of inclusion (Safety Lead-in part) or randomisation, or any other skin toxicity precluding participation in the study according to investigator's discretion.

36a. Drainage for ascites, pleural effusion or pericardial fluid within 4 weeks prior to inclusion (Safety Lead-in part) or randomisation.

37. Known, untreated central nervous system (CNS) or leptomeningeal metastases, or spinal cord compression; participants with any of these not controlled by prior surgery or radiotherapy, or participants with symptoms suggesting CNS involvement for which treatment is required.

38. Other malignancies including those which were radically treated and for which the remission period at the time of screening is less than five years. Exemptions for this minimally required duration of remission period may be applied for carcinoma in situ

of the cervix, basal cell skin cancer and carcinoma in situ of gastric and oesophageal cancer that are deemed to be cured by adequate treatment.

39a. Treatment with systemic immunosuppressive therapy within 4 weeks prior to inclusion (Safety Lead-in part) or randomisation (except steroids given in prophylactic setting or at a chronic low dose [≤ 20 mg/day prednisone equivalent]).
40a. Prior radiotherapy if completed less than 4 weeks before the inclusion visit (Safety Lead-in part) or randomisation visit, except if provided as a short course for symptoms palliation only. Tumour lesions if previously irradiated cannot be chosen as target lesions for response evaluation.
41. Known or suspected hypersensitivity to:
    - Any of the excipients of formulated futuximab/modotuximab and trifluridine/tipiracil and of the NIMPs.
    - Cetuximab or Panitumumab (Grade 3 or 4 hypersensitivity reactions during prior therapy with either Cetuximab or Panitumumab).
42. In the investigator's opinion, any clinically significant medical condition (*e.g.* organ dysfunction) or laboratory abnormality likely to jeopardise the participant's safety or to interfere with the conduct of the study.
43. Hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
44. Active or history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.

For concomitant medication, refer to Section 6.3.

5.5. Definition of women of childbearing potential and contraception methods

Women of childbearing Potential
A WOCBP, *i.e.* fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Contraception methods
Definition of highly effective contraception methods for the study:
Highly effective methods of birth control refer to those which result in a low failure rate (*i.e.* less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception when associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices, intrauterine hormone-releasing system, true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), bilateral tubal occlusion, male sterilization (vasectomy).

Women using hormonal contraceptive must also use a barrier method *i.e.* male or female condom, or cap, diaphragm or sponge with spermicide.

Definition of acceptable contraception methods for the study:
Acceptable contraception methods for the study are those considered as highly effective methods.

As it is unknown whether trifluridine/tipiracil may reduce the effectiveness of hormonal contraceptives, hormonal contraceptives could be used but must not be relied upon for contraceptive efficacy. Women using hormonal contraceptive must also use a barrier method *i.e.* male or female condom, or cap, diaphragm or sponge with spermicide.

5.6. Retest management during screening period

A participant who has (a) laboratory result(s) that does not satisfy the entrance criteria may have the test(s) repeated providing that the investigator judges it relevant according to the participant previous results, or medical history and if s/he considers those laboratory abnormalities are likely to be transient. Results of the test(s) repeated should be obtained within the allowed screening period. In this case the participant will not be required to sign another informed consent, and the original participant ID number assigned by the investigator will be used.

In any case, the last result available for each parameter must be considered for the participant inclusion.

5.7. Additional information recorded at the screening/inclusion visit

Not applicable.

5.8. Participant withdrawal

5.8.1. Withdrawal criteria

A participant may be withdrawn from the study at any time for any reason (*e.g.* lost to follow-up, withdrawal of consent, AE). Premature discontinuation of IMP does not mean that the participant prematurely stops the participation in the study.

Information to be collected during the last visit of these participants is given in Section 5.8.2. These follow-up modalities are used to ensure the efficacy and safety evaluation of all participants who received IMP.

The reasons for **premature IMP discontinuation** are:

- **Adverse events,** incompatible with continuation of the IMP according to the judgment of the investigator, including no recovery in safety parameters.
- **Pregnancy** (for reporting, see Section 8.9.2.3).
- **Major protocol deviation** if it interferes with the study evaluations and/or if it jeopardises participant's safety, *e.g.* any medical event requiring administration of an unauthorised concomitant treatment (Section 6.3).
- **Radiologic progressive disease** documented by CT-scan or MRI.
- **Clinical progressive disease** manifested by symptomatic deterioration.
- **Non-medical reason** (*e.g.* consent withdrawal, participant's removal).
- **Other, physician decision** (for reasons that cannot be included in any of the criteria listed above for example: availability of a better therapeutic alternative for the participant).

5.8.2. Procedure

Upon discontinuation of study treatment, the investigator must:

- Notify the sponsor immediately.
- Register the end of treatment for the patient in the IWRS for Randomised part.

- Record this information in the e-CRF, specifying the reason for the study participant's withdrawal. If there are several reasons, the investigator must indicate the main reason. The investigator should document the discontinuation in the corresponding medical file.

A withdrawal visit should always be suggested to the participant and should take place within 4 weeks after the last IMP administration and prior to the start of a new anticancer therapy.

In the case of discontinuation due to an AE (event requiring immediate notification [ERIN] or not), the investigator must make every effort to collect the information relating to the outcome of the event. If necessary, the information will be collected afterwards (Section 8.9.2.1). This information is recorded in that part of the e-CRF form which concerns AEs. If the investigator cannot collect the information from a visit, he must collect it from the doctor ensuring the follow-up of the participant.

In case of discontinuation due to an ERIN, please refer to Section 8.7.

Follow-up period:
After the withdrawal visit, a follow-up will be done every 8 weeks (± 10 calendar days):

- For tumour assessment (unless patient had discontinued IMPs for radiologic disease progression or withdrawal of consent) until radiologic progression regardless of initiation of a new anticancer therapy.
- For survival status until death or the end of the study (whichever occur first). This follow-up can be done remotely by using various telecommunication technologies including but not limited to phone, internet and shared electronic medical records.

Participants are at any time free to discontinue their participation in the study. If participants wish to withdraw their consent to treatment period (*i.e.* both IMPs and study assessments), they will be asked if they are willing to continue with Follow-up period for survival status (which can be done by phone). If participants wish to withdraw their consent to further participation in the study entirely (treatment period and follow-up period), this should be clearly documented in the patient notes and in the clinical study database. During the post-withdrawal follow-up period, the patient can participate to another clinical trial.

A patient is considered discontinued from follow-up period only if one of the following occurs:

- Participant dies.
- At the end of study or if study is terminated by the sponsor or Competent authorities.

The dispositions to be taken after the IMP discontinuation are described in Section 6.5. Subsequent anticancer therapy should be collected in the e-CRF.

5.8.3. Lost to follow-up

When the investigator has no news of the participant, he/she must make every effort to contact him/her or a person around him/her (phone calls, letters including registered ones, etc.), to establish the reason for the discontinuation of IMP and to suggest the participant comes to a withdrawal visit. If all these attempts to contact the participant fail, the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the corresponding medical file.

6. TREATMENT OF PARTICIPANTS

6.1. IMPs and NIMPs administered

Safety Lead-In part: Futuximab/modotuximab administered in combination with trifluridine/tipiracil.

Randomised part: Arm A futuximab/modotuximab administered in combination with trifluridine/tipiracil *versus* Arm B trifluridine/tipiracil.

For treatment dose adaptations due to toxicities, please refer to Section 8.11.

Specific COVID-19 situation:
In case of highly suspected COVID-19 infection (based on typical symptoms or typical chest CT scan images) or confirmed COVID-19 infection (based on positive COVID-19 biological testing), the study treatment(s) should be immediately interrupted.

The study treatment(s) could be restarted if participant is asymptomatic and a period of at least 7 days after the diagnosis has been respected, and with a negative test (if the testing is required by the institutional site). Vaccination against COVID-19 is highly encouraged for all patients, preferably before study inclusion or whenever possible for patients included in the study. In this case, it is recommended to avoid vaccination 48 hours before or after futuximab/modotuximab administration if possible, for all cycles.

6.1.1. Administration of futuximab/modotuximab

6.1.1.1. Dose

- Loading dose: 9 mg/kg on C1D1.
- Maintenance doses: 6 mg/kg weekly (± 2 days), beginning on C1D8.

The dose level of futuximab/modotuximab to be administered will be multiplied by the participant's weight in kilograms to arrive at the total dose to be delivered. During the Randomised part the number of vials needed for each dose will be automatically calculated by the IWRS based on weight as measured at the beginning of each cycle. Participants will continue to be treated with futuximab/modotuximab at that same assigned dose throughout the duration of the treatment period unless dose reduction is required.

Dose adjustments should be made in the event of noted weight change (± 10%) as measured at the beginning of dosing cycle (CxD1). Weight fluctuations due to “third-space”/interstitial fluid accumulation (*e.g.*, oedema, ascites, pleural effusion) or medications that result in fluid retention (*e.g.*, glucocorticoids) do not require dose adjustment.

6.1.1.2. Route of Administration

Futuximab/modotuximab will be administered by the IV route, via a venous access catheter. The infusion set must contain an in-line filter (0.2-micron pore size). Infusion line should be flushed, per standard practice. The catheter may be placed into a peripheral vein (if accessible); administration via central venous catheter or port (if in place) is allowed.

In those instances when futuximab/modotuximab administration is associated with PK sampling, and administration is via peripheral IV catheter, infusions will be delivered into the arm contralateral to that from which blood samples for PK analysis are being obtained.

6.1.1.3. Schedule

- Once weekly on Day 1, Day 8, Day 15, and Day 22 (± 2 days) of each cycle (4 weeks [28 days] equals 1 dosing cycle).

A weekly dosing schedule is to be maintained, unless delay is required to allow for amelioration of toxicities (or in the event of scheduling difficulties associated with extended weekends, holidays, etc.). Futuximab/modotuximab should be administered after trifluridine/tipiracil intake.

6.1.1.4. Diluent and Delivery

Commercially available sterile 0.9% Sodium Chloride Injection, USP or local equivalent will be utilised as the diluent.

Once diluted for IV administration, futuximab/modotuximab should be administered within 8 hours, the infusion must be completed before the 8 hours maximum in-use time.

6.1.1.5. Volume of Infusion

- 9 mg/kg dose will be delivered in a total volume of 500 mL.
- 6 mg/kg dose (or lower in the event of a dose reduction) will be delivered in a total volume of 250 mL.

6.1.1.6. Duration of Infusion

- 9 mg/kg to be administered over 1 hour (+ 10 min). The maximum infusion rate of 500 mL/hour should not be exceeded throughout the administration.
- 6 mg/kg to be administered over 30 minutes (+ 10 min), maintaining the maximum infusion rate of 500 mL/hour.

Administration should be at a constant rate using a programmable volumetric infusion pump to ensure accuracy of delivery. Start and stop times of each infusion, and any interruptions in infusion will be recorded on the participant's e-CRF.

Note: In the event of an IRR, instructions for prolongation of the current and subsequent infusions are provided (Sections 8.11.2.1 and 8.12.4.1).

6.1.1.7. Observation requirements

The participants will be observed for a minimum of 2 hours following completion of the first administration of futuximab/modotuximab on C1D1 and a minimum of 1 hour following completion of subsequent infusions of futuximab/modotuximab (C1D8, onwards). Participants could be hospitalized for 24 hours after the administration of futuximab/modotuximab per the investigator's discretion and/or local practice per country, to enable a close in-patient safety monitoring. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary.

Futuximab/modotuximab infusions will take place under the close supervision of physician or other study personnel experienced in administration of IV agents and in an environment where full resuscitation facilities are immediately available.

6.1.2. Premedication before futuximab/modotuximab administration

6.1.2.1. Premedication for Infusion-Related Reactions

6.1.2.1.1. Infusion-Related Reactions

There is an inherent risk for infusion-related reactions (IRRs) with the administration of mAbs. An IRR is defined as an AE occurring during the futuximab/modotuximab infusion and up to 24 hours after the end of infusion (EoI), which is assessed by the investigator to be related to the infusion. Signs and symptoms of IRRs may include but are not limited to:

- Facial flushing and swelling.
- Rash including urticaria.
- Headache.
- Fever.
- Chills, rigors.
- Diaphoresis.
- Tachycardia.
- Hypotension.
- Nausea.
- Dry mouth.
- Chest/back/abdominal pain/discomfort.
- Chest and throat tightness.
- Shortness of breath.
- Cough, wheeze, stridor.
- Hypoxia.
- Bronchospasm.
- Laryngeal edema.
- Angioedema.
- Shock.

The risk of an IRR is highest for the first administration of a mAb and diminishes with subsequent infusions. If an IRR occurs, it should be classified according to the NCI-CTCAE v5.0.

Guidelines for grading and management of IRRs of all severities are provided (Appendix 9).

6.1.2.1.2. Premedication for IRRs (Beginning with the First Dose)

Premedication for prophylaxis of IRRs will be mandatory prior to each dose of futuximab/modotuximab. The following agents are required; recommended doses are provided:

- Glucocorticoid therapy: equivalent to 80 mg-100 mg IV methylprednisolone, approximately 0.5 to 2 hours prior to the start of futuximab/modotuximab infusion (glucocorticoid premedication may be omitted in participants with insulin-dependent diabetes).

- Antihistamine (H1 antagonist): equivalent to 25 mg-50 mg IV diphenhydramine, approximately 0.5 hours prior to the start of futuximab/modotuximab infusion (Appendix 9).

The following agents are optional, and may be added to the premedication regimen at any time during the study at the investigator's discretion; recommended doses are provided:

- Antihistamine (H2 antagonist): equivalent to 50 mg IV ranitidine or 20 mg IV famotidine or equivalent, approximately 0.5 hours prior to the start of futuximab/modotuximab infusion.
- Acetaminophen: 1000 mg IV (where available, or PO), or equivalent, approximately 0.5 hours prior to the start of futuximab/modotuximab infusion.

Note: Doses may be adjusted based on institutional practices. Administration of oral dexamethasone, 10 mg po, (or equivalent) 12 hours and 6 hours prior to administration of futuximab/modotuximab is permissible in participants experiencing IRRs or if an increased incidence or severity of IRRs is observed.

6.1.2.1.3. Premedication for IRRs (following an IRR)

For IRRs while on study, the following premedication instructions are provided:

- For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedication for subsequent infusions.
- For Grade 4 reactions, not applicable as no further treatment with futuximab/modotuximab is allowed (Appendix 9).

6.1.2.2. Premedication for skin toxicity

Management of skin toxicity will be done throughout the study according to the investigator's discretion. PABA free SPF ≥ 15 UVA and UVB sunscreen protection is recommended to be applied to exposed skin areas before going outdoors. Guidelines for grading and management of dermatologic AEs of all severities are provided (Appendix 10).

6.1.2.3. Premedication for other futuximab/modotuximab-related toxicities

If following the first dose, a participant experiences symptoms suggestive of other mild-to moderate futuximab/modotuximab-related reactions (*e.g.*, diarrhoea,), the participant may be premedicated with standard therapies to reduce the potential for such reactions in the future.

Based on ongoing review of participant safety data, the sponsor (or DMC) may implement additional mandatory premedication for all participants treated in this study should a pattern emerge of other mild-to-moderate futuximab/modotuximab-related reactions (*e.g.*, IRRs and/or any other trends in futuximab/modotuximab-related toxicities) that are amenable to prophylaxis with standard agents. Such action will occur following discussions between the investigator(s) and the sponsor.

Any medications administered for either prophylaxis or therapy of signs/symptoms related to futuximab/modotuximab will be documented on the appropriate page of the participant's e-CRF.

6.1.3. Administration of trifluridine/tipiracil

6.1.3.1. Dose/Route

- 35 mg/m²/dose, orally; maximum of 80 mg per dose based on the trifluridine component.

6.1.3.2. Schedule

- Trifluridine/tipiracil should be administered before futuximab/modotuximab administration.
- Trifluridine/tipiracil should only be given on Days 1 through 5 and Days 8 through 12 of each cycle. If doses are missed or held on those days, the participant should not make up for missed doses. Extension of study treatment into Days 6 to 7 or into the rest period (Days 13 through 28) is not permitted.
- Trifluridine/tipiracil should be taken with a glass of water within 1 hour after completion of morning and evening meals (or in accordance with the local SmPC of trifluridine/tipiracil).
- Any missed doses reported by the participant should be recorded in the e-CRF.
- Trifluridine/tipiracil dosage is calculated according to BSA (Body Surface Area). Table (6.1.3.2) 1 shows the number of tablets that are needed per calculated BSA for a dose of 35 mg/m². Table (6.1.3.2) 2 shows the number of tablets that are needed per calculated BSA for a reduced dose (30 mg/m², 25 mg/m² and 20 mg/m²).
  The BSA will be calculated by the site (in Safety Lead-In part) or IWRS (in Randomised part) using the following DuBois formula[30] all BSA calculations are rounded to 2 decimal places): BSA (m²) = ([Body Weight (kg)]$^{0.425}$ x [Height (cm)]$^{0.725}$) x 0.007184.
- If at the beginning of the new treatment cycle, a participant's body weight decreases by ≥ 10% from baseline, the site (in Safety Lead-In part) or IWRS (in Randomised part), will recalculate the participant's BSA and adjust trifluridine/tipiracil dosage.
- In case of change of dose level in Randomised part, the IWRS will provide the study site with the adjusted trifluridine/tipiracil dosage.
- No increase in trifluridine/tipiracil dose due to increase in BSA is permitted.

Table (6.1.3.2) 1 - Number of tablets of trifluridine/tipiracil per dose (standard dose) according to body surface area

Trifluridine/tipiracil Dose (2 x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose (2x daily)	
				15 mg/6.14 mg	20 mg/8.19 mg
35 mg/m^2	< 1.07	35	70	1	1
	1.07 - 1.22	40	80	0	2
	1.23 - 1.37	45	90	3	0
	1.38 - 1.52	50	100	2	1
	1.53 - 1.68	55	110	1	2
	1.69 - 1.83	60	120	0	3
	1.84 - 1.98	65	130	3	1
	1.99 - 2.14	70	140	2	2
	2.15 - 2.29	75	150	1	3
	≥ 2.30	80	160	0	4

BSA = body surface area (calculate to 2 decimal places)

Table (6.1.3.2) 2 - Number of tablets of trifluridine/tipiracil per dose (reduced dose) according to body surface area

Trifluridine/tipiracil Dose (2 x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose (2x daily)	
				15 mg/6.14 mg	20 mg/8.19 mg
Level 1 Dose reduction: From 35 mg/m^2 to 30 mg/m^2					
30 mg/m^2	< 1.09	30	60	2	0
	1.09 - 1.24	35	70	1	1
	1.25 - 1.39	40	80	0	2

Trifluridine/tipiracil Dose (2 x daily)	BSA (m^2)	Dosage in mg (2x daily)	Total daily dose (mg)	Tablets per dose (2x daily)	
				15 mg/6.14 mg	20 mg/8.19 mg
	1.40 - 1.54	45	90	3	0
	1.55 - 1.69	50	100	2	1
	1.70 - 1.94	55	110	1	2
	1.95 - 2.09	60	120	0	3
	2.10 - 2.28	65	130	3	1
	≥ 2.29	70	140	2	2
Level 2 Dose Reduction: From 30 mg/m^2 to 25 mg/m^2					
25 mg/m^2	< 1.10	25[a]	50[a]	2 (PM) [a]	1 (AM) [a]
	1.10 - 1.29	30	60	2	0
	1.30 - 1.49	35	70	1	1
	1.50 - 1.69	40	80	0	2
	1.70 - 1.89	45	90	3	0
	1.90 - 2.09	50	100	2	1
	2.10 - 2.29	55	110	1	2
	≥ 2.30	60	120	0	3
Level 3 Dose Reduction: From 25 mg/m^2 to 20 mg/m^2					
20 mg/m^2	< 1.14	20	40	0	1
	1.14 - 1.34	25[a]	50[a]	2 (PM)[a]	1 (AM)[a]
	1.35 - 1.59	30	60	2	0
	1.60 - 1.94	35	70	1	1
	1.95 - 2.09	40	80	0	2
	2.10 - 2.34	45	90	3	0
	≥ 2.35	50	100	2	1

[a] At a total daily dose of 50 mg, participants should take 1 x 20 mg/8.19 mg tablet in the morning (AM) and 2 x 15 mg/6.14 mg tablets in the evening (PM). BSA = body surface area (calculate to 2 decimal places)
Note: could be done in accordance with the local SmPC

6.1.4. Premedication for trifluridine/tipiracil

Trifluridine/tipiracil is associated with a moderate emetic potential; anti-emetic therapy is recommended to prevent nausea and vomiting. For more details see Section 8.12.1.

6.1.5. Retreatment criteria

These criteria are applicable after any dose delay and before the start of each cycle:

- ANC ≥ 1.5 x 10^9/L.
- Platelets ≥ 75 x 10^9/L.
- Ongoing AEs (IMP-related) should NOT meet study discontinuation criteria.
- Ongoing AEs (IMP-related) should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of Grade 2 clinical events that are being adequately controlled with best supportive care (*e.g.* nausea, vomiting, diarrhoea, fatigue, rash) and asymptomatic laboratory abnormalities that are considered clinically insignificant and uncomplicated or that are resolving spontaneously or with conventional medical interventions.
- Ongoing AEs which, in the opinion of the investigator, should make it advisable to delay the administration of treatments.
  Note: Safety criteria to be met prior to the start of each cycle could be in accordance with the local SmPC of trifluridine/tipiracil.

6.2. IMP and NIMPs dispensing

IMPs (futuximab/modotuximab and trifluridine/tipiracil) will be dispensed by the pharmacist/responsible of the healthcare establishment upon prescription of the investigator only.

The investigator may only use the IMPs provided for the participants involved in the study and treated under his/her responsibility. Further instructions for the preparation and dispensation of futuximab/modotuximab are described in the Pharmacy Manual.

All dosages of IMPs prescribed to the participant and all dose changes during the study must be recorded in the e-CRF. The exact dates and times at which futuximab/modotuximab was administered by the investigator and trifluridine/tipiracil was taken by the participant must be reported in the e-CRF.

The detachable portion of the label on the IMP box must be stuck by the responsible of the healthcare establishment on an IMP label collection form or on the prescription form where the IMPs are dispensed by a pharmacist.

NIMPs will be dispensed in accordance with Section 6.1.2.

For the Randomised part the treatment arm will be allocated via IWRS using a central randomisation (1:1) to trifluridine/tipiracil in combination with futuximab/modotuximab or trifluridine/tipiracil monotherapy with stratification by ECOG PS (0 *versus* 1), ECD EGFR mutation (presence *versus* absence) and previous regimens of treatment (2 *versus* ≥ 3). A connection to the IWRS should be performed at each concerned visit to know the allocated kit number(s) to be dispensed to the participant (please see details in IWRS manual).

6.3. Previous and concomitant treatments

Collect all the anticancer therapies given for the colorectal cancer since the diagnosis of the disease. Collect all other therapies and medications, prescription and over-the-counter, from the time of ICF signature through the WV. Use of concomitant treatments should be documented in the patient's source documents. At the Follow-Up Visit(s), collect any new anticancer therapy and the dates of treatment.

In general, the use of any concomitant medication deemed necessary for the care of the participant is permitted in this study, except as specifically prohibited. Concomitant administration of a drug could result in DDI that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or trifluridine/tipiracil and/or futuximab/modotuximab.

Before any intake of a new concomitant treatment from 7 days before the first IMP administration, during the study treatment period, and within 7 days following last IMP administration, the investigator should assess the potential DDIs with trifluridine/tipiracil and futuximab/modotuximab using the summary of product characteristics of the new concomitant treatment. The sponsor should be contacted in case of any doubt. If a medication appears on both 'prohibited' and 'to be used with caution' category, the medication is prohibited.

In all cases, the use of herbal products should be avoided. Comedications could be monitored if necessary.

6.3.1. Prohibited treatments

6.3.1.1. Before the study

Participants are not permitted to receive:

- Previous investigational or anticancer therapy for mCRC within 4 weeks prior to inclusion visit (Safety Lead-in part) or randomisation visit.
- Prior trifluridine/tipiracil.
- Treatment with systemic immunosuppressive therapy within 4 weeks prior to inclusion (Safety Lead-in part) or randomisation (except steroids given in prophylactic setting or at a chronic low dose [≤ 20 mg/day prednisone equivalent]).
- Radiotherapy within 4 weeks prior to inclusion visit (Safety Lead-in part) or randomisation visit (except if provided as a short course for symptoms palliation only).

6.3.1.2. During the study treatment period

Participants are not permitted to receive:

- Any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or endocrine therapy.
- Treatment with systemic immunosuppressive therapy (except steroids given in prophylactic setting or at a chronic low dose [≤ 20 mg/day prednisone equivalent] or short-term administration of steroids at daily doses higher than authorised by the protocol in situations of acute care management).

6.3.2. Authorised treatments

- Prophylaxis for protocol therapy-related AEs: for participants receiving futuximab/modotuximab, premedication for IRRs are mandatory throughout the study. Premedication for other participant-specific futuximab/modotuximab-related AEs may be implemented as indicated at the investigator's discretion. For participants receiving trifluridine/tipiracil, antiemetic therapy is recommended to prevent nausea and vomiting.
- Treatment of AEs or concomitant diseases: For participants receiving futuximab/modotuximab, instructions for management of hypomagnesemia are provided (Appendix 11). Clinical judgment should be used in the treatment of any other treatment-related AEs or concurrent diseases/conditions that require management during the study and follow-up period.
- Radiotherapy for pain control against non-target lesions, provided it does not substantially influence bone marrow function is allowed. As far as possible, the irradiation of target lesions must be avoided. Pre-clinical data showed that trifluridine/tipiracil is a radiosensitizer, but no clinical data are available for the concomitant treatment with trifluridine/tipiracil and radiotherapy, so caution is required and close monitoring of participants is needed.
- Surgical procedures: Participants requiring a minor surgical procedure (*e.g.*, port placement, stent placement, skin abscess drainage) may continue at the investigator's discretion following discussion with the sponsor. A brief interruption in therapy may be considered. Participants requiring a more extensive or major surgical procedure should have protocol therapy interrupted but may resume treatment once fully recovered and at a minimum 2 weeks after the procedure. Protocol retreatment criteria must be met. As far as possible, the surgery of target lesions must be avoided.
- Warnings related to trifluridine/tipiracil:

- Trifluridine and tipiracil are not substrates, inhibitors or inducers of cytochrome P450 (CYP450) enzymes. Therefore, CYP450-related DDIs with trifluridine/tipiracil are unlikely to occur.
- Trifluridine is activated by Thymidine Kinase (TK), metabolized by Thymidine Phosphorylase (TPase) and transported by the nucleoside transporters CNT1, ENT1 and ENT2, while Tipiracil is a substrate for OCT2 and MATE1 transporters. Therefore, the following drug categories should be used with caution when coadministered with trifluridine/tipiracil:
  - CNT1, ENT1 and ENT2 substrates.
  - OCT2 inhibitors.
  - MATE1 inhibitors.
  - TK substrates *e.g.*, zidovudine that may compete with the effector trifluridine. Monitor for possible decrease in efficacy and consider switching to alternative antiviral drugs that are not TK substrates (*e.g.*, lamivudine, didanosine and abacavir).

It is unknown whether trifluridine/tipiracil may reduce the effectiveness of hormonal contraceptives. Therefore, hormonal contraceptives can be used but must not be relied upon for contraceptive efficacy.

6.4. IMP compliance

The number of injectable vials (for futuximab/modotuximab) dispensed and the number of tablets (for trifluridine/tipiracil) returned by the participant are to be counted by the investigator or a designated person from his/her team and recorded in the e-CRF and therapeutic unit tracking form, or an equivalent document.

If the participant did not bring back all blisters of trifluridine/tipiracil dispensed at the previous visit, the investigator must estimate the number of IMP units taken by the participant since the previous visit, by questioning him/her. Each participant must record the exact time of intake of trifluridine/tipiracil in a diary provided by the sponsor. A paper diary will be used for the Safety Lead-In part and an electronic device (e-PRO) will be used for the Randomised part. The compliance will be assessed from the method described above.

6.5. Discontinuation of the IMP

After the discontinuation of the IMPs, participant's treatment is left to the physician's discretion. Futuximab/modotuximab is not licenced and not available on the market.

After completion of the study (see Section 4.1.1 for end of study definition), participants currently being treated will be offered the option to continue the treatments.

The sponsor will be responsible for the IMPs dispensing to the participants who are eligible to continue the treatments. The IMPs will be not assigned through IWRS, and IMPs will be manually assigned to participants by the investigator and/or pharmacist of the study site, based on the participant's BSA/weight at the time of study completion.

Specific rules may be followed in some countries according to local regulation.

7. ASSESSMENT OF EFFICACY

7.1. Efficacy measurements

The tumour assessments to be performed during the study are indicated in Table (4.1.2) 1 and Table (4.1.2) 2.

7.2. Methods and measurement times

7.2.1. Measurement times

Tumour assessments/imaging of the chest, abdomen, and pelvis at a minimum (other localisations if clinically indicated) will be obtained at each time point listed below for all participants:

- **Baseline**: tumour assessment will be done within 28 days prior to the first administration of first IMP. Images obtained prior to participant signed ICF may be used if the date of the images is within 28 days of randomisation (first administration of first IMP for Safety Lead-In part) and if in line with methods and techniques that will be used during study.
- **Treatment period**: tumour assessments will be done every 8 weeks from C1D1 (± 7 calendar days) until radiologic progression is documented.
- **Withdrawal visit**: tumour assessments will be done only if not performed within previous 8 weeks. Every effort should be made to perform the WV tumour assessments prior to the start of new anti-cancer therapy.
- **Follow-up period**: tumour assessments will be done for participants who were withdrawn for reasons other than radiologic disease progression or consent withdrawal, every 8 weeks (± 10 calendar days) during the follow up period until the participant experienced radiologic progression, regardless of the initiation of a new anticancer therapy.

Note: If the investigator determines that a participant develops clinical progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the participant should stop study treatments. Symptoms of clinical progression must be documented in the participant's source documents and in AE form (if judged by the investigator to be more severe than expected for the participant's condition). Tumour assessments will continue every 8 weeks (± 10 calendar days) until a radiologic progression is documented.

Note: Evaluation of secondary anti-tumour efficacy endpoints in the Randomised part (PFS, OR, DC, DoR, TTR) will be based on the investigator's assessment.
All imaging data acquired for efficacy purposes (*e.g.*, CT/magnetic resonance imaging (MRI) scans) will be transmitted to an imaging vendor for quality check and storage. Image transmission to the imaging vendor should be performed according to the imaging vendor manual. Blinded Independent Central Review (BICR) review of stored imaging data will be performed only if needed, retrospectively, and will not be provided to investigators for decisions regarding patient treatment. Should BICR be needed, the images will be read by readers who are blinded to treatment assignment and to other clinical data as specified in the BICR charter.

7.2.2. Method of imaging

- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Images must be acquired of the chest, abdomen and pelvis at a minimum (other localisations if clinically indicated) at each time point.
- Only CT or MRI must be used for tumour measurement (see specific cases below).
- Contrast enhanced CT is the preferred method for tumour assessments. If contrast agent is contraindicated in a participant, obtain at least a non-contrast chest CT and MRI of the abdomen and pelvis.

Specific cases:

- If new lesions are identified by ultrasound in the course of the study, a confirmation by CT or MRI is needed.
- Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (*e.g.* skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- In case of PET CT-scan, the CT portion of the PET–CT can be used for RECIST measurements.

7.2.3. Tumour definitions

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as describe in Sections 7.2.3.1, 7.2.3.2, and 7.2.3.3.

7.2.3.1. Measurable lesions

- Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT-scan with a CT-scan slice thickness no greater than 5 mm (when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness).
  - 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT-scan (CT-scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

7.2.3.2. Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- All non-measurable lesions can only be selected as non-target lesions.

7.2.3.3. Special considerations regarding lesion measurability

- Bone lesions:

- Bone scan, PET-scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

- Cystic lesions:
  - Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.
- Lesions with prior local treatment: tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

7.2.4. Documentation of "target" and "non-target" lesions

7.2.4.1. Target lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then, only the short axis is added into the sum.
- The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

Specific situations:

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.* 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. In this case a value must be recorded on the case report form. If it is the opinion of the radiologist that the lesion

has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.
- An option of 'Not Assessable' for a lesion will only apply to lesions that that cannot be read due to technical reasons, for example:
  - CT artefact.
  - Participant positioning where the lesions are obstructed or cannot be seen.
  - Lesion that may not be seen in their entirety due to CT slice thickness.

7.2.4.2. Non-target lesions

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.

For additional guidance refer to RECIST 1.1[31] and RECIST 1.1: Update and clarification.[32]

7.2.4.3. Response criteria

On-site assessments will include the assessment of:

- Target and non-target tumour responses.
- New lesions if any.
- Overall response.

7.2.4.4. Target and Non-target Response Assessments

Tumour assessments will be performed as per RECIST version 1.1[31] at baseline and then every 8 weeks from C1D1 (± 7 calendar days) until radiologic progression, death or end of study, whichever occurs first. The definition of responses for Target and Non-target lesions is presented in Table (7.2.4.4) 1 and Table (7.2.4.4) 2 respectively.

Table (7.2.4.4) 1 - Target lesions response definitions

TARGET LESIONS	
Lesions Response	**Definition**
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.

TARGET LESIONS	
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameter while on study.

Table (7.2.4.4) 2 - Non-target lesions response definitions

NON-TARGET LESIONS	
Lesions Response	**Definition**
Complete Response (CR)	The disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological morphologically (*i.e.*, < 10 mm in short axis in size).
Non-CR/Non-PD	A persistence of ≥ 1 non-target lesion(s) and/or maintenance of tumour marker level above the normal limits (not reaching the extent of 'unequivocal progression).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see definition below). (Note: the appearance of one or more new lesions is also considered progression).

When the participant has measurable disease and non-measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Tumour markers alone cannot be used to assess objective tumour response. If carcinoembryonic antigen level is initially above the upper normal limit, however, it must normalise for a participant to be considered in CR.

For additional guidance refer to RECIST 1.1[31] and RECIST 1.1: Update and clarification.[32]

7.2.4.5. New lesions

- The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: *i.e.* not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show partial or complete response.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

- For new lesions discovered by fluorodeoxyglucose (FDG)-PET scan please refers to RECIST 1.1.[31]

7.2.4.6. Overall Response Assessment

Assessments will be based on the definitions provided in Table (7.2.4.6) 1.

Table (7.2.4.6) 1 - Time point response for participants with target, or/and non-target disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	Not evaluable (NE)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.2.5. Best Overall Response Assessment

The best overall response (BOR) as per RECIST 1.1 is the best response recorded from the start of the study treatment until the end of treatment.

In this study, the minimum time from baseline to assess a response of “stable disease” is 6 weeks.

8. ASSESSMENT OF SAFETY

All AEs and other situations relevant to the safety of the participants must be followed up and fully and precisely documented to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.1. Specification of safety parameters

The safety measurements to be performed during the study are listed in Table (4.1.2) 1 and Table (4.1.2) 2.

The safety assessments will include:
- Concomitant medication/procedure surveys.
- ECOG PS assessment.
- Vital sign assessment.
- Physical examination.
- Height and weight.
- Dermatologic examination (additional for futuximab/modotuximab participants in Safety Lead-In part and Arm A in Randomised part).
- Haematology panel.
- Biochemistry panel.
- Serum magnesium (Mg), total calcium (Ca), potassium (K) (additional for futuximab/modotuximab participants in Safety Lead-In part and Arm A in Randomised part).

- Coagulation panel.
- Urinalysis.
- Pregnancy testing (if applicable).
- Electrocardiogram (ECG) 12-lead.

8.2. Methods and measurement times

The following safety measurements will be performed per the schedule outlined in Table (4.1.2) 1 and Table (4.1.2) 2.

8.2.1. Vital signs

Vital signs, including body temperature, pulse rate, respiratory rate, blood pressure and oxygen saturation by pulse oximetry to be obtained at the following time points:

- Inclusion

  Futuximab/modotuximab participants (Safety Lead-In part and Arm A in Randomised part)
- Cycle 1:
  - C1D1:
    - Pre-dose*.
    - EoI (± 5 min).
  - C1D8 (Pre-dose**).
  - C1D15 (Pre-dose**).
  - C1D22 (Pre-dose**).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
  - CxD8 (Pre-dose**).
  - CxD15 (Pre-dose**).
  - CxD22 (Pre-dose**).
- WV.
- As clinically indicated.

  Trifluridine/tipiracil participants (Arm B in Randomised part)
- Cycle 1:
  - C1D1 (Pre-dose*).
  - C1D15.
- All subsequent cycles:
  - CxD1 (Pre-dose**).
  - CxD15.
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part on CxD1).*

Obtain all the vital signs in a position that is consistent for all time points for each participant. Blood pressure should be measured with the participant in supine position.

When measuring blood pressure, particular care should be taken to:

- Take measurements after at least 5 minutes rest.

- Use a cuff appropriate to arm width and place the cuff at heart level.

8.2.2. ECOG Performance Status

ECOG performance status score (Appendix 2) to be performed at the following time points:

- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
- Withdrawal visit.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

8.2.3. Physical Examination

Complete physical examination, including BSA calculation, and dermatologic examination to be performed at the following time point:

- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

8.2.4. Height and weight

Participant's height to be obtained during the screening period.

Body weight to be collected at the following time point:

- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

For weight measurement, only scales with a valid calibration certificate must be used throughout the study.

8.2.5. Dermatologic examination (Only for futuximab/modotuximab-treated participants (Safety Lead-In part and Arm A of Randomised part)

Timepoints shown are in addition to dermatologic examination performed as part of scheduled physical examinations; intention is to achieve weekly assessment during the treatment period.

Dermatological examination to be performed at the following time point:

- Inclusion.
- Cycle 1:
  - C1D8, C1D15, C1D22 (Pre-dose**).
- All subsequent cycles:
  - CxD8, CxD15, CxD22 (Pre-dose**).
- As clinically indicated.

***Study procedures obtained within 48 hours prior to study treatments administration*

8.2.6. Electrocardiogram (ECG)

To include standard 12-lead ECG with measurement of PR interval, QRS duration, QT interval, RR interval, and QTc interval [ms] (using Fridericia's formula $QTcF = QT / \sqrt[3]{RR}$), as well as heart rate [beats per minute (BPM)]).

To be evaluated locally; ECGs should be performed using the calibrated instrument at each study centre and should be conducted after the participant has been supine (or semi-recumbent) for > 10 minutes. Participants with a QTc interval >480 ms at baseline are excluded. Participants with a QTc interval >480 ms during the treatment period should not be treated; dosing to be delayed.

In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. An ECG should be performed in the event of ≥ Grade 3 hypomagnesemia.

ECG to be performed at following time point:

- Inclusion
- Cycle 1:
  - C1D1 (Pre-dose*).
- Cycle 2:
  - C2D1 (Pre-dose**).
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*

***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

8.2.7. Laboratory Assessments

Laboratory tests will be collected and analysed by the study site's certified laboratory during screening period and at C1D1 only if there is more than 7 days since screening assessment. In all cases, the full validated set of normal ranges values will be collected, as well as any update in these values during the study and must be documented on the corresponding page of the e-CRF.

It is preferable for all biochemistry blood samplings to be taken in fasting conditions except if the participant's general health status does not permit it.

Laboratory tests are to be performed as required per protocol. All laboratory values that are out of the normal range are to be evaluated for their clinical significance before exposing the participant to the next dose of study medication.

Any laboratory abnormality that has a clinical impact on the participant, *e.g.*, results in delay of study medications dosing, study discontinuation, requires treatment due to abnormal values, or is considered by the investigator to be medically important, must be reported as an AE, unless it is considered a supporting analysis to a clinical diagnosis that is already reported as an AE.

All laboratory data will be analysed using NCI-CTCAE grade criteria (version 5.0).

Repeat the evaluation of any clinically significant laboratory test, as clinically indicated, until the value returns to the baseline level or clinically stabilises, or until another treatment is given.

8.2.7.1. Haematology

Sample for haematological assessments to be collected at the following time points:

- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
  - C1D15 (Pre-dose**).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
  - CxD15 (Pre-dose**).
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (only for CxD1: trifluridine/tipiracil intake in Arm B of Randomised part).*

Measure the following haematology parameters: haemoglobin, red blood cell count, white blood cell (WBC) count and differential count (neutrophils, lymphocytes), platelets.

Note: for neutrophils and lymphocytes, parameters must be available in absolute value (not in percentage of WBC).

8.2.7.2. Biochemistry

Samples for biochemistry assessments to be collected at the following time points:

- Inclusion
- Cycle 1
  - C1D1 (Pre-dose*)
  - C1D15 (Pre-dose**)
- All subsequent cycles
  - CxD1 (Pre-dose**)
  - CxD15 (Pre-dose**)
- WV

- As clinically indicated
  **Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
  ***Study procedures obtained within 48 hours prior to study treatments administration (only for CxD1: trifluridine/tipiracil intake in Arm B of Randomised part).*

Measure the following serum biochemistry parameters: albumin, ionogram (sodium, potassium, chloride, total calcium, magnesium, phosphate), blood urea nitrogen (BUN), serum creatinine, glucose, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, total bilirubin (in case of elevation in total bilirubin, fractionation (direct/indirect) should be performed), LDH.

Note: If BUN is not available, use the following conversion:

Table (8.2.7.2) 1 - Correspondence between urea and BUN values

BUN (mmol/L) = UREA (mmol/L)
BUN (mg/dL) = UREA (mg/dL) x 0.467
BUN (mg/dL) = UREA (mmol/L) / 0.3571

8.2.7.3. Serum Magnesium, Calcium, and Potassium (Only for futuximab/modotuximab-treated participants (Safety Lead-In part and Arm A of Randomised part)

Samples for serum magnesium, total calcium, and potassium assessment to be collected at the following time points:

- Cycle 1:
  - C1D8 (Pre-dose*).
  - C1D22 (Pre-dose*).
- All subsequent cycles:
  - CxD8 (Pre-dose*).
  - CxD22 (Pre-dose*).
- As clinically indicated**.
  **Study procedures obtained within 48 hours prior to study treatments administration*
  *** An ECG should be performed in the event of ≥ Grade 3 hypomagnesemia and if otherwise clinically indicated.*

Timepoints shown are in addition to testing performed as part of scheduled biochemistry panels; intention is to achieve weekly magnesium, total calcium, and potassium testing during the treatment period.

8.2.7.4. Coagulation

Samples for coagulation assessments to be collected at the following time points:

- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

To include the following coagulation parameters: partial thromboplastin time [PTT] and/or activated PTT [aPTT], prothrombin time.

8.2.7.5. Urinalysis

Samples to be collected at the following time points:
- Inclusion.
- Cycle 1:
  - C1D1 (Pre-dose*).
- All subsequent cycles:
  - CxD1 (Pre-dose**).
- WV.
- As clinically indicated.

**Study procedures prior to the first study treatments administration: to be done at C1D1 prior to study treatments administration only if baseline procedures have been done more than 7 days prior to C1D1.*
***Study procedures obtained within 48 hours prior to study treatments administration (trifluridine/tipiracil intake in Arm B of Randomised part).*

Multipanel chemical test strips are acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocytes, nitrite, bilirubin, urobilinogen, and blood. Microscopic examination of sediment, if clinically indicated, to include assessment of cells [WBC and red blood cells (RBC)] per high power field and casts.

If dipstick proteinuria ≥ 2+, a 24 hours-collection urine is required, and quantitative assessment of proteinuria will be performed.

Note: If only quantitative proteinuria is done by the study site, the correspondence between quantitative and qualitative values must be clearly described.

If no correspondence is available, please use the one in the table below:

Table (8.2.7.5) 1 - Correspondence between qualitative and quantitative proteinuria values

- Negative < 10 mg/dL	- 2+ [100 - 300] mg/dL
- Trace [10 - 30] mg/dL	- 3+ [300 - 1000] mg/dL
- 1+ [30 - 100] mg/dL	- 4+ > 1000 mg/dL

8.2.7.6. Pregnancy Testing

If the participant is female of childbearing potential, perform pregnancy testing with serum beta-human chorionic gonadotropin (β-HCG) or highly sensitive urine test (except during screening period), and record the date, time, and test results in the participant's source documents:
Pregnancy tests should be performed at screening period (with serum βHCG test only, within 7 days prior to first administration of first IMP), at the beginning of each cycle during the treatment period, upon treatment discontinuation, at the first follow-up visit, and additionally if clinically indicated, for all relevant participants.

***Note*: more frequent pregnancy tests should be performed if required by local law or as clinically indicated.**

8.3. Definition of Adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a subject participating in a clinical study, whether or not there is a causal relationship with the IMP and/or experimental procedures, occurring or detected from the date the participant signs the information and consent form, irrespective of the period of the study (periods without administration of the IMP (*e.g.* run-in period) are also concerned).

An AE can therefore be:

- Any unfavourable and unintended sign (including an abnormal finding from an additional examination such as laboratory tests, X-rays, ECG, …) which is deemed clinically relevant by the investigator.
- Any symptom or disease.
- Any worsening during the study of a symptom or a disease already present when the participant entered the study (increase in frequency and/or intensity).
- Fatal studied disease progression.

and detected during a study visit or at an additional examination or occurred since the previous study visit (including relevant event reported in safety evaluation scale or e-PRO).

Of note:

- Any **hospitalisation for administration of anti-tumoural treatment and/or associated protocol (during or after the study) or other care measures for cancer (*e.g.* overnight hospital stay to receive a blood or platelets transfusion), for social reasons, educational purpose** (*e.g.* learning of diabetes management by the participant) or routine check-up should not be considered as an AE event and **should not be reported** in the e-CRF.
- Any clinical finding or clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the studied disease should not be considered as an AE unless judged by the investigator to be more severe than expected for the participant's condition.
- A non-fatal "studied disease progression" itself should not be considered as an AE.
- The following procedures, whether planned before the study or not, whether leading to a hospitalisation or not, **should not be reported in the e-CRF and kept in the source data (or participant file):**
  - Therapeutic procedures related to a non-aggravated medical history (*e.g.* cataract extraction not due to an aggravation of the cataract during the study, haemodialysis sessions related to a renal insufficiency not aggravated during the study).
  - Prophylactic procedures (*e.g.* sterilisation, wisdom teeth removal).
  - Comfort procedures (*e.g.* cosmetic surgery).
  - Control procedures of a pre-existing condition without aggravation (*e.g.* colonoscopy to control the remission of colon cancer).

8.4. Definition of Serious adverse events

Any AE that at, any dose:

- Results in death.
- Is life-threatening(1).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Is medically significant(2).
- Results in persistent or significant disability/incapacity(3).
- Is a congenital anomaly/birth defect(4).

(1) Life-threatening in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(2) Any event that might not be immediately life-threatening or result in death or hospitalisation, but might jeopardise the participant or might require intervention to prevent one of these outcomes (for example: oedema or allergic bronchospasm that required intensive treatment at home, blood dyscrasia, convulsions that do not result in hospitalisation, or development of drug dependence or drug abuse). The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor.

(3) Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

(4) Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

8.5. Definition of Overdose

This refers to any intake of a quantity of IMP or a product other than the IMP taken as part of the protocol (NIMP) which is above the maximum dose recommended in the study protocol, independently of the occurrence of any AE.

The quantity should be considered per administration or cumulatively regarding the maximum dose recommended in the study protocol.

An overdose with trifluridine/tipiracil is defined as taking a dose beyond the recommended dose in one day or beyond the recommended total dose in each cycle (*i.e.*, 35 mg/m²/dose or > 160 mg/day for trifluridine/tipiracil). There is no known antidote available in case of trifluridine/tipiracil overdose.

An overdose with futuximab/modotuximab is defined as administration of a dose above the recommended dose (above 9 mg/kg as loading dose or above 6 mg/kg for other administrations).

Overdose should be managed aggressively with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

For procedures to be followed in case of overdose, please see Sections 8.7 and 8.9.2.3.

8.6. Definition of Adverse event of special interest

Not applicable.

8.7. Definition of Events requiring an immediate notification (ERIN)

An event must be **notified immediately** (*i.e.* without delay and **within 24 hours of awareness** at the latest) to the sponsor if it is:

- A serious adverse event (SAE).
- An overdose of the IMP/NIMP even if asymptomatic.
- Any intake of IMP/NIMP by a person around the participant.
- A pregnancy.

8.8. Classification of an adverse event (seriousness, severity, causality, expectedness)

It is important that the investigator gives his/her own opinion regarding the **seriousness**, the **intensity** of the event as well as the **cause-effect relationship** between an AE and the research (IMP, NIMP or study protocol). This evaluation must be assessed by the investigator and reported in the AE form. In addition, the sponsor will be responsible for the evaluation the **expectedness** of the event (Section 8.9.3).

The Seriousness should be evaluated according to international guidance (see definition Section 8.4, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Topic E2A[33] and EU DIRECTIVE 2001/20/EC of 4 April 2001.[34]

The severity of all AEs will be graded according to the NCI-CTCAE on a five-point scale (Grade 1 to 5) (version 5.0):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[1].
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[2].
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

The cause-effect relationship

The investigator must make an assessment in the AE form whether the AE is related or not to the research, meaning:

- AE related to IMP(s).
- AE related to study protocol *i.e.* related to:
  - A procedure scheduled in the study protocol (*i.e.* exercise test, MRI, etc.), or
  - A change or withdrawal of previous / concomitant treatment related to the conditions of the protocol or
  - A product other than the IMP, taken as part of the protocol (NIMP or other).

[1] *Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

[2] *Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

Moreover, the investigator has to assess if the AE is related to disease progression. Cases ticked "related" by the investigator or judged by the sponsor as having a reasonable suspected causal relationship to the IMP (AE linked to the MoA of the IMP…), will be considered as suspected Adverse Drug Reaction. In general, if a relationship between AE and IMP is at least reasonably possible (*i.e.* the relationship cannot be ruled out) it is to be considered as "related".

If in the investigator's opinion there is a causal relationship with the NIMP, the AE must be considered as related to study protocol.

8.9. Reporting procedures

8.9.1. Time frame for AE reporting

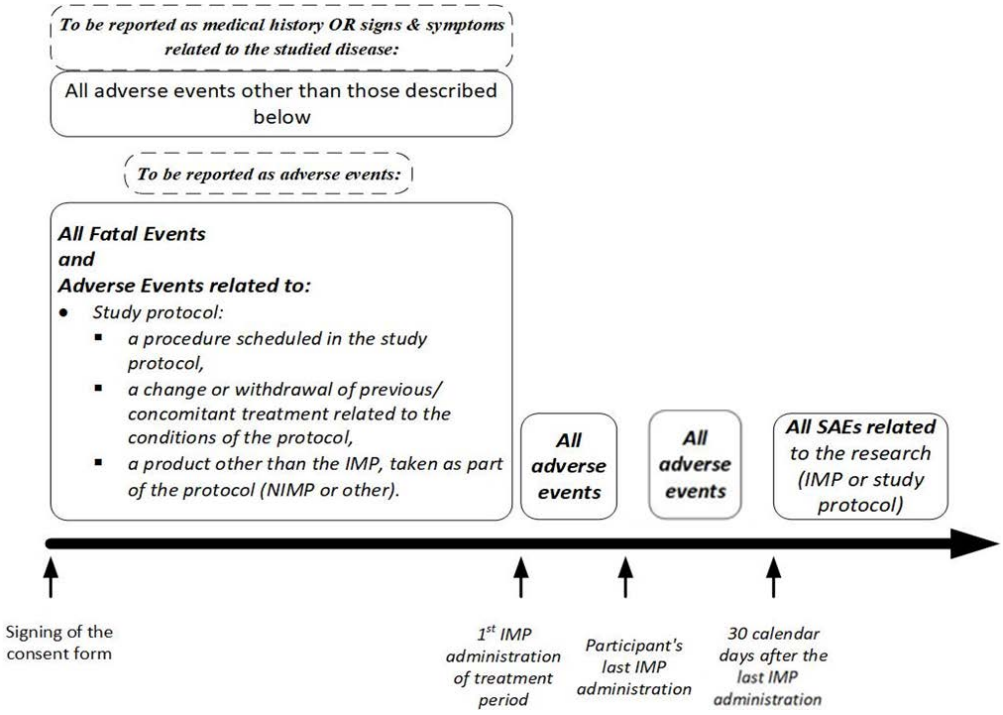
Any event meeting the above mentioned definitions (see Sections 8.3 and 8.7) must be reported to the sponsor on an adverse event form if it occurred:

- Before the first administration of IMP, **for fatal events and events related to the research**.
- At any time after the first administration of IMP up to the participant's last IMPs administration for all events.
- After the participant's last IMP administration:
  - Up to 30 calendar days after the participant's last IMPs administration for all AEs, regardless of the supposed role of the research.
  - Irrespective of the time of onset in case of serious AE related to the research.

Of note, events occurring between the signature of the ICF and the first administration of the IMP for which the investigator does not consider an association with the research must be reported **as medical history or as signs or symptoms related to the studied disease** in the dedicated form of the e-CRF.

Fatal events, related or not to the research, occurring after ICF signature and before first IMP administration, must be reported on AE form.

Figure (8.9.1) 1 - Rules for Adverse Event reporting



8.9.2. Responsibilities of the investigator

For any AE and special situation mentioned above the investigator must:

- **Note in the participant's medical file** the date on which he/she learned of the event (at a follow-up visit or a telephone contact with the participant or a third person, …) and any other relevant information which he/she has learned of the event.
- **Assess** the event in terms of seriousness, severity and causality.
- **Report the event to the sponsor** using the AE form (in case of ERIN, the reporting should be done immediately).
- **Document** the event with additional useful information.
- Ensure the **follow-up** of the event.
- **Fulfil his/her regulatory obligations** to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, the investigator must report to the sponsor and/or to the IRB/IEC and/or to the Competent Authorities in accordance with the local regulation, any new information that might materially influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the clinical investigation.

8.9.2.1. Documentation of the event

The investigator must ensure that all events are well documented. He/she should provide the sponsor on request, with anonymized copies of relevant documents (*e.g.* autopsy report and terminal medical reports [ICH E6 R2]).[35]

8.9.2.2. Follow-up of adverse events

The investigator must ensure that follow-up of the participant is appropriate to the nature of the event, and that it continues until resolution if deemed necessary.

Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an AE already reported must be written up in a new complete evaluation of the event documented on the "Adverse event" page previously created for the event.

If the AE has not resolved at the participant's final visit, the participant must be followed up suitably and any information on the outcome of the event will be noted on the "Adverse Event" page previously created for the event.

If the follow-up of the participant is not done by the investigator him/herself (hospitalisation, followed by a specialist or the participant's general practitioner, …), the investigator will do everything to establish/maintain contact with the person/department in charge of follow-up of the participant.

8.9.2.3. Special situations (pregnancy, overdoses, intake of IMP/NIMP by a person around the participant)

Pregnancy

If a female participant in the study becomes pregnant, the investigator must:

- Stop immediately the study treatments.
- Report it on an "Adverse Event" page as well as on the specific paper pregnancy form (1st page) to be notified immediately (ERIN).
- Contribute to the follow-up of this pregnancy and provide the sponsor with information concerning this follow-up (notably using the 2nd page of the specific paper pregnancy form).

If the partner of a participant becomes pregnant during the study, the pregnancy should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

Overdose of IMP or NIMP

- In case of overdose, the investigator should report it on an "Adverse Event" page to be notified immediately (ERIN).
- Overdose should be followed-up to ensure that the information is as complete as possible with regards to:
  - Dose details (number of units, duration, …) and, if multiple overdose, details regarding other medicinal products or substance.
  - Context of occurrence, *i.e.* intentional (suicide attempt, other reason) or accidental (error in prescription, administration, dispensing, dosage).
  - Related signs and symptoms ("No related adverse events" to be reported otherwise).
  - Outcome.
- Insofar as possible, a blood sample should be collected for assay of the IMP taken.

Intake of IMP or NIMP by a person around the participant This event should not be reported in the e-CRF. The investigator should **immediately** contact the sponsor (contact details provided in the investigator's study file) who will inform him/her about the procedure to be followed.

8.9.2.4. Recording Methods in the e-CRF

Adverse events must be documented on the "Adverse Event" page of the e-CRF.

In case of chronic disease:

- If the disease is known when the participant enters in the study, only worsening (increased frequency and/or intensity of the episodes/attacks) will be documented as an adverse event.
- If a disease is detected during the study and if repeated episodes enable diagnosis of a chronic disease, the episodes will be grouped on the "Adverse Event" page previously created for the event which will clearly describe the diagnosis.

8.9.2.5. Procedure for an event requiring an immediate notification

In case of an event requiring an immediate notification, the investigator must:

- **Immediately** after being informed of this event, **fill in** the **participant's medical file** as well as the **"Adverse Event" page** of the e-CRF according to the general instructions available in the e-CRF, without waiting for the results of the clinical outcome or of additional investigations. When data will be submitted into the e-CRF system, an e-mail will be immediately and automatically sent to the sponsor.
- Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC, in accordance with local regulations.

Moreover, on request, the investigator should provide the sponsor with the documents required in Section 8.9.2.1.

If an adverse event initially non-serious worsens and becomes a serious adverse event, this must be reported **immediately** on an "Adverse event" page of the e-CRF.

In case the e-CRF is unavailable when the investigator was informed of the ERIN, he/she should:

- **Immediately** fill in a paper "Adverse event" page:
  - For serious event on a paper "Adverse event – Initial information" page.
  - For event initially non-serious on a paper "Adverse event – Initial information" page, and the worsening leading to seriousness on a paper "Adverse event – Additional information" page.
- Immediately send the page(s) by fax or a scan of them by e-mail to the person(s) designated in the contact details provided in the investigator's study file or outside working hours, the 24-hour phone line.
- As soon as the e-CRF becomes available, the investigator should enter these data in the "Adverse Event" page of the e-CRF.

8.9.3. Responsibilities of the sponsor

In accordance with international guidance, the assessment of the seriousness and the causality of adverse events are usually made by the investigator but falls also under sponsor's duties, who is responsible for ensuring that all suspected unexpected serious adverse reactions are reported to Competent Authorities and Ethics Committees.

The sponsor will review the seriousness of the adverse events and the causality of (at least) the serious adverse events, whether reported by the investigator or upgraded by the sponsor. The causality and the seriousness may be upgraded (but never downgraded). Anonymized copies of relevant documents may be asked for the event assessment. If the assessments of the investigator and the sponsor are different, both will be reported in the clinical study report.

In addition, the sponsor is responsible for determining whether an AE is **expected or unexpected**. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the IMP.

Independently of the regulatory obligations of the investigator, the sponsor must report the pharmacovigilance data and any new safety finding likely to affect the benefit /risk balance of the product, required in ICH GCP guidelines and local regulations, to the appropriate Authorities, to all the investigators involved and to the trial participants involved - through the investigators - as mentioned in Section 13.4.

The concerned authorities will be notified as soon as possible by the sponsor of the DMC recommendations if any, where relevant for the safety of subjects (*i.e.* modification or termination of the study).

8.10. Responsibilities of Data Monitoring Committee

In accordance with the DMC charter and the rules for DMC functioning, the DMC is responsible for reviewing the efficacy (including disease-related events) and safety data on a regular basis and providing written recommendations to the International Coordinator and the sponsor regarding the conduct of the study (modification or termination). For more detail refer to Section 12.4.

8.11. Management of treatment dose adaptations due to toxicities

For participants who have experienced a dosing modification, reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the participant's source documents and recorded in the e-CRF.

In the futuximab/modotuximab plus trifluridine/tipiracil arm doses of either futuximab/modotuximab, or trifluridine/tipiracil, or both drugs can be modified, depending on the toxicity observed.

General rules:
Before starting a new treatment cycle, toxicity must have resolved as specified in the Sections 8.11.1 and 8.11.2 and the safety criteria to be met as specified in the Section 6.1.5.

- If toxicity due to any of the IMPs does not resolve during the given cycle to Grade 1 or baseline, the start of the next cycle will be delayed for a maximum of 30 days for trifluridine/tipiracil and 21 days for futuximab/modotuximab (see Sections 8.11.1 and 8.11.2). If more than the maximum delay period is needed for recovery, the next cycle should be started with the IMP not concerned by the toxicity.
- If, in the opinion of the investigator, the toxicity is clearly related to one of the treatments, reduction of one and not the other agent is appropriate. If, in the opinion of the investigator, the toxicity is related to the futuximab/modotuximab only futuximab/modotuximab should be reduced according to recommended dose modifications. If, in the opinion of the investigator, the toxicity is related to the trifluridine/tipiracil only trifluridine/tipiracil should

be reduced according to recommended dose modifications. If the toxicity is related to the combination of two agents, both agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications.

- Participants may have trifluridine/tipiracil discontinued and continue on futuximab/modotuximab alone. Similarly, participants may discontinue futuximab/modotuximab and continue on trifluridine/tipiracil alone if appropriate.

8.11.1. Management of treatment dose adaptations due to trifluridine/tipiracil toxicities

All toxicities related to trifluridine/tipiracil must have resolved to Grade 1 or baseline before the start of a new treatment cycle.

In the event of haematological and/or non-haematological toxicities, rules for trifluridine/tipiracil dose interruption and resumption are provided in Table (8.11.1) 1; rules for dose modifications are provided in Table (8.11.1) 2 and Table (8.11.1) 3.

Treatment interruptions are regarded as lost treatment days and missed doses should not be replaced; the planned treatment schedule should be maintained.

A new treatment cycle with trifluridine/tipiracil can be started only if neutrophils count is ≥ 1.5 x 10^9/L and platelets count is ≥ 75 x 10^9/L.

Table (8.11.1) 1 - Dose interruption and resumption criteria for haematological toxicities related to myelosuppression

Parameter	Interruption criteria*	Resumption criteria**
Neutrophils	$< 0.5 \times 10^9$/L	$\geq 1.5 \times 10^9$/L
Platelets	$< 50 \times 10^9$/L	$\geq 75 \times 10^9$/L

** Interruption criteria apply only during active treatment intake period (i.e., D1-5 and D8-12) based on an unscheduled laboratory assessment.*
***Resumption criteria apply to the start of the next cycle for all participants regardless of whether or not the interruption criteria were met.*

Table (8.11.1) 2 - Recommended dose modifications in case of haematological adverse event related to myelosuppression

Adverse event related to myelosuppression	Recommended dose modifications
Febrile neutropenia	Don't start a new treatment cycle until the resumption criteria are met (Table (8.11.1) 1) When resuming dosing, decrease the dose level by 5 mg/m² from the previous dose level (Table (6.1.3.2) 2) Dose reductions are permitted to a minimum dose of 20 mg/m²/dose twice daily Do not increase dose after it has been reduced
NCI-CTCAE Grade 4 neutropenia count $< 0.5 \times 10^9$/L that results in more than 1 week's delay in start of next cycle	
NCI-CTCAE Grade 4 thrombocytopenia $< 25 \times 10^9$/L that results in more than 1 week's delay in start of next cycle	

Table (8.11.1) 3 - Recommended dose modifications in case of non-haematological adverse event related to trifluridine/tipiracil

Adverse event related to trifluridine/tipiracil	Recommended dose modifications
NCI-CTCAE non-haematologic grade 3 or 4 adverse reaction; except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrheal medicinal products.	Don't start a new treatment cycle until toxicity resolves to Grade 1 or baseline When resuming dosing, decrease the dose level by 5 mg/m² from the previous dose level (Table (6.1.3.2) 2) Dose reductions are permitted to a minimum dose of 20 mg/m²/dose twice daily Do not increase dose after it has been reduced

If the participant recovers from toxicities requiring treatment interruption:

- During the 2-week active treatment intake period of a cycle (treatment D1-D12):
  - If no dose reduction is required, trifluridine/tipiracil may be resumed during that cycle. Missed doses must not be caught up.
  - If a dose reduction is required, trifluridine/tipiracil should be resumed at the start of the next treatment cycle at the appropriate dose level.
- During the rest period (D13-28):
  - Start the next cycle on schedule at the appropriate trifluridine/tipiracil dose level.

If the toxicity does not resolve during the given cycle to Grade 1 or baseline, the start of the next cycle may be delayed by a maximum of 30 days from the last dose of trifluridine/tipiracil administered to allow the initiation of both IMPs at the same time in the next cycle. If more than 30 days from the last dose administered are needed for recovery, the next cycle should be started by omitting trifluridine/tipiracil doses as needed (i.e. next cycle is started with only S95026 and trifluridine/tipiracil is reintroduced later) or the participant may have trifluridine/tipiracil discontinued, according to investigator's judgement.

Note: Interruption/resumption criteria and recommended dose modifications of trifluridine/tipiracil could be done in accordance with the local SmPC (Summary of Product Characteristics)).

8.11.2. Management of treatment dose adaptations due to futuximab/modotuximab toxicities

Anticipated AEs that may be experienced with futuximab/modotuximab are detailed in this protocol (Section 2.6 and Section 2.8), as well as in the Investigator's Brochure (IB). Participants will be evaluated throughout the course of the trial for acute as well as delayed and/or cumulative toxicities.

If a significant toxicity thought to be related to futuximab/modotuximab is experienced at any point during the participant's participation in the study, the investigator will determine appropriate management, including determining whether that toxicity warrants a change in premedication (Section 6.1.2), or a dose modification such as infusion prolongation (in the event of an IRR) (Section 8.11.2.1), temporary dose delay (Section 8.11.2.2), or dose reduction (Section 8.11.2.3).

8.11.2.1. Decrease of infusion rate

For IRRs, infusion prolongation instructions are provided in Section 8.12.4.1.

To enhance participant safety following an infusion prolongation, subsequent infusions will be administered with a lower infusion rate at the prolonged rate.

8.11.2.2. Dose Delay

Toxicities may be managed by delay in dosing, provided they do not meet the criteria for IMP discontinuation (Section 5.8.1). In such cases, the period between any 2 scheduled doses may be extended up to 3 days (inclusive) to allow an improvement of the toxicity. Such delays will be considered an extension within the current cycle. If a delay of more than 3 days from the schedule dose date is necessary, the dose should be omitted and proceed to the next scheduled dose (i.e. 14 days from the last dose).

If 3 consecutive doses are needed to be omitted (i.e. more than 21 days from the last dose of futuximab/modotuximab), the participant should be discontinued from futuximab/modotuximab. All delays of futuximab/modotuximab must be documented on the appropriate page of the participant's e-CRF.

If toxicity does not resolve during the given cycle to Grade 1 or baseline, the start of the next cycle may be delayed by a maximum of 21 days from the last dose of futuximab/modotuximab administered to allow the initiation of both IMPs at the same time in the next cycle. If more than 21 days from the last dose administered are needed for recovery, futuximab/modotuximab should be discontinued and the next cycle will start with only trifluridine/tipiracil.

Dosing may be restarted at the same dose, as clinically indicated. However, administration of futuximab/modotuximab may only be restarted provided retreatment criteria are met (Section 6.1.5).

For treatment restart with no dose reduction:

- If treatment restart after the omission of 1 dose (i.e. treatment delay up to 14 days from the last dose), it is recommended that dosing restart with maintenance dose of 6 mg/kg;
- If treatment restart after the omission of 2 consecutive doses (i.e. treatment delay up to 21 days from the last dose), it is recommended that dosing re-start with the re-administration of a loading dose of 9 mg/kg followed by weekly maintenance doses of 6 mg/kg.

For treatment restart with dose reduction, see Section 8.11.2.3.

8.11.2.3. Dose Reduction

In the event of Grade 3 treatment-related AEs, the participant may continue on study if there is evidence of clinical benefit as judged by the treating physician, but could do so at a reduced dose of futuximab/modotuximab once retreatment criteria are met (Section 6.1.5) (specific instructions for dose reduction linked to IRR, dermatologic AEs, and hypomagnesemia, are provided in Appendices 9, 10 and 11, respectively). All dose reductions of futuximab/modotuximab must be documented on the appropriate page of the participant's e-CRF.

If toxicity is to be managed by dose reduction, the futuximab/modotuximab dose will be decreased as shown in (Table (8.11.2.3) 1). Dose reduction may occur either during treatment cycles, or between cycles, as clinically indicated.

Table (8.11.2.3) 1 - Dose reduction of futuximab/modotuximab

	Starting dose (Dose level 0)	Dose level -1	Dose level -2
Futuximab/modotuximab*	6 mg/kg	4.5 mg/kg	3 mg/kg

**Note: Dose Reductions for 9 mg/kg loading dose not applicable. The number of dose reductions allowed is limited to 2*
Abbreviations (in alphabetical order): kg, kilogram; mg, milligram

A maximum of 2 dose reductions for futuximab/modotuximab-related toxicity are allowed (to a minimum dose of 3 mg/kg). Do not re-escalate dose after it has been reduced.

8.12. Recommendations regarding treatment of toxicities

8.12.1. Management of nausea and vomiting

Trifluridine/tipiracil has emetogenic potential.

- A single antiemetic agent, such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide may be considered for prophylaxis.
- If a participant experiences acute or delayed nausea or vomiting due to trifluridine/tipiracil, it is advised that, at the next cycle, a higher antiemetic regimen may be given.
- In case a participant experiences of anticipatory nausea and vomiting, benzodiazepines are recommended. The above is based on Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) guidelines[36] and Hesketh *et al.* (2016).[37]

8.12.2. Management of diarrhoea

Educate both participants and participants' families regarding the potential seriousness of chemotherapy-induced diarrhoea. Instruct participants to immediately contact the study site

staff at the first sign of loose stool. The participant should be instructed to record the number of stools and report symptoms indicating a complicated diarrhoea (see list below).

- Educate the participant regarding the dietary measures to be taken in case of diarrhoea.
- Provide participants with loperamide (or other standard antidiarrheal therapy) and instruct the participant on how to use it at the first sign of diarrhoea.
- Monitor the participant's fluid and electrolyte balance, with appropriate intervention as clinically indicated with fluids and electrolyte replacement [38]

Mild to moderate diarrhoea (Grade 1 or 2 according to NCI-CTCAE without complications):

- It is recommended to start dietary modifications and standard antidiarrheal therapy for example loperamide at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/day).
- If diarrhoea resolves with antidiarrheal therapy, the dietary modifications should be continued (with a gradually addition of solid foods). Antidiarrheal therapy may be discontinued when the participant has been diarrhoea-free for at least 12 hours.
- If diarrhoea persists for more than 24 hours, the dose of antidiarrheal therapy should be increased (for loperamide increase to 2 mg every 2 hours), and oral antibiotics may be started as prophylaxis for infection.
- If diarrhoea has not resolved after 48 hours on initial treatment, the participant should be started on a second-line antidiarrheal agent.

Complicated diarrhoea:

- Any Grade 3 or 4 diarrhoea is classified as "complicated". In addition, Grade 1 or 2 diarrhoea and at least one of the following symptoms are also considered as complicated:
  - Fever, sepsis, moderate to severe cramping.
  - Grade 2 nausea/vomiting.
  - Decreased performance status.
  - Neutropenia.
  - Frank bleeding.
  - Dehydration.
- Aggressive management of complicated cases should involve:
  - Intravenous (IV) fluids.
  - Octreotide at a starting dose of 100 to 150 µg subcutaneous tid or IV (25 to 50 µg/h) if the participant is severely dehydrated, with dose escalation up to 500 µg until diarrhoea is controlled.
  - Administration of antibiotics (*e.g.*, fluoroquinolone).
- Stool work-up (evaluation for blood, faecal leukocytes, *C difficile*, *Salmonella*, *E coli*, *Campylobacter*, and infectious colitis), complete blood count, and electrolyte profile should be performed.
- Continue intervention as described until the participant has been diarrhoea-free for 24 hours.

8.12.3. Management of febrile neutropenia and anaemia

Administer haematologic support as medically indicated (*e.g.*, blood transfusions, granulocyte colony-stimulating factor [G-CSF], erythropoietin, etc.) according to the institutional site standards.

If there are no standard procedures for the use of growth factors, follow Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice

Guideline Update, available at http://www.instituteforquality.org/practice-guidelines; or the European Organization for Research and Treatment of Cancer (EORTC) update to 2010 guidelines for the use of G-CSF, available at https://www.eortc.org/guidelines/.

8.12.4. Management of Infusion related reactions

There is an inherent risk for IRRs with the administration of mAbs, therefore premedication for prophylaxis of IRRs will be mandatory prior to each dose of futuximab/modotuximab. All participants will be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen. Recommended premedication doses are provided (Section 6.1.2.1 and Appendix 9).

Should a participant experience an IRR while in the study, guidelines for premedication following an IRR are provided (Section 6.1.2.1.3). Guidelines for the grading and management of IRRs of all severities are also provided (Section 8.11.2.1 and Appendix 9).

Instructions for the grading and management of IRRs are provided. In all cases the investigator should use best clinical judgment in managing such reactions.

- For Grade 3 reactions, the infusion will be STOPPED. The participant will be either discontinued from treatment or must receive subsequent treatments at a reduced dose and at a prolonged infusion rate.
- For Grade 4 reactions, the infusion will be STOPPED and the participant will be permanently discontinued from treatment.

8.12.4.1. Decrease of infusion rate

For IRRs, the following infusion prolongation instructions are provided:

- For mild IRR (Grade 1), the infusion rate must be decreased by 50% from the prior rate. This lower infusion rate must be maintained in all subsequent infusions.
- For moderate IRR (Grade 2), interrupt the infusion for a minimum of 30 minutes, and at least until there is either amelioration to ≤ Grade 1 severity or return to baseline status. Administer supportive care, as medically indicated. Restart the infusion with an infusion rate decreased by 50% from the prior rate. This lower infusion rate must be maintained in all subsequent infusions.
- For Grade 3 reactions, STOP the infusion. Administer supportive care. The participant will be either discontinued from treatment or must receive subsequent treatments at a reduced dose and with a decreased infusion rate (≥ 50% of decrease).
- For Grade 4 reactions, STOP the infusion. Administer supportive care. The participant will be permanently discontinued from treatment.
- All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the participant's e-CRF.

Note: Any assessments to be performed or samples to be collected (*e.g.*, vital signs, PK) at the end of or following the EoI will still be performed or collected beginning at the delayed EoI timepoint.

To enhance participant safety following an infusion prolongation, subsequent infusions will be administered with a lower infusion rate.

8.12.5. Management of dermatologic toxicity

Participants who received futuximab/modotuximab will be monitored weekly for evidence of dermatologic AEs. Dose delay and/or intrapatient dose-reduction(s) will be required upon occurrence of Grade 3 AEs and may be implemented in the event of a Grade 2 dermatologic reaction that is debilitating for the participant.

Recommendations for management of Grade 1 to 3 dermatologic AEs are provided. Participants must be withdrawn from IMP treatment in the event of a Grade 4 dermatologic AE. Guidelines for grading and management of dermatologic AEs and dose reductions to be implemented in the event of such reactions are also provided (Appendix 10).

8.12.6. Management of hypomagnesemia, hypocalcemia, and hypokalemia

Participants will be monitored weekly for hypomagnesemia, hypocalcemia, and hypokalemia. In the event of Grade 3-4 hypomagnesemia, repletion is required as well as predosing electrocardiograms (ECG) to monitor for corrected QT (QTc) prolongation. For Grade 4 hypomagnesemia that is refractory to IV magnesium-replacement therapy, dosing with futuximab/modotuximab should be delayed or reduced. Full management instructions are provided in Appendix 11.

9. OTHER ASSESSMENTS NOT SPECIFICALLY RELATED TO EFFICACY OR SAFETY

9.1. Assessments related to screening/inclusion criteria

9.1.1. Assessments related to inclusion criteria

9.1.1.1. Informed consent

Obtain signed and dated ICF from the patient during the screening visit prior to the implementation of study procedures required by the protocol. Please refer to Section 13.3.

9.1.1.2. Histological/Cytological Confirmation

Histological confirmation of adenocarcinoma of the colon or rectum should be documented in the patient's source documents. The pathology report should be available in the patient's source documents.

9.1.1.3. KRAS/NRAS/BRAF status

Genomic analysis from peripheral whole blood sample for defining patient eligibility and stratification will be based on assessment of ctDNA in plasma with an oncogene panel. The sample will be submitted for mutation analysis prior to first administration of first IMP (for Safety Lead-In part) and to randomisation. The genomic analysis includes a series of genes frequently mutated in cancer, but will be focused on the following genes:

- BRAF CCI [redacted]
- KRAS & NRAS CCI [redacted] CCI [redacted] CCI [redacted]
- EGFR-ECD mutation analysis (for stratification purpose: "WT" if no mutation and "mutated" if one or more CCI [redacted] mutations are detected).

Backup DNA extracts from included participants and screened participants non included will be stored, with the consent of the participant, for a maximum of 25 years after the end of the study according to local regulation for retrospective analysis restricted to the study of the pathology and the response to the treatment. All samples may be destroyed at any time on participant's or sponsor's request.

Additional details and the sample collection instructions are provided in laboratory manual.

9.1.2. Assessments not related to inclusion criteria

9.1.2.1. Patient Numbering (Only for Randomised part)

Once the patient has signed ICF, the study site will connect to the IWRS for patient's registration and to obtain a patient's number (see the IWRS manual for details). Each patient will be assigned a unique patient number. This patient number will be maintained throughout the study and will not be reassigned. Participants who withdraw consent or discontinue from the study after being assigned a patient number will retain their initial number.

9.1.2.2. ECOG performance status

Collect ECOG performance status score (Appendix 2).

9.1.2.3. Medical history

Obtain a complete medical history.
Of note, events occurring between the signature of the ICF and the first study treatments administration for which the investigator does not consider an association with any procedure/condition required by the study protocol must be reported as medical history in the dedicated form of the e-CRF.

9.1.2.4. Previous surgery, radiotherapy and treatments related to the colorectal cancer

Collect previous surgery, radiotherapy and treatments related to the colorectal cancer.

9.1.2.5. Baseline Signs and Symptoms

Signs and symptoms related to the colorectal cancer present following ICF signature and before the first study treatments administration should be recorded in the patient's source documents.

9.1.2.6. MMR/MSI status

MMR/MSI status will be collected in the e-CRF if available.

9.1.2.7. Demography

Collect demography data (age, sex, ethnic origin).

9.2. Measurement of drug concentration

9.2.1. Sample Collection Timepoints

Blood samples for the evaluation of PK are to be collected at the timepoints listed in Table (9.2.1) 1 and Table (9.2.1) 2. The accurate sampling dates and times must be recorded in the e-CRF.

Table (9.2.1) 1 - Sample collection timepoints for futuximab/modotuximab and trifluridine/tipiracil (Pharmacokinetics during the Safety Lead-In and Arm A of Randomised part)

	Futuximab and modotuximab assessment	Trifluridine and tipiracil assessment
C1D1	Pre-dose*	Pre-dose*
	End of infusion**	End of infusion**
	1-2 hours after end of infusion	1-2 hours after end of infusion
C1D8	Pre-dose*	Pre-dose*
	End of infusion**	End of infusion**
	30 min-1 hour after end of infusion	30 min-1 hour after end of infusion
C1D15	Pre-dose*	
	End of infusion**	
	30 min-1 hour after end of infusion	
C1D22	Pre-dose*	
	End of infusion**	
	30 min-1 hour after end of infusion	
C2D1	Pre-dose*	Pre-dose*
	End of infusion**	End of infusion**
	30 min-1 hour after end of infusion	30 min-1 hour after end of infusion
C2D8	Pre-dose*	Pre-dose*
	End of infusion**	End of infusion**
	30 min-1 hour after end of infusion	30 min-1 hour after end of infusion
C2D15	Pre-dose*	
	End of infusion**	
	30 min-1 hour after end of infusion	
C2D22	Pre-dose*	
	End of infusion**	
	30 min-1 hour after end of infusion	
CXD1	Pre-dose*	
WV	During the visit	During the visit

**i.e. 5-60 minutes before infusion of futuximab/modotuximab*
***i.e. within 10 minutes before to the end of infusion of futuximab/modotuximab*

Table (9.2.1) 2 - Sample collection timepoints for trifluridine/tipiracil (Pharmacokinetics in Arm B of Randomised part)

	Trifluridine and tipiracil assessment
C1D1	At the beginning of the visit
	At the end of the visit
C1D15	During the visit
C2D1	During the visit
C2D15	During the visit
WV	During the visit

9.2.2. Sampling Methods

For **Trifluridine and tipiracil assessment**, 4 mL of blood will be taken at each timepoint (Appendix 12). Concentrations of trifluridine and tipiracil will be determined in sodium heparinised plasma, using a mass spectrometry, validated according to current regulatory guidelines.

For **Futuximab and modotuximab assessment**, 2.5 mL of blood will be taken at each timepoint (Appendix 12). Futuximab/modotuximab will be determined in serum, using an enzyme-linked immunosorbant assay, and validated according to current regulatory guidelines.

Preparation and management of the bioanalytical samples will be described in a separate document.

9.3. Pharmacodynamic measurements

Not applicable.

9.4. Assessment of biomarkers

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a sampling collection, or not perform or discontinue an analysis due to either practical or strategic reasons (*e.g.* inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of the sponsor.

Peripheral whole blood (20 mL) will be collected pre-dose on C1D1, C2D1, C3D1 then every 2 cycles along with tumour assessment and at withdrawal visit, and analysed centrally for ctDNA monitoring. Potential predictors of response as well as mechanisms of resistance could be explored. The collection is mandatory for all participants. Backup DNA extracts will be stored, with the consent of the participant, for a maximum of 25 years after the end of the study according to local regulation for retrospective analysis restricted to the study of the pathology and the response to the treatment. All samples may be destroyed at any time on participant's or sponsor's request.

Additional details and the sample collection instructions are provided in laboratory manual.

9.4.1. Mandatory assessment

Participation in the study implies a systematic participation in the mandatory investigation. All participants will have to consent to this investigation by signing the main information and consent form for participation in the study. In addition, in case of consent withdrawal, related samples will be destroyed after mandatory assessment is completed and in any case before the clinical study report final version is made available.

Overall results of the genomics biomarkers assessment may be transmitted to the participant upon his/her request through the investigator, according to local regulations if applicable.

9.4.1.1. Sampling, processing and storage

In all participants, 20 mL of blood will be taken at each timepoint.

The plasma will be separated by centrifugation and stored at < -70°C in appropriate labelled storage cryotubes and sent on dry ice. DNA will be extracted from plasma sample and subjected to genomic analysis for circulating tumour DNA monitoring. Preparation and management of the samples will be described in a separate document.

These samples are dedicated to retrospective analysis if participants consent and will be destroyed at the end of the storage period. If participants withdrawn his/her Informed consent form, please refer to Section 9.4.1.

Table (9.4.1.1) 1 - Biomarker(s) experimental conditions

Biomarker(s) assessed	Experimental conditions		
	Sampling time points	Matrix	Purpose
Circulating tumour DNA	C1D1, C2D1, C3D1 CxD1 (every 2 cycles) Withdrawal visit	Blood	ctDNA monitoring

9.4.1.2. Labelling and transfer to analytical centre

Samples will be single coded with a unique number and thus will not carry any personal identifiers.

Samples collection information must be entered as required on the appropriate sample collection e-CRF page(s) and requisition form(s).

Detailed instructions for the samples labelling and shipments are outlined in the laboratory manual (or equivalent) for the study.
The randomisation list will be sent to the analytical centre in order to select the samples to be analysed.

9.4.1.3. Transfer of analytical results

Final analytical results will be transferred to Data Management according to Section 14.2.

9.4.2. Retrospective analysis

Retrospectives analyses involving human biological samples are considered as **optional** assessments and are performed after the end of the study (planned or not in the clinical study protocol).

Participation in these retrospective analyses is optional and is not mandatory for the inclusion of a given participant in the study.

If the participant agrees, some additional samples / remaining biomarker samples may be stored after the end of the study.

They could be further analysed to address scientific questions related to the product or disease including research related to improvements or enhancements in the development of bioanalytical methods.

A decision to perform such exploratory biomarker research studies will be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

Samples will be kept in suitable conditions in a central bio-repository specialized in storage of biological samples until further notification from the sponsor and may be retained stored up to 25 years after study closure completion.

9.4.3. Transfer of pharmacogenomics results

If the analysis is required during the study, final analytical results will be transferred to Data Management at the end of the study.

9.4.4. Interpretation

If relevant for the project, an evaluation will be carried out and reported in a separate document. This evaluation will be performed by analysing the associations between polymorphisms in relevant absorption, distribution, metabolism, and excretion (ADME) genes and the pharmacokinetics of futuximab/modotuximab.

9.5. Immunogenicity

Blood samples (2.5 mL) for the evaluation of immunogenicity will be collected at the timepoints listed in Table (9.5) 1. The accurate sampling dates and times must be recorded in the e-CRF.

Table (9.5) 1 - Sample Collection Timepoints for futuximab/modotuximab (during the Safety Lead-In and Arm A of Randomised part)

	Futuximab/modotuximab assessment
C1D1	Pre-dose*
C1D15	Pre-dose*
C2D1	Pre-dose*
C2D15	Pre-dose*
CXD1	Pre-dose*,**
WV	During the visit

**i.e. 5-60 minutes before infusion of futuximab/modotuximab*
***The frequency of futuximab/modotuximab immunogenicity assessments will be reduced to every 2 months after the first 6 months in the first year and every 4 months after the first year.*

In all participants, 2.5 mL of blood will be taken at each timepoint (Appendix 12). ADA will be determined in serum, using an Immunoassay method, validated according to current regulatory guidelines.

ADA Backup samples will be stored, for a maximum of 3 years after the end of the study, to allow additional analyses related to immunogenicity assessment to be performed in case of agencies' request during their review process. All samples will be destroyed at the latest at the end of the storage period or at any time on participant's or sponsor's request.

9.6. Quality of Life Assessments (Only for Randomised part)

EORTC Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) (Appendix 6) and EQ-5D-5L (Appendix 5) will be completed by the participant on an e-PRO, independently of the study personnel at the following time points, at the beginning of each visit at the following time point:

- Inclusion.
- After the end of cycle 1 (C2D1)
- Every 2 cycles during the treatment period (C3D1, C5D1…).
- WV.
- Every 2 months during the follow-up period, until death or until end of the study is reached (whichever occur first).

Participants will be provided with specific instructions in order to be comfortable with the e-PRO device and enhance the quality of the data. In case the participant is not able to use e-PRO, a caregiver (not a medical/investigator staff) will be allowed to read the questions to the

participant and to collect the answer without any interpretation of the questions and the answers. Data entered by the participant will be sent to a central database via a secured transfer.

10. STATISTICS

10.1. Statistical analysis

A Statistical Analysis Plan (SAP), and associated templates for Tables, Listings and Graphs, will be written and completed before database lock. These specifications will detail the implementation of all the planned statistical analyses in accordance with the main characteristics stated in the protocol.

10.1.1. Analysis sets / Treatment groups

10.1.1.1. Analysis sets

Full Analysis Set (FAS): In accordance with the ITT principle and Section 5.2.1 of ICH E9 guideline,[39] all participants to whom a therapeutic unit was randomly assigned using IWRS. Participants in the FAS will be analysed in the arm they were assigned by randomisation. FAS will be used in all efficacy analyses of Randomised part, unless otherwise specified.

Safety Set (SS): All participants having taken at least one dose of IMPs. Participants will be analysed according to the treatment actually received. SS will be used in all analyses of Safety Lead-In part and safety analyses of Phase 3 part.

Per-Protocol Set (PPS): all participants in the FAS who do not violate the terms of the protocol in a way that would affect the study outcome significantly. Participants not fulfilling one of the following criteria will not be included in the PPS:

- Must have histologically or cytologically confirmed adenocarcinoma of mCRC [Screening criterion #2].
- Should be without RAS (KRAS and NRAS) mutations and without BRAF mutation [Screening criterion #3].
- Must have received at least 2 prior regimens of standard chemotherapy for mCRC and had demonstrated progressive disease or intolerance to their last regimen [Screening criterion #5].
- Should have received previous treatment with commercially available anti-EGFR mAbs for ≥ 16 weeks [Screening criterion #6].
- ECOG performance status 0 or 1 [Screening criterion #9].
- Currently receiving or having received anticancer therapies within 4 weeks prior to first IMP administration [Non-screening criterion #14].

PRO Analysis Set: All participants from the FAS who have completed screening and at least one post baseline assessment. Quality of life (QoL) endpoints will be evaluated on PRO Analysis Set.

10.1.1.2. Treatment groups

Treatment considered for the analysis of Safety Lead-In part will be the following:
- Futuximab/modotuximab + trifluridine/tipiracil.

Treatment groups considered for the analysis of Randomised part will be the following:
- Futuximab/modotuximab + trifluridine/tipiracil (Arm A).
- Trifluridine/tipiracil (Arm B).

10.1.2. Statistical methods

10.1.2.1. General considerations

The data from Safety Lead-In part and Randomised part will summarized, analysed and listed separately.

The following descriptive statistics will be provided depending on the nature of considered data:
- Qualitative data: number of observed values, number and percentage of participants per class.
- Quantitative data: number of observed values, mean and standard deviation, median, first and third quartiles, minimum and maximum.
- Survival data (time to event occurrence or to censoring): total number of participants, total number and percentage of participants having an event overall, number of participants at risk, number of participants with censored data, number of participants with event of interest.

10.1.2.2. Disposition and baseline characteristics

The participants' disposition and baseline characteristics will be described in SS for Safety Lead-In part and in the FAS by treatment arms and overall for Randomised part.

The number of participants in each study population and the reasons for exclusion, along with any randomisation and/or stratification errors will be summarized as well as the disposition of participants, including reasons for discontinuation and protocol deviations at baseline and during study.

Characteristics of participants including demography, characteristics of the disease at diagnosis and study entry, medical history, prior therapy and concomitant medication at baseline will be summarised.

10.1.2.3. Treatments of participants

Extent of exposure and treatment compliance, as well as concomitant medication during treatment period will be described in the SS. Extent of exposure includes number of cycles, cumulative dose, dose intensity, relative dose intensity, dose modifications.

The follow-up duration will be calculated overall and in each arm with the reverse Kaplan-Meier method.

The non-study cancer treatment after study treatment discontinuation will be summarized. Any use of non-study cancer treatment during the study treatment period will also be presented as protocol deviation.

10.1.2.4. Efficacy analysis

10.1.2.4.1. Safety Lead-In part

The proportion of participants with objective evidence of CR or partial response (PR) (ORR) according to RECIST version 1.1 criteria and using investigator's tumour assessment will be summarized descriptively.

The proportion of participants with BOR according to RECIST version 1.1 criteria and using investigator's tumour assessment will be summarized descriptively.

The proportion of participants with objective evidence of CR or PR or stable disease (SD) (DCR) according to RECIST version 1.1 criteria and using investigator's tumour assessment will be summarized descriptively.

PFS is defined as the time from the first administration of IMP date until the date of the investigator-assessed radiological disease progression according to RECIST version 1.1 or death, whichever occurs first. PFS will be summarized using Kaplan Meier curve and further characterised in terms of the median and survival probabilities at 2, 4, 6 and 8 months along with the corresponding 2-sided 95% CI for the estimates.

OS is defined as the time from the first administration of IMP date until the date of death due to any cause. OS will be summarized using Kaplan Meier curve and further characterised in terms of the median and survival probabilities at 6, 12 and 18 months along with the corresponding 2-sided 95% CI for the estimates.

10.1.2.4.2. Randomised Part

Primary objective
The primary objective is to demonstrate the superiority of futuximab/modotuximab in combination with trifluridine/tipiracil over trifluridine/tipiracil monotherapy in terms of OS in participants with chemotherapy pre-treated (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents, and anti-EGFR mAb therapy for ≥ 16 weeks) metastatic colorectal cancer that are KRAS/NRAS and BRAF WT (Double negative [DN]).

Key secondary objective
The key secondary objective is to demonstrate the superiority of futuximab/modotuximab in combination with trifluridine/tipiracil over trifluridine/tipiracil monotherapy in terms of OS in participants with chemotherapy pre-treated (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents, and anti-EGFR mAb therapy for ≥ 16 weeks) metastatic colorectal cancer that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]).

Secondary objectives
Secondary objectives are to estimate the effect of futuximab/modotuximab in combination with trifluridine/tipiracil *versus* trifluridine/tipiracil monotherapy in terms of PFS, OR, DC, DoR, TTNT, TTR, and TtPS2 in participants with chemotherapy pre-treated (including oxaliplatin, irinotecan and 5-fluorouracil, anti-VEGF agents, and anti-EGFR mAb therapy for ≥ 16 weeks) metastatic colorectal cancer.

Other secondary objectives are to compare the safety and tolerance, and the impact on QoL of futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil monotherapy in participants with chemotherapy pre-treated metastatic colorectal cancer.

Intercurrent events

During the study the following intercurrent events could occur:

- Administration of further anti-cancer therapy.
- Treatment discontinuation.
- Treatment switch (from futuximab/modotuximab in combination with trifluridine/tipiracil to trifluridine/tipiracil monotherapy and from trifluridine/tipiracil monotherapy to futuximab/modotuximab in combination with trifluridine/tipiracil).

Estimands of interest

The attribute treatment will be the same for all estimands of interest:

- Treatment: Futuximab/modotuximab + trifluridine/tipiracil *versus* trifluridine/tipiracil monotherapy.

The following estimands will be studied:

Table (10.1.2.4.2) 1 - Studied estimands

Estimand	Variable	Population level summary	Handling intercurrent events (IEs)	Population
Primary estimand: effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS and BRAF WT (Double negative [DN]) regardless of whether or not intercurrent events occur	OS	HR	Treatment policy strategy	FAS
Key secondary estimand: effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]) regardless of whether or not intercurrent events occur	OS	HR	Treatment policy strategy	FAS restricted to Triple negative [TN] subjects
Effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS and BRAF WT (Double negative [DN]) before participants receive further anti-cancer therapy	OS	HR	While on treatment strategy	FAS
Effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]) before participants receive further anti-cancer therapy	OS	HR	While on treatment strategy	FAS restricted to Triple negative [TN] subjects
Effect of the randomised treatments on progression-free survival before participants receive further anti-cancer therapy	PFS	HR	While on treatment strategy	FAS
Effect of the randomised treatments on progression-free survival regardless of whether or not intercurrent events occur	PFS	HR	Treatment policy strategy	FAS
Effect of the randomised treatments on response before participants receive further anti-cancer therapy	OR DC	Risk difference	While on treatment strategy	FAS

Table (10.1.2.4.2) 1 (Cont'd) - Studied estimands

Estimand	Variable	Population level summary	Handling intercurrent events (IEs)	Population
Effect of the randomised treatments on the response duration before participants receive further anti-cancer therapy	DoR	HR	While on treatment strategy	FAS
Effect of the randomised treatments on the time from the randomisation to initiation of the next systemic anti-cancer therapy	TTNT	HR	While on treatment strategy	FAS
Effect of the randomised treatments on the time from randomisation until first radiologically confirmed tumour response (CR or PR) before participants receive further anti-cancer therapy	TTR	HR	While on treatment strategy	FAS
Effect of the randomised treatments on the time from the date of randomisation to the date when ECOG PS score of ≥ 2 is observed for the first time before participants receive further anti-cancer therapy	TtPS2	HR	While on treatment strategy	FAS

With:

- OS: overall survival defined as the time from date of randomisation into the study to death from any cause.
- PFS: progression-free survival defined as the time from date of randomisation until the date of the investigator-assessed radiological disease progression or death, whichever occurs first.
- OR: overall response defined as the achievement of confirmed CR or PR according to RECIST version 1.1 criteria and using investigator's tumour assessment.
- DC: disease control defined as the achievement of best response of CR or PR or SD according to RECIST version 1.1 criteria and using investigator's tumour assessment.
- DoR: duration of response defined as the time from the first documentation of confirmed tumour response (CR or PR) according to RECIST version 1.1 criteria and using investigator's tumour assessment to the first documentation of objective tumour progression or to death due to any cause.
- TTNT: time to next treatment defined as the time from the randomisation to initiation of the next systemic anti-cancer therapy.
- TTR: time to response defined as the time from randomisation until first radiologically confirmed tumour response (CR or PR) according to RECIST version 1.1 criteria and using investigator's tumour assessment.
- TtPS2: time to ECOG performance status ≥ 2 defined as the time from the date of randomisation to the date when ECOG PS score of ≥ 2 is observed for the first time.

Estimands and the way for handling IEs will be detailed in the following paragraphs.

10.1.2.4.2.1. Primary estimand based on the OS

The primary estimand of interest is the effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS and BRAF WT (Double negative [DN]) regardless of whether or not intercurrent events occur (treatment policy strategy). The motivation for this choice is to assess the efficacy of the futuximab/modotuximab in combination with trifluridine/tipiracil compared to trifluridine/tipiracil monotherapy under the ITT principle (intercurrent events are considered to be part of the treatments being compared).

All data collected during the trial regardless of occurrence of an IE will be used. This is aligned with the treatment policy strategy.

Primary analysis

The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).

OS for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median and survival probabilities at 6, 12 and 18 months along with the corresponding 2-sided 95% CI for the estimates.

The hazard ratio of OS with its 95% confidence interval will be estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

For missing data (not linked to intercurrent events), *i.e.* participants without documentation of death (lost to follow-up, withdrawal of consent, administrative end of study), the OS will be censored on the last contact date the participant was known to be alive or the cut-off date, whichever is earlier.

Sensitivity analyses

As sensitivity analyses, the following analyses will be done:

- The proportional hazards assumption will be checked. If relevant, other statistical method could be used.
- OS analysis based on PPS.

Other sensitivity analyses will be defined in the SAP if necessary.

Supplementary analyses

Subgroup analyses

OS subgroup analyses are planned to further explore the homogeneity of the treatment effect across participant subsets. Depending on the sample size, the following subgroups will be examined: ECOG PS (0, 1), extracellular domain EGFR mutations (ECD) (presence, absence), previous regimens of treatment (2, ≥ 3), region (North America, European Union, Asia, Rest of the World), time since diagnosis of 1st metastasis (< 18, ≥ 18 months), location of primary disease (right, left), gender (female, male), age (< 70, ≥ 70 years), prior surgical resection (yes, no), number of metastatic sites (1-2, ≥ 3), neutrophils to lymphocytes ratio (NLR < 3, NLR ≥ 3), neutrophils to lymphocytes ratio (NLR < 5, NLR ≥ 5), response to previous treatment with anti-EGFR (CR/PR, SD), last previous regimen (anti-EGFR, no anti-EGFR), previously treated with anti-VEGFs treatment (yes, no), skin toxicity with previous anti-EGFR (yes, no), skin toxicity with previous anti-EGFR (Grade 1-2, Grade 3-4, no toxicity), duration of previous anti-EGFR (< 8, ≥ 8 months), Race (White, American Indian/Alaska native, Asian, Black/African

American, Native Hawaiian/Other pacific islander), Premedication with antibiotics for skin toxicity (yes, no).

A stratified Cox-regression model with treatment arm as predictor variable will be fitted separately for each subgroup category. The hazard ratio for treatment along with the associated 95% confidence interval will be provided.

Exploratory analysis
A multivariate OS analysis will be performed using a stratified Cox proportional hazard model (3 stratification factors (ECOG PS (0 *versus* 1), extracellular domain EGFR mutations (ECD) (presence *versus* absence) and previous regimens of treatment (2 *versus* ≥ 3)). Treatment will be included in the model and a stepwise selection process (p-value to enter < 0.15, p-value to remain < 0.10) will be applied to identify potential additional prognostic factors among the following covariates: region (North America, European Union, Asia, Rest of the World), time since diagnosis of 1st metastasis (< 18, ≥ 18 months), location of primary disease (right, left), gender (female, male), age (< 70, ≥ 70 years), prior surgical resection (yes, no), number of metastatic sites (1-2, ≥ 3), neutrophils to lymphocytes ratio (NLR < 3, NLR ≥ 3), neutrophils to lymphocytes ratio (NLR < 5, NLR ≥ 5), response to previous treatment with anti-EGFR (CR/PR, SD), last previous regimen (anti-EGFR, no anti-EGFR), previously treated with anti-VEGFs treatment (yes, no), skin toxicity with previous anti-EGFR (yes, no), skin toxicity with previous anti-EGFR (Grade 1-2, Grade 3-4, no toxicity), duration of previous anti-EGFR (< 8, ≥ 8 months), Race (White, American Indian/Alaska native, Asian, Black/African American, Native Hawaiian/Other pacific islander), Premedication with antibiotics for skin toxicity (yes, no).

10.1.2.4.2.2. Key secondary estimand based on the OS

The key secondary estimand of interest is the effect of the randomised treatments on the survival duration in all subjects that are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]) regardless of whether or not intercurrent events occur (treatment policy strategy). The motivation for this choice is to assess the efficacy of the futuximab/modotuximab in combination with trifluridine/tipiracil compared to trifluridine/tipiracil monotherapy under the ITT principle (intercurrent events are considered to be part of the treatments being compared).

All data collected during the trial regardless of occurrence of an IE will be used. This is aligned with the treatment policy strategy.

The following analyses will be done as primary analyses:
- The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- OS for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median and survival probabilities at 6, 12 and 18 months along with the corresponding 2-sided 95% CI for the estimates.
- The hazard ratio of OS with its 95% confidence interval will be estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

As OS in TN population is identified as the key secondary estimand, closed sequential testing procedure will be used to statistically evaluate and interpret OS in TN population only if the

primary estimand, OS in DN population, is statistically significant. Therefore, the family-wise error rate is strongly controlled.

The following analyses will be done as sensitivity analyses:

- The proportional hazards assumption will be checked. If relevant, other statistical method could be used.
- OS analysis based on PPS.

Other sensitivity analyses will be defined in the SAP if necessary.

For missing data (not linked to intercurrent events), *i.e.* participants without documentation of death (lost to follow-up, withdrawal of consent, administrative end of study), the OS will be censored on the last contact date the participant was known to be alive or the cut-off date, whichever is earlier.

The same subgroup analyses as used for the primary estimand will be done.

10.1.2.4.2.3. Supplementary estimand based on OS

One supplementary estimand based on OS is defined in order to assess the effect of the randomised treatments on the survival time in all subjects who are KRAS/NRAS and BRAF WT (Double negative [DN]) before participants receive further anti-cancer therapy (while on treatment strategy).

The other estimand based on OS is defined in order to assess the effect of the randomised treatments on the survival time in all subjects who are KRAS/NRAS, BRAF WT and EGFR-extracellular domain WT (Triple negative [TN]) before participants receive further anti-cancer therapy (while on treatment strategy).

The aim of this estimand is to evaluate the effect of the study treatment without a potential effect of another therapy.

The use of data post intercurrent events will be different according to the IE:

- For IE “administration of further anti-cancer therapy” and “treatment switch”: data obtained post IE will not be used for the analysis. OS will be censored at the time of administration of further anti-cancer therapy.
- For IE “treatment discontinuation”: time of death for any cause after treatment discontinuation will be taken into account.

These strategies are aligned with those estimands.

The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).

For missing data (not linked to intercurrent events), *i.e.* participants without documentation of death (lost to follow-up, withdrawal of consent, administrative end of study), the OS will be censored on the last contact date the participant was known to be alive or the cut-off date, whichever is earlier.

Other estimands will be defined in the SAP if necessary.

10.1.2.4.2.4. Secondary estimands based on PFS, OR, DC, DoR, TTNT, TTR and TtPS2

Secondary estimand based on PFS

One secondary estimand of interest is the effect of the randomised treatments on progression-free survival in all subjects before participants receive further anti-cancer therapy (while on treatment strategy). For participants who start the subsequent anti-cancer therapy before disease progression or death will be censored at the date of last evaluable tumour assessment prior to the date of any subsequent anti-cancer therapy. This is aligned with the estimand and the while on treatment strategy.

The other secondary estimand of interest is the effect of the randomised treatments on progression-free survival in all subjects regardless of whether or not intercurrent events occur (treatment policy strategy). All data collected during the trial regardless of occurrence of an IE will be used. This is aligned with the treatment policy strategy.

The following analyses will be done as primary analyses:

- The distribution of PFS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- PFS for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median and survival probabilities at 2, 4, 6 and 8 months along with the corresponding 2-sided 95% CI for the estimates.
- The hazard ratio of PFS with its 95% confidence interval will be estimated with a stratified Cox proportional hazard model (stratification factors based on IWRS data).

The following analyses will be done as sensitivity analyses:

- An analysis that considers clinical progression and administration of further anti-cancer therapy as PFS events in addition to the radiological progression or death.
- PFS analysis based on PPS.

For missing data (not linked to intercurrent events), *i.e.* participants who were lost to follow-up or who have withdrawn their consent without radiological progression or reached the time point of analysis without a known record of death or radiological progression, the PFS will be censored at the date of last evaluable tumour assessment or the cut-off date, whichever is earlier.

The same subgroup analyses as used for the primary estimand will be done for PFS.

Secondary estimands based on ORR and DCR

Other secondary estimand of interest are the effect of the randomised treatments on response in all subjects before participants receive further anti-cancer therapy.

Responses recorded after intercurrent event will be excluded. This is aligned with the estimand and the treatment while on treatment strategy.

The following analyses will be done:

- OR based on the investigator's tumour assessment will be compared in the FAS between treatment arms using a stratified Cochran-Mantel-Haenszel (CMH) test. A 2-sided 95% CI for the difference in ORR between the two treatment arms will also be provided based on the normal approximation. If required, a Fisher's exact test and 2-sided 95% Clopper-

Pearson CIs will be used. A 2-sided 95% CI for the difference in ORR between the two treatment arms will also be provided based on the normal approximation.

- DC based on the investigator's tumour assessment will be compared in the FAS between treatment arms using a stratified CMH test. A 2-sided 95% CI for the difference in DCR between the two treatment arms will also be provided based on the normal approximation. If required, a Fisher's exact test and 2-sided 95% Clopper-Pearson CIs will be used. A 2-sided 95% CI for the difference in DCR between the two treatment arms will also be provided based on the normal approximation.

Secondary estimands based on DoR, TTNT, TTR and TtPS2
Responses recorded after intercurrent event will be excluded. This is aligned with the estimand and the treatment while on treatment strategy.

The following analyses will be done:

- The distribution of DoR per investigator's tumour assessment will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- DoR per investigator's tumour assessment for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median along with the corresponding 2-sided 95% CI for the estimate.
- The distribution of TTNT will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- TTNT for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median along with the corresponding 2-sided 95% CI for the estimate.
- The distribution of TTR per investigator's tumour assessment will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- TTR per investigator's tumour assessment for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median along with the corresponding 2-sided 95% CI for the estimate.
- The distribution of TtPS2 will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance (stratification factors based on IWRS data).
- TtPS2 for each arm will be summarized using Kaplan Meier curves and further characterised in terms of the median along with the corresponding 2-sided 95% CI for the estimate.

10.1.2.5. Quality of Life analysis

Endpoints:

- EORTC QLQ-C30 questionnaire.
- EORTC EQ-5D-5L questionnaire.

10.1.2.5.1. Analysis

10.1.2.5.1.1. EORTC QLQ-C30

The raw QoL data will be scored according to the EORTC scoring manual and the change in score from baseline in the global health status (GHS) scale is identified as the primary QoL variable of interest.

The completion and compliance rates will be summarised by treatment group for each scheduled assessment timepoints.

The completion rate is defined as the rate of participants who completed the QoL instrument among participants in the QoL analysis set.

The compliance rate is defined as the rate of participants who completed the QoL instrument among participants still on treatment at each visit.

Baseline values and changes in scores from baseline (GHS and each sub-scale score) will be summarized at each scheduled assessment time point descriptively.

A repeated-measures mixed-effects model (SAS PROC MIXED) that includes terms for treatment arms, baseline stratification factors, baseline sub-scale score and time of visit will be used to compare the two treatment groups with respect to changes from baseline in the GHS and each sub-scale score longitudinally over time.

Time to definitive ≥ 10 points deterioration from baseline in the GHS and in each sub-scale, will be compared between the two treatment arms in the QoL analysis set using the stratified log-rank test at a 2-sided 5% level of significance (strata based on IWRS data). Death will be considered to be a deterioration event of QoL. Participants receiving any further anti-neoplastic therapy before definitive worsening will be censored at the date of their last QoL assessment before starting this therapy. Participants who have not worsened as of the cut-off date for the analysis will be censored at the date of their last assessment (questionnaire) before the cut-off. Participants without evaluable questionnaire at baseline will be censored at their randomisation date + 1 day. The distributions will be described using Kaplan-Meier curves including the median time to definitive 10 points deterioration.

10.1.2.5.1.2. EORTC EQ-5D-5L

The dimensional 5-level system will be converted into a single index utility score: the utility index will be derived according to specific country algorithms.

The completion and compliance rates will be summarised by treatment group for each scheduled assessment timepoints.

The completion rate is defined as the rate of participants with evaluable EQ-5D-5L assessment among participants of the EQ-5D-5L analysis set.

The compliance rate is defined as the rate of participants with evaluable EQ-5D-5L assessment among participants still on treatment at each visit.

A breakdown table to include the proportions of reported problems (no problems, slight problems, moderate problems, severe problems, or extreme problems) at baseline *versus* each scheduled assessment timepoint will be presented in each dimension of EQ-5D-5L by treatment arms in the EQ-5D-5L analysis set.

Baseline values and changes in score from baseline in EQ-5D-5L VAS and EQ-5D-5L health utility index will be presented by treatment arms at each scheduled assessment timepoint by descriptive statistics (N, mean/proportion median, SD, Q1, Q3).

A repeated-measures mixed-effects model (SAS PROC MIXED) that includes terms for treatment, baseline stratification factors, baseline score and time of visit will be used to compare the two treatment groups in the EQ-5D-5L analysis set with respect to changes from baseline in the EQ-5D-5L VAS and EQ-5D-5L health utility index.

10.1.2.6. Safety analysis

All participants included in the Safety set (SS) will be evaluated by treatment arms unless otherwise specified.

10.1.2.6.1. Adverse events

Treatment-emergent adverse events are defined as any AEs reported from the date of first administration of IMP to 30 days after the last date of IMP. Frequency and percentages of participants will be summarized for: any grade TEAE, Grade 3 or higher TEAE, IMP related TEAE, serious TEAE, TEAE leading to dose modification, TEAE leading to IMP discontinuation, death and TEAE leading to death. Adverse events will be summarized by SOC and preferred term. All AE data will be listed by participant.

Of note, the seriousness and the relationship to the IMP of the adverse event correspond to the investigator opinion or, in case of events upgraded by the sponsor for seriousness or for causality in case of SAE, to the sponsor opinion.

Number and percentage of participants who experienced a DLT will be summarized and listed for Safety Lead-In part.

10.1.2.6.2. Clinical laboratory evaluation

For haematological, biochemistry, urinary and coagulation parameters, descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and, on change from baseline to last post-baseline value under treatment will be provided.

For all clinical laboratory parameters (except urinary parameters), the following analysis will be performed: Laboratory parameters classified (number and percentage of participants in each class) according to these reference ranges and using shift tables from baseline to the worst (high and/or low) values under treatment.

10.1.2.6.3. Vital signs, clinical examination and other observations related to safety

10.1.2.6.3.1. Vital signs and clinical examination

Vital signs and clinical examination will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment.

10.1.2.6.3.2. Electrocardiogram

ECG parameters will be described, in terms of value at baseline, value at each post-baseline visit under treatment and last post-baseline value under treatment; as well as, for quantitative endpoints, in terms of change from baseline to each post baseline visit under treatment and to last post-baseline value under treatment. Moreover, values and changes form baseline of corrected QT interval will be described in classes, considering thresholds defined in ICH E14

(*i.e.*, ≤ 450,] 450; 480],] 480; 500] and > 500 ms for values, and ≤ 30,] 30; 60] and > 60 ms for changes).

10.1.2.7. Biomarkers analysis

Based on ctDNA, pharmacodynamic biomarkers, potential predictors of response as well as mechanisms of resistance could be explored. More details will be described in the SAP.

10.1.2.8. Interim analysis

There are 3 planned interim analyses: an early futility interim analysis (interim 0) will be triggered when ~83 PFS events have observed in DN population which is designed under a hypothetical Phase 2 study that would have 95% power to detect a true hazard ratio for PFS of HR ≤ 0.525 (assumptions of mPFS 4 months *versus* 2.1 months) with a one-sided alpha level of 0.10. This futility analysis will use both PFS and OS data to calculate the Predictive Probability of Success incorporating historical data based on an extension of the methodology proposed by Saint Hilary *et al.*[40] for decision making. More details on the methodology and PPoS calculation will be provided in SAP. Study will be stopped for futility if the calculated PPoS < 10%. If the study proceeds, an interim OS analysis for futility (interim 1) will be conducted when approximately 33.3% of the planned final number of OS events in DN population (*i.e.* 128 of 383 OS events) have been observed. If the study proceeds, a second interim analysis will occur to evaluate futility and efficacy (interim 2) when 255 events (66.7% of the planned final number of OS events) have occurred in DN population.

10.2. Determination of sample size

Approximately 25 participants will be evaluated in Safety Lead-In part. The DMC will initially determine tolerability after 6 evaluable participants have been treated. If ≤ 2 participants out of the first 6 experience a DLT, and the DMC based on the totality of safety data determines the doses to be tolerable, then the Safety Lead-In will be expanded by an additional cohort of 6 participants. The DMC will again assess the tolerability when 12 participants have been enrolled and the 12th participant has completed the first treatment cycle. If ≤ 3 participants experience a DLT, and the DMC based on the totality of safety data determines the doses to be tolerable, the Safety Lead-In will be expanded to add another 13 participants, for a total of 25 participants. The DMC will meet again at the end of the Safety Lead-In part when approximately 25 participants have been treated.

The primary endpoint of Randomised part will be OS in DN population, the key secondary endpoint will be OS in TN population. The primary hypothesis will test whether treatment with trifluridine/tipiracil in combination with futuximab/modotuximab compared with trifluridine/tipiracil alone leads to OS prolongation in DN population. A total of 500 patients will be randomised in a 1:1 ratio to the 2 treatment arms and followed-up until at least 383 OS events are observed across the 2 treatment arms will provide 90% power to detect a true hazard ratio (HR) ≤ 0.71 (median OS: 8.5 *vs* 12 months) using a stratified log-rank test (stratified by Performance Status [PS] [0 *vs* 1], extracellular domain EGFR mutations [extracellular domain (ECD)] [presence *vs* absence] and previous regimens of treatment [2 *vs* ≥ 3]), with an overall 1-sided significance level of 0.025 for the primary endpoint (adjusted for OS interim analyses). Assuming enrolment over 21 months with a ramp-up to a maximum of 30 patients per month and a lost-to-follow-up rate of 7% across both treatment arms, the timing of the primary analysis is expected to be at 37.5 months after 1st randomisation.

To control type I and type II errors, the planned interim analyses for OS will utilise O'Brien Fleming alpha spending function (the Lan-DeMets method)[41] for efficacy boundaries determination and Hwang-Shih-Decani (non-binding)[42] beta spending function with γ parameter equal to -1.5 for futility boundary determination. If OS in DN population is significant at final analysis when 383 OS events have occurred in the DN population, OS in the TN population will be tested at the full alpha level, *i.e.*, 0.025. The OS testing plan for the primary endpoint has 90% power conditional on passing the early futility interim analysis (interim 0).

Since the boundary is dependent on the number of OS events, the actual boundary used will be re-calculated, incorporating the spending function as defined, based on the number of actual OS events analysed at the time of the interim analysis relative to the planned 383 events. The boundary for the final analysis will similarly be adjusted in accordance with the amount of remaining alpha. The interim analysis specifications per the plan are provided in Table (10.2) 1.

Table (10.2) 1 - Interim analysis specifications

Analysis	IF	# OS Events	Efficacy				Futility			
			$Z_{boundary}$	$P_{boundary}$	α spend	HR_{crit}	$Z_{boundary}$	$P_{boundary}$	β spend	HR_{crit}
Interim 1	0.334	128	NA	NA	NA	NA	-0.132	0.553	0.019	1.024
Interim 2	0.666	255	2.511	0.006	0.006	0.73	0.997	0.159	0.049	0.883
Final	1	383	1.993	0.023	0.025	0.816	1.993	0.023	0.1	0.816

IF = information fraction. $Z_{boundary}$ is the critical test statistic value at which futility (< Z) or efficacy (> Z) would be concluded. $P_{boundary}$ is the critical one-sided p-value threshold for the comparison (> p for futility, < p for efficacy). α spend and β spend are the amount of type I and type II error spent at each analysis, respectively. HR_{crit} is the observed hazard ratio threshold (> HR for futility, < HR for efficacy).

The DMC will be responsible for evaluating the interim futility and efficacy analysis and making a recommendation about early termination due to observed study results.

10.3. Pharmacokinetic analyses and PK/PD analysis

10.3.1. Safety Lead-In part

In order to inspect the pharmacokinetic profiles of futuximab/modotuximab and trifluridine/tipiracil when given in combination, external Visual Predictive Check on the individual serum for futuximab/modotuximab and plasma for trifluridine/tipiracil concentrations will be performed. For this, previously developed population PK models for futuximab/modotuximab, and trifluridine/tipiracil, will be used to perform simulations (1000 replicates) of the expected concentration-time profile of these compounds administered as monotherapies. The [P5; P95] prediction interval (*i.e.* encompassing 90% of overall predicted concentrations) and the median of the overall simulated plasma/serum concentration-time curves will be calculated and will be graphically superimposed with observed concentration-time data.

10.3.2. Randomised Part

Concentrations of futuximab/modotuximab and trifluridine/tipiracil will be analysed by a population modelling approach, described in a separated Data Analysis Plan (DAP). This analysis will provide pharmacokinetic parameters (such as Cmax and AUC) and their associated variability in participants and will be the object of a separate report. Interim analyses using this approach could be performed if required.

Exploratory assessment of the relationship between exposure and pharmacodynamics (as safety and efficacy) will be performed and if applicable, population pharmacokinetic-pharmacodynamic (PK/PD) models will be developed and a DAP will be set

up and reported separately. The pharmacometrics analysis may require other model-based approaches to better describe the PK/PD of the compound. In this case a description of these methods would be included in a specific DAP.

The data of the present study could be pooled with data from previous or future clinical studies, if relevant. It could also be combined with literature data if required.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator will allow the monitors, the persons responsible for the audit, the representatives of the IRB/IEC, and of the Competent Authorities to have direct access to source data / documents.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Study monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the structure mentioned in document entitled Administrative part of clinical study protocol.

If on-site monitoring cannot be accomplished, remote Source Data Verification may be performed in accordance with local regulations

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

12.1.1. Before the study

The investigator will allow the monitor to visit the site and facilities where the study will take place to ensure compliance with the protocol requirements.

Training sessions may be organised for the investigators and/or instruction manuals may be given to the investigators.

12.1.2. During the study

The investigator will allow the monitor to:

- Review of the study site's processes and procedures.
- Verify appropriate clinical investigator supervision of study site staff and third-party vendors.
- Inspect the site, the facilities and the material used for the study.
- Meet all members of his/her team involved in the study.
- Consult the documents relevant to the study.

- Have access to the e-CRF (*i.e.* Access to an analogic phone line or his/her computer) and/or to the e-PRO service provider's database to check that they been filled out correctly.
- Check that the e-CRF and e-PRO have been filled out correctly.
- Directly access source documents for comparison of data therein with the data in the electronic case report forms and/or to the e-PRO/e-COA service provider's database.
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements.

The study monitoring will be carried out at regular intervals, depending on the recruitment rate and / or the investigation schedule, and arranged between the investigator and monitor.

All information dealt with during these visits will be treated as strictly confidential.

12.2. Computerised medical file

If computerised medical files are used, and if the computer system allows, no change made in the medical files by the investigator should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information (*i.e.* audit trail). The investigator will save data at regular intervals.

The investigator must guarantee the integrity of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

If the computerised medical files are considered as not validated by the sponsor, the investigator undertakes:

- At the start of the study, to print the medical files of all participants allowing a reliable verification of the study criteria (*e.g.* Medical history/previous treatments/ characteristics of the studied disease documented within the period of time defined by the study protocol).
- During the study, to print in real time each data entry and each data change.

The investigator or designated person of the site team will personally sign, date and give the number of pages on the first or last page of each print-out. At each visit by the monitor, the investigator will provide all the print-outs of the medical files of the participants. The monitor will personally sign and date the first (or last) page then initial all pages in each paper print-out.

If the computer system allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

If the computerised medical files are considered as validated by the sponsor, the investigator undertakes to give access to the monitor to the computerised medical files of all participants. If the monitor cannot access to the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the records of the changes made to the medical files of the participants. Each print-out will be personally dated and signed, by the investigator and the monitor on the first page. The number of pages will also be indicated by the investigator and the monitor on the first page.

The investigator undertakes to keep:
- All medical file print-outs signed and dated by him/her and by the monitor when the computer system is considered as not validated by the sponsor.
- If the computer system used allows changes to be made, the print-outs of the audit trail when the computer system is considered as not validated by the sponsor or when the monitor cannot access to the audit trail in the computer system.
- All original source-documents (originals of specific examinations, informed consent forms, therapeutic unit tracking form...).

12.3. Audit - Inspection

The investigator should be informed that an audit may be carried out before, during or after the end of the study.

If on-site auditing cannot be accomplished, remote audit may be performed in accordance with local regulations.

The investigator should be informed that the Competent Authorities may also carry out an inspection in the facilities of the sponsor and/or the study centre(s). The sponsor will inform the investigators concerned immediately upon notification of a pending study centres inspection. Likewise, the investigator will inform the sponsor of any pending inspection.

The investigator must allow the representatives of the Competent Authorities and persons responsible for the audit:
- To inspect the site, facilities and material used for the study.
- To meet all members of his/her team involved in the study.
- To have direct access to study data and source documents.
- To consult all the documents relevant to the study.

If the computerised medical file is considered as not validated, the investigator undertakes to provide all the source-documents and the print-outs of the medical files of the participants and, if the computer system used allows, the record of the changes made during the study.

If the computerised medical file is considered as validated, the investigator undertakes to:
- Give access to the representatives of the Competent Authorities and persons responsible for the audit to the computerised medical files of all participants.
- Provide the print-outs of the changes made during the study, if the tracking of the changes made to the medical files cannot be accessed in the computer.

12.4. Supervisory committees

12.4.1. Steering Committee

The Steering Committee (SC) members will be appointed by the sponsor prior to the initiation of the study. The SC will comprise experts in colorectal cancer and sponsor representatives. The SC will be involved in the overall supervision of the study, will implement measures if needed to reduce deviations from the protocol to a minimum and will be involved in periodic reviews of the progress of the study. Details on the role of the SC and working procedures will be defined in the SC Charter.

12.4.2. Data Monitoring Committee

Safety data collected during the Safety Lead-In part will be reviewed by a DMC to assess if 1) the drug combination is tolerable, 2) if the MTD has been exceeded, and 3) if the randomised portion of the study may proceed.

During the Safety Lead-In part, the DMC will initially determine tolerability after 6 evaluable participants, then after 12 participants treated and finally when all 25 participants will have been enrolled.

Throughout the Safety Lead-in part DLT occurrence will be followed on a continuous base and if the number of participants who experienced at least one DLT in each cohort exceeds the maximum number of DLTs that is considered safe (≥ 3/6 evaluable participants, ≥ 4/12 evaluable participants, ≥ 6/18 evaluable participants and ≥ 8/25 evaluable participants), at any time during the Safety Lead-In part the enrolment will be halted, an urgent DMC meeting will be organized and DMC will provide recommendations on study continuation, modification or discontinuation.

For Safety Lead-In safety and tolerability evaluation process see Section 4.1.3.4.

During the Randomised part the DMC will meet approximately every 4 months in the first year and approximately twice a year thereafter and at the planned interim analysis as well.

The composition and role of the DMC will be described in a charter finalised before the trial is initiated.

DMC recommendations will be forwarded to the IRB/IEC / Competent Authorities only if relevant for the safety of participants.

12.4.3. Blinded Independent Central Review (only for Randomised part)

All imaging data acquired for efficacy purposes (*e.g.*, CT/MRI scans) will be transmitted to an imaging vendor for quality check and storage. Image transmission to the imaging vendor should be performed according to the imaging vendor manual. BICR review of stored imaging data will be performed only if needed, retrospectively, and will not be provided to investigators for decisions regarding patient treatment. Should BICR be needed, the images will be read by readers who are blinded to treatment assignment and to other clinical data as specified in the BICR charter.

13. ETHICS

13.1. Institutional Review Board(s)/Independent Ethics Committee(s)

The study protocol, the "Participant information and consent form" document, the list of investigators, the insurance certificate, the futuximab/modotuximab Investigator's Brochure, the Product Information of trifluridine/tipiracil will be submitted to IRB(s)/IEC(s) by the investigator(s) or the national coordinator(s) or the sponsor in accordance with local regulations.

The study will not start in a centre before written approval by corresponding IRB/IEC(s) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved has been obtained.

13.2. Study conduct

The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki 1964, as revised in Fortaleza, 2013 (Appendix 1), with the GCP and with the applicable regulatory requirements.

13.3. Participant information and informed consent

In any case, the participant (and/or his/her legal representative, when required) must be informed that he/she is entitled to be informed about the outcome of the study by the investigator.

The investigator or a person designated by him/her is required to collect written consent from each participant before his/her participation in the study. Prior to this, the investigator or his/her delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study, as well as the nature of the IMPs.

The participant will be provided with an information and consent form in clear, simple language. He/she must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

One, or two if required by local regulation, original information and consent form(s)must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent. ICF will be available electronically if requested by the patient in the randomised part only. The electronic signature for the ICF will not be available.

If the participant is unable to read, an impartial witness should be present during the entire informed consent discussion. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent.

The participant will be given one signed copy (or original if required by local regulation) of the information and consent form. A signed original will be kept by the investigator.

A copy of the information and consent form in the language(s) of the country is given in the “Participant information and consent form” document attached to the protocol.

13.4. Modification of the information and consent form

Any change to the information and consent form constitutes an amendment to this document and must be submitted for approval to the IRB/IEC(s), and if applicable to the Competent Authorities.

A copy of the new version(s) of the information and consent form(s) in the language(s) of the country will be given in the amendment to the “Participant Information and consent form”.

Such amendments may only be implemented after written approval of the IRB/IEC has been obtained and compliance with the local regulatory requirements, except for an amendment required to eliminate an immediate risk to the study participants.

Each participant affected by the amendment and/or his/her legal representative must complete, date and co-sign one, or two if required by local regulation, original(s) of the new version of

the information and consent form together with the person who collected the informed consent (and an independent witness, if applicable). He/She/They will receive one signed copy (or original, if required by local regulation) of the amendment to the information and consent form(s). The signed original(s) will be kept by the investigator.

14. DATA HANDLING AND RECORD KEEPING

14.1. Study data

A 21 CFR Part 11-compliant electronic data capture system will be used in this study. An electronic case report form (e-CRF) is designed to record the data required by the protocol and collected by the investigator.

The e-CRF will be produced by I.R.I.S. in compliance with its specifications. The investigator or a designated person from his/her team will be trained for the use of the e-CRF by the sponsor.

Data entry at the investigator's site will be performed by the investigator or by the designated person from his/her team after completion of the participant's Medical File.

Upon entry, data will be transmitted via the Internet from the study centre to the study database.

The investigator or the designated person from his/her team agrees to complete the e-CRF, at each participant visit, and all other documents provided by the sponsor (*e.g.* documents relating to the IMP management…).

Data recorded directly on e-CRF and considered as source data (Section 4.5) must be collected immediately in the e-CRF. The other e-CRF forms must be completed as soon as possible following each visit.

All corrections of data on the e-CRF must be made by the investigator or by the designated person from his/her team using electronic data clarifications according to the provided instructions. All data modification will be recorded using the audit trail feature of the e-CRF software, including date, reason for modification and identification of the person who has made the change.

To ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorised personnel only, whether resident within the investigator's sites, the sponsor or third parties.

Data will be verified in accordance with the monitoring strategy defined for the study. After comparing these data to the source documents, the monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible.

Data can be frozen during the study after their validation. However, the investigator has the possibility to modify a data if deemed necessary via a request to the sponsor.

The investigator or authorised member for sign-off must confirm the authenticity of the data recorded in the e-CRF by signing the e-CRF in a timely manner as defined in the e-CRF completion guide.

After the last visit of the participant, the investigator or co-investigator must attest the authenticity of the data collected in the e-CRF by entering his/her username and password.

After the data base lock, the investigator or an authorised member of his/her team will have to download from the e-CRF an electronic file containing participant data from his/her centre for archiving it in the study file (Section 14.3).

14.2. Data management

Data are collected via an e-CRF and stored in a secured database.

For data collected on the e-CRF, the Clinical Data Management of I.R.I.S. is responsible for data processing including data validation performed according to a specification manual describing the checks to be carried out. As a result of data validation, data may require some changes. An electronic data clarification form is sent to the investigator who is required to respond to the query and make any necessary changes to the data.

For data transferred from e-PRO, the Clinical Data Management of I.R.I.S. is responsible for data transfer: e-PRO provider provides electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

For data transferred from IWRS, the Clinical Data Management of I.R.I.S. is responsible for data transfer: IWRS provider provides electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

For data transferring from central reading, the Clinical Data Management of I.R.I.S. is responsible for data transfer: central reading provider provides electronic transfer of computerised data to the Clinical Data Management of I.R.I.S. Data are transferred according to a transfer protocol issued by the I.R.I.S. data manager.

The Medical Data Department of I.R.I.S. is responsible for data coding including:
- medical / surgical history, adverse events and procedures using MedDRA.
- medications using World Health Organization, Drug Dictionary (WHO-Drug).

The coding process is described in a specification manual.

The investigator ascertains he/she will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its representatives monitoring the study, if any, to request approval of a protocol deviation, as no deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC it cannot be implemented. All important protocol deviations will be recorded and reported in the clinical study report.

When data validation is achieved, a review of the data is performed according to the sponsor standard operating procedure. When the database has been declared to be complete and accurate, it will be locked, and the study treatments codes will be unblinded and made available for data analysis.

14.3. Archiving

The investigator will keep all information relevant to the study for at least 25 years after the end of the study, or more if specified by the local regulation.

At the end of the study, the investigator or an authorised member of his/her team will download an electronic copy of each participant's data from the e-CRF and should keep it in a reliable, secure and durable location. The file includes all data and comments reported in the e-CRF, the history of all queries and signatures and the full audit trail reports.

The file must include appropriate restrictions (password protection) and adequate protection from loss, physical damage or deterioration for the duration of the archiving period.

All data reported in e-COA, e-PRO will be provided to the investigator's site.

15. INSURANCE

I.R.I.S., or any parent company of SERVIER GROUP in charge of the management of clinical trials, is insured under the liability insurance program subscribed by LES LABORATOIRES SERVIER to cover its liability as sponsor of clinical trials on a worldwide basis.

Where an indemnification system and/or a mandatory policy are in place, I.R.I.S. or any parent company of SERVIER GROUP will be insured under a local and specific policy in strict accordance with any applicable law.

All relevant insurance documentation is included in the file submitted to any authorities' approval of which is required.

16. OWNERSHIP OF THE RESULTS - DATA SHARING POLICY AND PUBLICATION POLICY

I.R.I.S., acting as the study sponsor, assumes full responsibilities relating to this function and retains exclusive property rights over the results of the study, which it may use as it deems fit.

I.R.I.S. will ensure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalisation of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Any project of publication and/or communication relative to the study and/or relative to the obtained results during the study or after the study end shall be submitted to the sponsor. in accordance with the guidelines set forth in the applicable publication policy or financial agreement.

The investigator, who submitted the project, shall take the sponsor's comments into due consideration.

As the study is a multicentre one, the first publication must be performed only with data collected from several study sites and analysed under the responsibility of I.R.I.S. The investigator commits himself not to publishing or communicating data collected in only one centre or part of the centres before the publication of the complete results of the study, unless prior written agreement from the other investigators and I.R.I.S. has been provided.

Data Sharing Policy is available at https://clinicaltrials.servier.com/data-request-portal/. Researchers can ask for a study protocol, participant-level and/or study-level clinical trial data including clinical study report.

They can ask for all interventional clinical studies:

- submitted for new medicines and new indications approved after 1 January 2014 in the European Economic Area (EEA) or the US.
- Where Servier or an affiliate are the Marketing Authorisation Holders. The date of the first Marketing Authorisation of the new medicine (or the new indication) in one of the EEA Member States will be considered within this scope.

In addition, Servier's data sharing policy includes all interventional clinical studies in participants:

- Sponsored by Servier.
- With a first participant enrolled as of 1 January 2004 onwards.
- For New Chemical Entity or New Biological Entity (new pharmaceutical form excluded) for which development has been terminated before any marketing authorisation approval.

The datasets generated and/or analysed during the current study will be available upon request from www.clinicaltrials.servier.com after the Marketing Authorisation has been granted.

Summary results and a lay summary will be published on clinicaltrials.servier.com within 12 months after the end of the study.

The results will be submitted for publication in scientific literature within 18 months after the end of the study.

17. ADMINISTRATIVE CLAUSES

17.1. Concerning the sponsor and the investigator

17.1.1. Persons to inform

In accordance with local regulations, the investigator and/or the sponsor will inform, the Director of the medical institution, the pharmacist involved in the study and the Director of the analysis laboratory.

With the agreement of the participant, the investigator will inform the participant's general practitioner about his/her participant's participation in a clinical study.

17.1.2. Substantial protocol amendment and amended protocol

If the protocol must be altered after it has been signed, the modification or substantial amendment must be discussed and approved by and approved by the International Coordinator and the sponsor.

The substantial protocol amendment must be drafted in accordance with the sponsor standard operating procedure and an amended protocol must be signed by both parties. Both documents must be kept with the initial protocol.

All substantial amendments and corresponding amended protocols must be sent by the investigator(s) or the coordinator(s) or the sponsor, in accordance with local regulations, to the IRB/IEC that examined the initial protocol. They can only be implemented after a favourable opinion of the IRB/IEC has been obtained, local regulatory requirements have been complied with, and the amended protocol has been signed, except for a measure required to eliminate an immediate risk to the study participants.

When the submission is performed by the investigator or the International Coordinator, the latter must transmit a copy of IRB/IEC's new written opinion to the sponsor, immediately upon receipt.

Furthermore, the substantial amendment and amended protocol are to be submitted to the competent authorities in accordance with local regulations.

17.1.3. Final study report

The study report(s) will be drafted by Biostatistics - Centre of Excellence Methodology and Valorisation of Data of I.R.I.S. in compliance with I.R.I.S. standard operating procedure.

The sponsor's representative and International Coordinator must mutually agree on the final version. One copy of the final report must be dated and signed by the International Coordinator and by the Director of the Therapeutic Area.

The clinical study report, the summary of the results of the clinical trial together with a summary that is understandable to a layperson will be submitted where applicable within 1 year after the end of the clinical trial worldwide.

If the clinical trial is still on-going but ended in the European countries, the statistical analysis will not be relevant before the end of the study worldwide. Therefore, the timelines defined above still apply.

17.2. Concerning the sponsor

The sponsor undertakes to:

- Supply the investigator with adequate and sufficient information concerning the IMP and the NIMP administered during the study to enable him/her to carry out the study.
- Supply the investigator with the trifluridine/tipiracil Product Information.
- Supply the investigator with the futuximab/modotuximab Investigator's Brochure, the one best suited to ensure participant safety, and any potential updated version during the study:
  - For the IMP if marketed, to be appended to Investigator's Brochure (Section 4. Guidance for the investigator).
  - For all reference products used in the study.
  - For all NIMPs available on the market.
- Obtain any authorisation to perform the study and/or import licence for the IMPs and NIMPs administered that may be required by the local authorities before the beginning of the study.
- Provide the International Coordinator annually, or with another frequency defined by the local regulations, with a document describing study progress which is to be sent to the IRB/IEC(s).
- Take all the necessary precautions to maintain the safety of the processed data, in particular their confidentiality, their integrity and their availability, by assessing risks identified concerning personal data protection. The following measures will be implemented (non-exhaustive):
  - Management of authorisation to access to personal data (e-CRF).
  - Identification and authentication measures before accessing personal data (e-CRF).
  - Traceability measures for the access to and modification of personal data (e-CRF).
  - Secured data transfer.
  - Time limit for storing personal data.
- Handle any security breach by implementing an internal committee (including CISO, DPO, communication department…) in order to qualify the security incident (Information systems, nature and number of personal data impacted), to define an action plan for corrective actions and to notify to relevant person (authority and/or if needed individuals).

17.3. Concerning the investigator

17.3.1. Confidentiality - Use of information

All documents and information given to the investigator by the sponsor with respect to futuximab/modotuximab and trifluridine/tipiracil and study CL3-95026-001 are strictly confidential.

The investigator expressly agrees that data on his/her professional and clinical experience is collected by the sponsor on paper and computer and stored for its sole use relating to its activities as the sponsor of clinical trials, in accordance with GCP.

He/she has a right to access, modify, and delete his/her own personal data by applying to the sponsor.

In case participant wants to exercise his/her rights regarding personal data protection, he/she will contact the investigator. The investigator will forward the request to the sponsor (Appendix 8).

The investigator agrees that he/she and the members of his/her team will use the information only in the framework of this study, for carrying out the protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the sponsor. The clinical study protocol given to the investigator may be used by him/her or his/her colleagues to obtain the informed consent of study participants. The clinical study protocol as well as any information extracted from it must not be disclosed to other parties without the written authorisation of the sponsor.

The investigator must not disclose any information without the prior written consent from I.R.I.S., except to the representatives of the Competent Authorities, and only at their request. In the latter case, the investigator commits himself/herself to informing I.R.I.S. prior to disclosure of information to these authorities.

A participant screening log and a full identification and enrolment list of each participant will be completed and kept in a safe place by the investigator who should agree to provide access on site to the auditor and/or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

The participant screening log must be completed from the moment the investigator checks that a participant could potentially take part in the study (by assessment of participant medical history during a visit or by examination of the medical file).

17.3.2. Organisation of the centre

Every person to whom the investigator delegates under his/her responsibility a part of the follow-up of the study (co-investigator, nurse…) and any other person involved in the study for this centre (cardiologist, pharmacist…) must figure in the "Organisation of centre" document.

This document should be filled in at the beginning of the study and updated at any change of a person involved in the study in the site.

17.3.3. Documentation supplied to the sponsor

The investigator undertakes before the study begins:

- To provide his/her dated and signed English Curriculum Vitae (CV) (maximum 2 pages) or to complete in English the CV form provided by the sponsor and to send it to the sponsor, together with that of his/her co-investigator(s).
- To provide a detailed description of the methods, techniques, and investigational equipment, and the reference values for the parameters measured.
- To provide any other document required by local regulation.
- To send a copy of the IRB/IEC's opinion with details of its composition and the qualifications of its constituent members.

The CV of other members of the team involved in the study (if possible, in English) will be collected during the course of the study (at least, members involved in the participants' medical follow-up/study-related decision process and persons involved in the measurement of main assessment criteria).

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19. APPENDICES

Appendix 1: World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington DC, USA, 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of participants, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on participants or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their participants in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the participants who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risk, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor on-going studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious participants, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the participants who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Intervention in Clinical Practice

In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Patient performance status

Status Karnofsky	Grade	Status ECOG* - ZUBROD / WHO
Normal, no complaints; no evidence of disease.	100	
	0	Fully active, able to carry on all pre-disease performance without restriction.
Able to carry on normal activity; minor signs or symptoms of disease.	90	
Normal activity with efforts; some signs or symptoms of disease.	80	
	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work.
Cares for self; unable to carry on normal activity or to do active work.	70	
Requires occasional assistance, but is able to care for most of his personal needs.	60	
	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
Requires considerable assistance and frequent medical care.	50	
Disabled; requires special care and assistance.	40	
	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Severely disabled; hospital admission is indicated although death not imminent.	30	
Very sick; hospital admission necessary; Active supportive treatment necessary.	20	
	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Moribund; fatal processes progressing rapidly.	10	
Dead	0 5	Dead

** As published in Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.*

Appendix 3: Cockroft formula

Cockroft formula (Cockroft *et al.*, 1976)

CreatClear [mL/min] = ((140 – Age [years]) / SerumCreat [µmol/L]) * Weight [kg]* Sex

Male = 1.23
Female = 1.04

Appendix 4: New York Heart Association (NYHA) classification

The Stages of Heart Failure NYHA Classification

In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the NYHA functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5: EQ-5D-5L

EQ-5D-5L	
EQ-5D-5L Tablet version	
English (UK)	Country (Language)
Health Questionnaire	Health Questionnaire
English version for the UK	Version (Target Language)
	Version (English)
Please tap the ONE box that best describes your health TODAY.	Instruction
MOBILITY	**Mobility**
I have no problems in walking about	MB1
I have slight problems in walking about	MB2
I have moderate problems in walking about	MB3
I have severe problems in walking about	MB4
I am unable to walk about	MB5
SELF-CARE	**Self-care**
I have no problems washing or dressing myself	SC1
I have slight problems washing or dressing myself	SC2
I have moderate problems washing or dressing myself	SC3
I have severe problems washing or dressing myself	SC4
I am unable to wash or dress myself	SC5
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*	**Usual Activities**
I have no problems doing my usual activities	UA1
I have slight problems doing my usual activities	UA2
I have moderate problems doing my usual activities	UA3
I have severe problems doing my usual activities	UA4
I am unable to do my usual activities	UA5
PAIN / DISCOMFORT	**Pain / Discomfort**
I have no pain or discomfort	PD1
I have slight pain or discomfort	PD2
I have moderate pain or discomfort	PD3
I have severe pain or discomfort	PD4
I have extreme pain or discomfort	PD5
ANXIETY / DEPRESSION	**Anxiety / Depression**
I am not anxious or depressed	AD1
I am slightly anxious or depressed	AD2
I am moderately anxious or depressed	AD3
I am severely anxious or depressed	AD4
I am extremely anxious or depressed	AD5
We would like to know how good or bad your health is TODAY.	Vas Line 1
This scale is numbered from 0 to 100.	Vas Line 2
100 means the best health you can imagine.	Vas Line 3
0 means the worst health you can imagine.	Vas Line 4
Please tap on the scale to indicate how your health is TODAY.	Vas Line 5
The best health you can imagine	Top Scale
The worst health you can imagine	Bottom Scale
YOUR HEALTH TODAY	Box Health
Next	button.next
Previous	button.previous
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Disclaimer: *This is a preview of the EQ-5D instrument. It demonstrates the text, questions and response options included in this version. This preview does not represent the final product and should not be used as an official EQ-5D instrument.*	

Appendix 6: EORCT QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

As published in Aaronson NK, *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." Journal of the national cancer institute, 1993:365-376.

Appendix 7: New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1), Eisenhauer, 2009

Measurability of tumour at baseline

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm),
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable),
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT-scan (CT-scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET-scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions,
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above,
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts,
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Tumour response evaluation

Assessment of overall tumour burden and measurable disease

To assess OR or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements.

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (*e.g.* 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

Evaluation of target lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.* 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT-scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions
This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.
Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
PD: Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease
The concept of progression of non-target disease requires additional explanation as follows:
When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
When the patient has only non-measurable disease. This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: *i.e.* an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: *i.e.* not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET (a 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 1: Time point response: patients with target (+/- non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable

When patients have non-measurable disease only (therefore non-target), Table 2 is to be used.

Table 2: Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	on-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = Not evaluable.

1 = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response **is not** required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments.

For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.
Best response determination in trials where confirmation of complete or PR **is** required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = Not evaluable.

1 = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (e-CRF).
In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.
Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an OR: it is a reason for stopping study therapy. The OR status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.
For equivocal findings of progression (*e.g.* very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of tumour re-evaluation
Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certainnon-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.
After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (*e.g.* time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

Confirmatory measurement/duration of response
Confirmation
In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, *i.e.* in randomised trials (Phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response
The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).
The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease
Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).
The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.
Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 8: DATA PROTECTION / GDPR (General Data Protection Regulation of 27 April 2016 n°2016/679) -

INSTRUCTIONS TO INVESTIGATOR FOR HANDLING DATA RIGHTS REQUESTS

In the framework of a research study/clinical trial, a participant to the study may exercise his/her rights, *i.e.* may ask I.R.I.S. (as data controller) for:

- Access to his/her data.
- Rectification of inaccurate/incomplete information.
- Restriction of processing of data.
- Objection to processing of data.
- Data portability (receiving his/her data in a readable format).

In accordance with the Informed Consent Form and information notice provided to participant, we requested participant to contact you first for exercising their rights.

Request for exercise of rights:

- Has to be a written one (either originating from an (e)-mail from a participant or from request expressed orally to you and put in written).
- Has to be sent **by you** by e-mail or by mail **to** I.R.I.S. (as data controller) to central address dataprivacy@servier.com or local Servier address as mentioned in ICF/information notice provided/available.

DO **Instructions to be followed by you**	**DON'T** **What you should not do**
E-mail title: Data protection rights	Do not forward participant e-mail (if applicable)
Study name/number	
Participant number	**No information regarding participant identity**: No participant's name, e-mail address, participant's signature
As soon as possible without exceeding a week	

I.R.I.S. and INVESTIGATOR responsibilities

GDPR requirement:
It is mandatory for I.R.I.S. as data controller to provide an answer to participant/volunteer within 1 month following the request (article 12 of GDPR)
Clinical trials requirements:
It is prohibited for I.R.I.S. as a sponsor to know the identity of the participants/volunteer participating to studies

	I.R.I.S. responsibility	**Investigator responsibility**
Forward/inform I.R.I.S. of the request		YES
Timelines	Answer within 1 month once expressed by the participant	Request: transmitted to I.R.I.S. as soon as expressed by the participant Answer: transmitted by you to participant as soon as sent by I.R.I.S.
Answer the request	YES	

Appendix 9: Management of Infusion-related Reactions

A. Prophylaxis for Infusion-Related Reactions

Premedication for prophylaxis of IRRs will be mandatory prior to each dose of futuximab/modotuximab. All participants must be premedicated with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to include an H2 antagonist and/or acetaminophen.

Required and optional agents, as well as recommended doses, are provided bellow

Premedications for Infusion-Related Reactions		
Drug Class	**Recommended Dose**	**When to Administer prior**
Required Agents		
Glucocorticoid	80-100 mg IV methylprednisolone or equivalent*	approximately 0.5 to 2 hours
Antihistamine (H1 antagonist)	25-50 mg IV diphenhydramine or equivalent**	approximately 0.5 hours
Optional Agents		
Antihistamine (H2 antagonist)	50 mg IV ranitidine or equivalent, or 20 mg IV famotidine or equivalent	approximately 0.5 hours
Acetaminophen	1000 mg IV (where available, or PO) or equivalent	approximately 0.5 hours

Abbreviations (in alphabetical order): IV, intravenous; mg, milligram
**Glucocorticoid premedication may be omitted in participants with insulin-dependent diabetes.*
***Oral H1 antagonists could be used but they should be given 1 hour prior to infusion.*
Note: Doses may be adjusted based on institutional practices. Administration of oral dexamethasone, 10 mg po, (or equivalent) 12 hours and 6 hours prior to administration of futuximab/modotuximab is permissible in participants experiencing IRRs or if an increased incidence or severity of IRRs are observed.

For IRRs while in the study, the following premedication instructions are provided:

- For Grade 1, Grade 2, or Grade 3 reactions, consider additional premedication or adjustment to premedications for subsequent infusions.
- For Grade 4 reactions, not applicable as no further treatment with IMP is allowed.

B. Grading of Infusion-Related Reactions

The NCI-CTCAE v5* definition of IRRs (General Disorders and Administration Site Conditions) is shown below. Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term “Infusion-Related Reaction” and any additional terms (including those not listed here) that best describe the event. Those described should be graded as follows.

Grading of Infusion-Related Reactions					
Adverse Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion related reaction	Mild transient reaction; infusion Interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (*e.g.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterised by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

C. Guidelines for Management of Infusion-Related Reactions

Consistent with usual medical practice, selected parenteral medications may be utilised for Grade > 2 allergic/hypersensitivity reactions. The sponsor should be contacted immediately if questions arise concerning the grade of the reaction. The following are recommended

management guidelines for IRRs associated with IMP administration. In all cases the investigator should use best clinical judgment in managing such reaction.

Management of Infusion-Related Reactions	
Grade 1	- Consider slowing the infusion to 50% of the prior rate - Monitor the patient for worsening condition - If the infusion is extended, administer subsequent infusions at the prolonged rate - Consider additional premedication or adjustment to premedications for subsequent infusions
Grade 2	- Interrupt the infusion for a minimum of 30 minutes - Administer additional pharmacologic therapy (*e.g.*, diphenhydramine, acetaminophen) and appropriate supportive care (*e.g.*, oxygen), as medically indicated - Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to ≤ Grade 1 - Monitor the patient for worsening condition - Administer subsequent infusions at the prolonged rate - Consider additional premedication or adjustment to premedications for subsequent infusions
Grade 3	- Stop the infusion - Administer additional pharmacologic therapy (diphenhydramine, dexamethasone) and appropriate supportive care (*e.g.*, oxygen), as medically indicated - Administer epinephrine or bronchodilators as medically indicated - Hospital admission for observation may be indicated - Do not resume infusion after a ≥ Grade 3 reaction - Participants who have a Grade 3 infusion-related reaction will be either discontinued from treatment, or must receive subsequent treatments at a reduced dose and a prolonged infusion rate (slowed to 50% of the prior rate or longer) - Consider additional premedication or adjustment to premedications for subsequent infusions - Participants who have a > Grade 3 infusion-related reaction will be discontinued from treatment

In the Event of Infusion Prolongation

Any assessments to be performed or samples to be collected (*e.g.*, vital signs, PK) at the end of or following EoI will still be performed or collected beginning at the delayed EoI timepoint. All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's e-CRF.

Appendix 10: Management of Dermatologic Adverse Events

A. Grading and Management of futuximab/modotuximab-Related Dermatologic AEs

Recommendations for management of Grade 1 to Grade 3 futuximab/modotuximab-induced dermatologic AEs (*i.e.*, rash, xerosis, paronychia, pruritus, photosensitivity, and fissures) are summarized below. If a patient experiences any Grade 4 dermatologic AE, the patient must be withdrawn from futuximab/modotuximab treatment. It is strongly recommended that a dermatologist is consulted in the event of Grade 3 or Grade 4 dermatologic AE.

Futuximab/modotuximab - Management of Rash			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Rash**
1	Papules and/or pustules covering **< 10% body surface area (BSA)**, which may or may not be associated with symptoms of pruritus or tenderness	Continue at the same dose	Topical: Face and Chest Steroid creams of low potency; alclometasone 0.05% or desonide 0.05% or fluocinolone 0.01%; 2 × daily Topical: Rest-of-body moisturizers; 2 × daily Systemic[1]: minocycline 100 mg/day or doxycycline 200 mg/day; for at least 4 weeks
2	Papules and/or pustules covering **10-30% BSA**, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL); papules and/or pustules covering > 30% BSA with or without mild symptoms	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose reduction as outlined in the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below	Topical: See Grade 1 Systemic[1]: - minocycline 100 mg/day or doxycycline 200 mg/day; for at least 4 weeks - 1 week course of oral steroid: methylprednisolone 4 mg tablets: • Day 1: 2-1-1-2 • Day 2: 1-1-1-2 • Day 3: 1-1-1-1 • Day 4: 1-1-1 • Day 5 1-0-1 • Day 6: 1
3	Papules and/or pustules covering **> 30% BSA**, with moderate or severe symptoms; limiting selfcare ADL; IV antibiotics indicated	Delay dose of futuximab/modotuximab, continue skin treatment and re-assess. Refer to the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below for further guidelines on dose reduction	Topical: See Grade 1 Systemic[1]: See Grade 2

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0
1. Alternatives in case of intolerance: First generation cephalosporins, amoxicillin, erythromycin or limecycline.
If infection is suspected (yellow crusts, purulent discharge, painful skin/nares): Obtain culture and change to oral antibiotic based on sensitivity

Futuximab/modotuximab - Management of Xerosis			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Xerosis**
1	**< 10% BSA** and no associated erythema or pruritus	Continue at the same dose	Topical: Face moisturizing cream or ointment1; 2 × daily *and* Topical: Body ammonium lactate 6-12% cream; 2 × daily
2	**10-30% BSA** and associated with erythema or pruritus; limiting instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose reduction as outlined in the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below	Topical: Face moisturizing cream or ointment1; 2 × daily *and* Topical: Body ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream; 2×daily
3	**> 30% BSA** and associated with pruritus; limiting self-care ADL	Delay dose of futuximab/modotuximab, continue skin treatment and re-assess. Refer to the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below for further guidelines on dose reduction	Topical: Face moisturizing cream or ointment1; 2 × daily *and* Topical: Body ammonium lactate 12% cream or salicylic acid 3-6% cream or urea 10-20% cream; 2 × daily *and* Topical: Eczematous areas topical steroid (*e.g.*, triamcinolone acetonide 0.025% or desonide 0.05% or alclometasone 0.05% or fluticasone propionate 0.05%); 2 × daily

Abbreviations (in alphabetical order): ADL, activities of daily living; BSA, body surface area; NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0
1. If prescription is not available, recommendation by pharmacist/dermatologist is acceptable

Futuximab/modotuximab Management of Paronychia			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Paronychia**
1	Nail fold edema or erythema; disruption of the cuticle	Continue at the same dose	Topical: antibiotics (*e.g.*, clindamycin 1% or erythromycin 1%) *and* vinegar soaks (*i.e.*, soaking fingers or toes in a 1:1 solution of white vinegar in water for 15 min daily
2	Localized intervention indicated; oral intervention indicated (*e.g.*, antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose reduction as outlined in the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below	Same as for Grade 1 *and* Topical: silver nitrate application weekly (consultation with dermatologist or surgeon is recommended) *and* Systemic: bacterial culture, oral antibiotic if infection confirmed
3	Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL	Delay dose of futuximab/modotuximab, continue skin treatment and re-assess. Refer to the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below for further guidelines on dose reduction	Same as for Grade 1 *and* Topical: silver nitrate application weekly (consultation with dermatologist or surgeon is recommended) *and* consider nail avulsion (consultation with dermatologist or surgeon is recommended) *and* Systemic: bacterial culture, oral antibiotic if infection confirmed

Abbreviations (in alphabetical order): ADL, activities of daily living; NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0; IV, intravenous

Futuximab/modotuximab Management of Pruritus			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Pruritus**
1	Mild or localized; topical intervention indicated	Continue at the same dose	Topical: steroid (*e.g.*, triamcinolone acetonide 0.025%, desonide 0.05%, alclometasone 0.05%, Fluticasone propionate 0.05%); 2 × daily *or* anti-pruritics (*e.g.*, pramoxine 1%, doxepin 5% cream); 2 × daily
2	Widespread and intermittent; skin changes from scratching (*e.g.*, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose reduction as outlined in the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below	Same as for Grade 1 *and* Systemic: oral antihistamines (diphenhydramine 25-50 mg; hydroxyzine 25 mg; fexofenadine 60 mg; 3 × daily
3	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	Delay dose of futuximab/modotuximab, continue skin treatment and re-assess. Refer to the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below for further guidelines on dose reduction	Same as for Grade 2

Abbreviations (in alphabetical order): ADL, activities of daily living; NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0

Futuximab/modotuximab Management of Photosensitivity			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Photosensitivity**
1	Painless erythema and erythema covering **<10% BSA**	Continue at the same dose	Topical: broad spectrum sunscreen with an SPF of at least 15; reapplied every 2 hours or more frequently if swimming or perspiring *and* Systemic: bacterial culture, oral antibiotic if infection confirmed
2	Tender erythema covering **10-30% BSA**	Continue at the same dose If locally debilitating for the patient, consider following guidelines for dose-delay and dose reduction as outlined in the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below	Same as for Grade 1 *and* Topical: corticosteroids (*e.g.*, triamcinolone acetonide 0.025% or desonide 0.05% or alclometasone 0.05% cream or fluticasone propionate 0.05%); 2 × daily
3	Erythema covering **> 30% BSA** and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (*e.g.*, narcotics or NSAIDs)	Delay dose of futuximab/modotuximab, continue skin treatment and re-assess. Refer to the Dose Reduction for Grade 3 Dermatologic AEs table in Section B below for further guidelines on dose reduction	Same as for Grade 2

Abbreviations (in alphabetical order): BSA, body surface area; NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0; NSAID, nonsteroidal anti-inflammatory drug; SPF, sun protection factor

Futuximab/modotuximab Management of Fissures			
NCI-CTCAE Grade		**Action with futuximab/modotuximab**	**Treatment- Fissures**
1	Initiated at first occurrence	No action	Topical: - thick moisturizers of zinc oxide (13-40%) cream - liquid glues of cyanoacrylate to seal cracks
2	If no improvement after 2 weeks from initiation of Step 1	No action	Topical: - thick moisturizers of zinc oxide (13-40%) cream under occlusion at night - salicylic acid 6% cream or ammonium lactate/lactic acid 12%
3	If no improvement after 2 weeks from initiation of Step 2	Delay dose of futuximab/modotuximab, and re-assess. Discuss need for dose reduction and/or further dose omissions with sponsor or designee	Continue local treatment as described in Step 2

Prophylaxis for fissures includes careful use of moisturizing creams and/or ointments 3 times a day and after handwashing, using only fragrance-free soaps. Should fissures begin to form, a stepwise approach outlined above should be followed. **Topical application of cyanoacrylate tissue adhesive (*i.e.*, surgical glue) products may be considered to promote wound repair.**

If fissures occur which are unresponsive to intensive therapeutic treatment as specified above, futuximab/modotuximab dosing should be delayed. The need for dose-reduction and/or continued dose-delays should be discussed with the sponsor or designee, if adequate improvement is not seen after the initial dose-delay.

B. Dose Reduction Guidelines for futuximab/modotuximab-Related Dermatologic AEs

Dose delay and/or intrapatient dose reduction(s) will be required upon occurrence of Grade 3 anti-EGFR associated dermatologic AE, and should be implemented according to Table Dose Reduction for Grade 3 Dermatologic AEs

Futuximab/modotuximab Dose Reduction for Grade 3 Dermatologic AEs			
Dermatologic AE Grade 3	**Futuximab/modotuximab Immediate Action**	**Outcome Improvement**	**Futuximab/modotuximab**
First occurrence	Delay dose	Grade ≤ 1	Continue at same dose
		Grade 2	Reduce to 4.5 mg/kg
		No improvement	Discontinue
Second occurrence	Delay dose	Grade ≤ 1	Continue at same dose
		Grade 2	At dose of 6.0 mg/kg: Reduce to 4.5 mg/kg At dose of 4.5 mg/kg: Reduce to 3.0 mg/kg
		No improvement	Discontinue
Third occurrence	Delay dose	Grade ≤ 1	Continue at same dose
		Grade 2	At dose of 6.0 mg/kg: Reduce to 4.5 mg/kg At dose of 4.5 mg/kg: Reduce to 3.0 mg/kg At dose of 3.0 mg/kg: discontinue
		No improvement	Discontinue
Fourth occurrence	Discontinue	**Any**	Discontinue

Abbreviations (in alphabetical order): AE, adverse event; kg, kilogram; mg, milligram
Note: Dose reductions for 9 mg/kg loading not applicable. For dose delays, re-assess after < 2 weeks. Longer delays are allowed if no recovery to < Grade 2 after 2 weeks

In each case, the next treatment should be delayed, and the patient's condition should be reassessed after 1 week, and if necessary, 2 weeks. Treatment should be delayed further if the AE remains at Grade 3 after 2 weeks.

In the case of a Grade 2 dermatologic AE which is locally debilitating for the patient, the guidelines outlined above may be followed at the investigator's discretion.

Participants must be withdrawn from futuximab/modotuximab treatment in the event of a Grade 4 dermatologic AE.

Appendix 11: Management of Hypomagnesemia

A. NCI-CTCAE Grading of Hypomagnesemia and QTc Prolongation

Grading of Hypomagnesemia and QTc Prolongation					
Event	**1**	**2**	**3**	**4**	**5**
Hypomagnesemia	< LLN-1.2 mg/dL < LLN-0.5 mmol/L	< 1.2-0.9 mg/dL < 0.5-0.4 mmol/L	< 0.9-0.7 mg/dL < 0.4-0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L life-threatening consequences	Death
ECG QTc Interval prolonged	Average QTc 450-480 ms	Average QTc 481-500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-

Abbreviations (in alphabetical order): NCI-CTCAE, Common Terminology Criteria for Adverse Events v5.0; dL, deciliter; ECG, electrocardiogram; L, liter; LLN, lower limit of normal; mg, milligram; mmol, millimole; ms, millisecond; QTc, corrected QT interval

B. Management of Hypomagnesemia

Participants receiving futuximab/modotuximab will be monitored weekly for hypomagnesemia, which should be managed as follows

Management of Hypomagnesemia and QTc Prolongation	
Grade	**Action**
Grade 1	No replacement therapy required, but may be administered at treating physician's discretion, weekly monitoring to continue
Grade 2 or higher	Use of concomitant QTc-prolonging drugs* should be discontinued unless urgently needed for medical care and no alternative therapy is available
Grade 3-4	Administer MgSO4 (6g to 10g IV) at minimum 2 times per week until ≤ Grade 1 Perform predosing ECG (required) to monitor for QTc prolongation** In the event of Grade 3 QTc prolongation potentially due to hypomagnesemia, futuximab/modotuximab administration should be delayed while magnesium repletion is undertaken futuximab/modotuximab may be restarted with continued intensive magnesium therapy at the same dose or at a reduced dose once hypomagnesemia returns to ≤ Grade 1 severity, and once the QTc returns to WNL or baseline status In the event of TdP or other life-threatening arrhythmias discontinue futuximab/modotuximab
Grade 4	For Grade 4 hypomagnesemia that is refractory to IV magnesium-replacement therapy, dosing with futuximab/modotuximab should be delayed or reduced.

Abbreviations (in alphabetical order): g, gram; IV, intravenous; MgSO4, magnesium sulfate; QTc, corrected QT interval; TdP, Torsade de pointes; WNL, within normal limits
** Listings of QTc prolonging drugs may be found at: <https://crediblemeds.org/index.php?cID=222>*
*** ECG is required before futuximab/modotuximab administration to monitor QT prolongation that may result in severe arrhythmias such as TdP.*

Appendix 12: Maximum Total Blood Collection Volumes

	Treatment period													
	Volume/ sample	Screening /Inclusion		Cycle 1		Cycle 2		Cycle 3		Further from Cycle 4		Withdrawal Visit		Total (ml)
		#	Volume mL	#	Volume mL	#	Volume mL	#	Volume mL	#	Volume mL	#	Volume mL	Volume mL
Genomic analysis														
Blood sample for ctDNA	20	1	20		0		0		0		0		0	20
Biomarker														
*Blood exploratory biomarkers**	20	0	0	1	20	1	20	1	20	0	0	1	20	80
Safety assessment														
Haematology	5	1	5	2	10	2	10	2	10	2	10	1	5	50
Biochemistry	10	1	10	2	20	2	20	2	20	2	20	1	10	100
Additional Biochemistry for Mg, Ca, K	5	0	0	2	10	2	10	2	10	2	10	0	0	40
Coagulation	5	1	5	1	5	1	5	1	5	1	5	1	5	30
β hCG test	5	1	5	1	5	1	5	1	5	1	5	1	5	30
Pharmacokinetics														
PK evaluation for futuximab/modotuximab	2.5	0	0	12	30	12	30	1	2.5	1	2.5	1	2.5	67.5
PK evaluation for T/T	4	0	0	6	24	6	24	0	0	0	0	1	4	52
ADA														
*ADA (2.5 mL) for futuximab/modotuximab***	2.5	0	0	2	5	2	5	1	2.5	1	2.5	1	2.5	17.5
TOTAL volume (mL)			45		129		129		75		55		54	487

Abbreviations (in alphabetical order): #, number of samples; ADA, anti-drug antibody; Ca, calcium; K, potassium; Mg, magnesium; mL, millilitre; PK, pharmacokinetic; T/T, trifluridine/tipiracil
** C1D1, C2D1, C3D1 then every 2 cycles*
*** The frequency of ADA assessments will be reduced to every 2 months after the first 6 months in the first year and every 4 months after the first year.*
If sites can perform haematology, serum chemistry, and coagulation studies with smaller volumes of blood per sample, they are encouraged to do so. Required PK, ADA, and PD/biomarker volumes are fixed and should not be reduced.