PROTOCOL

TITLE:	**A RANDOMIZED, PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ONARTUZUMAB (MetMAb) IN COMBINATION WITH 5-FLUOROURACIL, FOLINIC ACID, AND OXALIPLATIN (mFOLFOX6) IN PATIENTS WITH METASTATIC HER2-NEGATIVE, MET-POSITIVE GASTROESOPHAGEAL CANCER**
PROTOCOL NUMBER:	YO28322
VERSION NUMBER:	2
EUDRACT NUMBER:	2012-001402-23
IND NUMBER:	115018
TEST PRODUCT:	Onartuzumab (MetMAb, RO5490258, PRO143966)
MEDICAL MONITOR:	Steve Hack, M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 11 April 2012
DATE AMENDED:	Version 2: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
Phan,See	Clinical Science Leader	12-Sep-2012 17:53:06

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol YO28322 has been amended for the following reasons:

- Based on review by and discussion with the U.S. Food and Drug Administration (FDA), the Met IHC stratification factor (formerly a clinical score of 1+ vs. 2+/3+ based on a ≥ 50% analytical cutoff) has been replaced with five stratification levels encompassing a ≥ 50% and ≥ 90% analytical cutoff (I, II, III, IV, and V; see Section 3.3.4.1).
- As the overall number of strata has been increased by additional levels to the Met IHC stratification factor, primary tumor location (GEJ vs. stomach) has been removed as a stratification factor.
- Per a request from the FDA, an electrocardiogram will be required at screening and as clinically indicated during the study (see Section 4.5.1.6 and Appendix 1).
- It has been clarified that baseline weight (rather than screening weight) will be used to calculate onartuzumab/placebo dosage (see Section 4.3.2.1).
- The exclusion criterion regarding history of malignancy has been modified for consistency across the onartuzumab clinical trial program (see Section 4.1.2).
- Per a request from ANSM (France), the exclusion criterion regarding known sensitivity to components of study treatment has been updated to also include known contraindications (see Section 4.1.2).
- Procedures for potential emergency unblinding have been revised (see Section 4.2).
- Per a request from ANSM, live vaccines have been added to the list of prohibited concomitant medications (see Section 4.4.2).
- Text concerning chemotherapy dose modification has been updated to improve clarity and consistency (see Section 5.1.1.1.2).
- Text has been added to indicate that patients must receive the first dose of study drug within 3 days after randomization (see Sections 3.1.1 and 4.5.2.2).
- The description of the tumor assessment schedule has been updated to clarify the requirement to perform CT or MRI scans of the chest, abdomen, and pelvis (see Section 4.5.1.8 and Appendix 1).
- For patients who remain on study treatment and follow-up for greater than one year, repeat chest, abdomen, and pelvis CT or MRI scans after the first 12 months is performed every 12 weeks (during the last week of every sixth cycle) rather than every 6 weeks (see Section 4.5.1.8 and Appendix 1).
- For patients who fail screening, HER2 status will be collected in the interactive voice/web response system in addition to Met status (see Section 4.2).

- As previously written, the protocol indicated that all study centers were required to collect serum samples from patients for the purposes of pharmacokinetic (PK) and anti-therapeutic antibody (ATA) evaluation. Based on site and country feasibility assessments conducted after protocol finalization, it has been determined that not all study centers have the capability to collect the samples required for PK testing. The protocol has been amended to specify PK/ATA evaluation at selected centers only (see Section 3.1.1 and Appendix 2).
- Specific exploratory biomarker assays that will be undertaken as part of the study have been listed (see Section 4.5.1.11).
- Based on FDA feedback, objective response rate (ORR) will be evaluated in all randomized patients (Section 6.4)
- The rationale for the study design has been updated (see Section 3.3 and subsections).
- Updated language has been incorporated regarding persistent and recurrent adverse events to better reflect a change in the severity of adverse events (see Section 5.3.5.3).
- Contact information for the Roche Medical Monitor has been updated (see Section 5.4.1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL AMENDMENT ACCEPTANCE

A Protocol Amendment Acceptance Form has been added.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The list of abbreviations and definitions of terms has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.2: Targeted Agents in Advanced Gastric Cancer

The REAL-3 trial evaluated the addition of panitumumab (an anti-EGFR antibody) to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced GEC (Waddell et al. 2012). The addition of panitumumab to EOC chemotherapy was associated with worsening of OS (the primary endpoint) in an unselected population with advanced GEC (HR = 1.37 [95% CI: 1.07, 1.76]; p = 0.013).

SECTION 1.3.5: Clinical Phase II

The first proof-of-concept study supporting the therapeutic value of Met inhibition with onartuzumab was a randomized, placebo-controlled Phase II trial evaluating erlotinib + placebo versus erlotinib + onartuzumab in patients who had received one to two prior treatments for metastatic NSCLC (Study OAM4558g; Spigel et al. 2011). The results of this study in the intent-to-treat (ITT; i.e., as-randomized) population demonstrated no incremental benefit when onartuzumab was added to erlotinib. However, in patients who had Met-positive tumors (~~IHC 2+/3+, see Appendix 3~~ ≥ *50% of tumor cells with moderate or strong Met staining intensity*), the addition of onartuzumab to erlotinib treatment resulted in clinically meaningful and statistically significant improvements in PFS and OS. . . .

SECTION 1.4.1: Met Pathway Upregulation, GEC Prognosis, and Response to Treatment

. . . In preclinical models, inhibition of HGF/Met signaling can bring about an increase in sensitivity to platinum drugs (Bowers et al. 2000; Bu et al. 2011; *Catenacci et al. 2011a*). . . .

SECTION 1.4.3: Onartuzumab Studies in Other Tumor Types

To date, onartuzumab has been studied in one Phase I trial (OAM4224g) and one randomized Phase II trial (OAM4558g). Randomized Phase II trials are currently ongoing in triple-negative metastatic breast cancer (OAM4861g), first-line metastatic colorectal cancer (GO27827/SCRI GI155), *relapsed glioblastoma (GO27819)*, and first-line

non–small cell lung cancer (squamous and non-squamous [GO27820 and GO27821, respectively]). A Phase III study in second/third-line NSCLC (OAM4971g) is open to enrollment. ~~A Phase II study in relapsed GBM is planned.~~

SECTION 2.2: SECONDARY OBJECTIVES

- To evaluate the safety of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 in patients with *metastatic* HER2-negative, *Met-positive* ~~metastatic~~ GEC, focusing on all adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities
- To compare patient-reported outcomes (PROs) following treatment with onartuzumab + mFOLFOX6 relative to placebo + mFOLFOX6, as measured by the EORTC QLQ-C30 and its gastric cancer module (the QLQ-STO22)~~, of the two treatment arms in the Met 2+/3+ subgroup and in the ITT population~~

SECTION 3.1.1: Overview

. . . . Tumor specimens from patients meeting eligibility criteria will be prospectively tested by *a* central laboratory to determine Met ~~IHC score~~ *expression status* using the Ventana® anti-Total c-MET (SP44) rabbit monoclonal antibody IHC assay (see Appendix 3), HER2 status, and Lauren histologic subtype. Only patients with Met–positive tumors will be enrolled (i.e., those with tumor samples ~~classified with a Met IHC score of 1+, 2+ or 3+~~ *with ≥ 50% of tumor cells showing weak, moderate, and/or strong staining intensity*; see Appendix 3). Eligible patients will be stratified ~~by~~ *according to the following stratification factors:*

- Met expression ~~status (1+ vs. 2+/3+)~~ *by IHC (level I, II, III, IV, or V; see Table 1 in Section 3.3.4.1)*
- World region (Asia-Pacific vs. other)
- ~~Primary tumor location (GEJ vs. stomach)~~
- Prior gastrectomy (yes vs. no)

Patients will be randomized in a 1:1 ratio to receive either onartuzumab + mFOLFOX6 or placebo + mFOLFOX6. *Patients must receive their first dose of study drug within 3 days after being randomized. . . .*

Tumor response evaluations will occur every 6 weeks (± 7 days) *during the first 12 months and then every 12 weeks (±14 days) until disease progression. . . .*

. . .

The PK and ATA profile of onartuzumab will be assessed in patients at selected centers. Centers will be selected based their ability and willingness to execute PK/ATA sampling.

Figure 2: Study Design

Figure 2 has been revised to reflect the changes to the protocol.

SECTION 3.1.2: Independent Data Monitoring Committee

The following text has been moved from Section 3.1.3 (Data Review at Interim Analysis) to Section 3.1.2:

Safety data provided to the IDMC will include demographic data, adverse events, serious adverse events (including copies of the serious adverse event forms received), laboratory abnormalities (hematology and biochemistry), and Met status; further information will be provided on request.

SECTION 3.3.2: Rationale for Patient Population

Patients with metastatic GEC will be enrolled into this trial. Historically, this patient population has a poor prognosis, with 5-year OS rates of approximately 20% (van Cutsem et al. 2011). ~~Met receptor overexpression and genomic amplification have been associated with a poor prognosis in patients with GEC.~~ *This prognosis is likely to be further worsened as a result of Met overexpression (Amemiya et al. 2002; Drebber et al. 2008; Toiyama et al. 2012).* Data from ~~a~~ randomized Phase II ~~study~~ *studies in* refractory NSCLC (OAM4558g; see Section 1.3.5) *and advanced GEC* provide~~s~~ proof of concept that blocking Met signaling ~~with onartuzumab~~ may be efficacious in patients with ~~NSCLC who have~~ Met-positive tumors ~~and received onartuzumab in combination with erlotinib~~ (Spigel et al. 2011; *Iveson et al. 2011; Oliner et al. 2012*).

~~Patients with Met-positive metastatic GEC will be enrolled into this Phase III study (YO28322), with Met positivity defined by an IHC score of ≥ 1+ (see Appendix 3). The definition of Met positivity used in this study is based on – but different than – that used in Study OAM4558g, where Spigel et al. classified NSCLC tumors as Met positive by IHC if ≥ 50% of cells showed moderate (2+) or strong (3+) staining for Met; tumors with ≥ 50% of cells with weak (1+) staining were defined as Met negative. In this study, the same proportional cutoff of ≥ 50% Met-positive tumor cells will be applied; however, the staining intensity cutoff will encompass 1+ staining.~~

~~The rationale for defining a Met-positive tumor as one with a Met clinical score of ≥ 1+ in this study is several fold. The shorter duration of PFS and OS observed by Spigel et al. (2011) in patients with Met-negative (0 or 1+) tumors were in a different tumor type (NSCLC) using a different treatment backbone (erlotinib). Post-hoc analysis revealed that there was no difference in treatment-emergent safety profile or cause of death between the treatment arms, or by Met diagnostic status. Preclinical studies did not predict the outcomes seen in this NSCLC clinical study. The adverse findings in the Met-negative NSCLC cohort by Spigel et al. (2011) cannot be explained using clinical baseline characteristics.~~

~~Preliminary data suggest that Met diagnostic criteria in the setting of advanced GEC are likely different from those developed in NSCLC. Iveson et al. (2011) demonstrated an enhanced treatment effect of rilotumumab plus chemotherapy in patients with Met-positive GEC where Met positivity was defined as ≥ 50% of tumor cells being positive for Met (staining intensity ≥ 1+). This diagnostic classification suggests that, unlike the~~

~~onartuzumab criteria developed for NSCLC, patients with gastroesophageal tumors with lower levels of Met staining may derive a treatment benefit. This hypothesis is supported by the observation of a durable CR in a patient with Met-positive (Met IHC 1+ according to NSCLC criteria), chemotherapy-refractory GEC with liver metastases treated with single-agent onartuzumab in a Phase I study (Catenacci et al. 2011); see Section 1.4.2 for additional details.~~

~~Met IHC score will be blinded both to the treating investigator and to the patient at the time of enrollment so as to avoid potential bias in patient treatment or evaluation between treatment cohorts. The IDMC will monitor safety data at pre-defined timepoints. Following documented disease progression per RECIST v1.1, patient and investigators will discuss further treatment options while remaining blinded to study treatment.~~

It is probable that the benefit of onartuzumab will only be seen in patients with tumors expressing the Met receptor at or above physiological levels. As a result, eligible patients with Met-positive metastatic GEC will be enrolled into this Phase III study (YO28322). An IHC assay will be used to measure Met receptor expression and to prospectively screen and enroll patients with Met-positive GEC. Tumor samples from eligible patients will be considered Met-positive if ≥ 50% of malignant cells stain positive for Met at weak, moderate, and/or strong intensity levels (see Appendix 3).

This IHC-based diagnostic definition of Met positivity is based on published data suggesting that the efficacy of HGF/Met axis inhibition is maximized in cases where the majority of tumor cells (≥ 50%) within a sample are found to be Met positive (Iveson et al. 2011; Oliner et al. 2012).

SECTION 3.3.3: Rationale for Control Group

There is no single standard, globally accepted first-line reference chemotherapeutic regimen for advanced gastric cancer. A fluoropyrimidine (5-FU or capecitabine) in combination with platinum agent (cisplatin or oxaliplatin) is an accepted standard of care in both Western and Asian countries (Kim et al. 1993; Ajani 2000; Ohtsu et al. 2003; Ajani et al. 2010; NCCN 2011). ~~Capecitabine and 5-FU and cisplatin and oxaliplatin respectively~~ *Both classes of agent* are considered to be interchangeable according to NCCN and ESMO treatment guidelines. . . .

SECTION 3.3.4: Rationale for Stratification

To balance the disease-related risk factors across the treatment arms, patients will be stratified at study entry. . . . Patients will be stratified by the following:

- Met *expression by* IHC ~~(1+ vs. 2+/3+)~~ *(level I, II, III, IV, or V; see Section 3.3.4.1 below)*
- World region (Asia-Pacific vs. other)
- ~~Primary tumor location (GEJ vs. stomach)~~
- Prior gastrectomy (yes vs. no)

SECTION 3.3.4.1: Met Expression *by IHC*

Met receptor overexpression is thought to be associated with poor prognosis in advanced GEC. The level of Met protein overexpression as determined by IHC may be correlated with the degree of clinical benefit associated with treatment with Met pathway inhibitors (Spigel et al. 2010; Iveson et al. 2011; *Oliner et al. 2012*). *As a result,* patients ~~with GEC tumors classified as Met 2+ or 3+~~ *with higher Met expression* may derive more benefit from treatment with onartuzumab compared with those ~~defined as Met 1+~~*with weaker levels of Met expression*. ~~Randomization by Met IHC scores (1+ vs. 2+/3+) will be employed to prevent an imbalance in treatment arms.~~

The IHC scoring system used to select and stratify patients with Met-positive GEC is a composite algorithm that encompasses both staining intensity (weak, moderate, or strong) and percentage of cells staining positive for Met (see Appendix 3). Patients are considered to be Met positive and eligible for the study if the majority (≥ 50%) of malignant cells in a specimen are found to express Met at weak, moderate, or strong intensity.

It is possible that a more stringent proportional cutoff in which ≥90% tumor cells are Met positive could better select patients for treatment with onartuzumab. To account for this possibility, both a 50% and 90% cutoff for percentage of cells staining positive for Met will be used for stratification. Stratification levels for Met IHC status are defined by a composite of both the 50% and 90% cutoff, leading to a total of five stratification levels (I, II, III, IV, and V; see Table 1).

Table 1 Met IHC Stratification Levels Defined According to ≥ 50% and ≥ 90% Cutoffs

		Met IHC by 90% Cutoff		
	Score	*2+/3+*	*1+*	*0*
Met IHC by 50% Cutoff	*2+/3+*	***I*** *≥50% m+s* *and ≥90% m+s*	***II*** *≥50% m+s* *and ≥90% w+m+s* *but <90% m+s*	***III*** *≥50% m+s* *and <90% w+m+s*
	1+	*Not applicable*	***IV*** *≥50% w+m+s* *but <50% m+s* *and ≥90% w+m+s* *but <90% m+s*	***V*** *≥50% w+m+s* *but <50% m+s* *and <90% w+m+s*

w=weak staining intensity; m=moderate staining intensity; s=strong staining intensity.

The randomization schema incorporating these five Met IHC stratification levels will increase the likelihood that the baseline demographic characteristics and disease-related risk factors remain well balanced across both treatment arms in the analysis populations as defined by a cutoff of either 50% or 90%.

See Appendix 4 for examples of how eligible patient assignments to the five Met IHC stratification levels (I–V; see Table 1 above) will be conducted during the trial.

SECTION 3.3.4.2: World Region

Although gastric cancer is a global disease, there is significant ~~geographic~~ heterogeneity *with respect to survival outcomes between Eastern and Western populations, with better OS reported in Eastern series. These differential outcomes may be driven by variations in initial staging, biology, or treatment practice (Bickenback and Strong 2012).* ~~There are differences in the presentation and management of gastric cancer patients in different countries and regions. Specifically, as observed in the ToGA and AVAGAST studies (Bang et al. 2010; Ohtsu et al. 2011), Asian patients with advanced GEC more commonly receive second and further lines of therapy, more frequently have a prior history of gastrectomy, present with a higher proportion of non-measurable disease, and have liver metastases or proximal or gastroesophageal junction tumors less frequently. There are imbalances in the histologic tumor types across the geographic regions and between the treatment arms within the respective regions. Asian trials have typically included more patients with diffuse histology than non-Asian trials (Shitara et al. 2011). Differences in independent prognostic factors and use of subsequent therapies may explain the different OS results between geographic regions.~~ Given the significant geographic heterogeneity in GEC, this study will stratify randomization according to world region (Asia-Pacific vs. other) in order to prevent an imbalance in study arms.

~~SECTION 3.3.4.3: Primary Tumor Location~~

~~Patients will be stratified according to the anatomic location of the primary tumor (GEJ vs. stomach). Proximal gastroesophageal tumors such as those arising in the GEJ or cardia tend to have a worse prognosis compared with more distal tumors. Met positivity may be more common in GEJ compared with gastric tumors (Lennerz et al. 2011).~~

SECTION 4.1: PATIENTS

. . . . Patients must have tumors ~~classified with a Met IHC score of 1+, 2+ or 3+~~ *defined as Met positive by IHC (≥ 50% of tumor cells with membrane and/or cytoplasmic staining at weak, moderate, or high intensity)* to be enrolled into this study.

SECTION 4.1.2: Exclusion Criteria

- History of another malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, *localized prostate cancer that has been treated surgically with curative intent and presumed cured,* or other malignancies with an expected curative outcome
- Known sensitivity *or contraindication* to any component of study treatment

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

. . . Randomization to one of the two treatment arms will occur in a 1:1 ratio in each cohort using a permutated block randomization method. Randomization will be stratified by Met IHC (~~1+ vs. 2+/3+~~ *levels I, II, III, IV, or V [see Table 1]* by central testing), world region (Asia-Pacific vs. other), ~~primary tumor location (GEJ vs. stomach),~~ and prior gastrectomy (yes vs. no). . . .

. . .

~~As per health authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious AEs (see Section 5.7) that are considered by the investigator to be related to study drug.~~

Treatment codes should not be broken except in emergency situations. If the investigator needs to know the study drug assignment for any reason, he or she should contact the Medical Monitor. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding because of a serious adverse event).

Data for patients who failed screening will be collected in IXRS to obtain more information on the prevalence of Met *and HER2* status ~~(positive vs. negative)~~ in patients with GEC.

SECTION 4.3: STUDY TREATMENT

Table 2 Treatment Regimen

Study Drug	Dose/Route	Initial 12 Treatment Cycles	Cycles 13 and Beyond
Premedication	• ~~Prophylactic anti-emetics (per local practice and manufacturer's instructions)~~ • *Premedication (e.g. anti-emetics, hydration, antihistamines, corticosteroids, etc.), should be given according to institutional standards and the respective product package insert(s)* • Prophylactic IV administration of Ca^{2+}/Mg^{2+} salts to reduce the incidence or severity of oxaliplatin-induced neuropathy is permitted at the discretion of the investigator		
Onartuzumab or placebo	10 mg/kg IV	First infusion over 60 (± 10) min, then 30 (± 10) min, on Day 1 q14d	Over 30 (± 10) min
Oxaliplatin	85 mg/m² IV	Over 2 hours on Day 1 q14d	Discontinue
Folinic acid [a]	400 mg/m^2	Over 2 hours on Day 1 q14d	Discontinue
5-FU	400 mg/m^2	Bolus	Discontinue
	2400 mg/m^2	Continuous IV infusion over 46–48 hours	Discontinue

IV = intravenous; min = minute; q14d = every 14 days.

[a] If folinic acid is unavailable, 200 mg/m^2 levofolinic acid may be used. Study treatment may be administered without either agent in the event that both are unavailable. *Folinic acid (or levofolinic acid) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care.*

SECTION 4.3.1.1: Onartuzumab and Placebo

Onartuzumab will be provided as a sterile liquid in a single-use 15-cc vial containing 600 mg *(10 mL)* or a single-use 20-cc vial containing 900 mg (*15 mL)* of onartuzumab.

SECTION 4.3.2.1: Onartuzumab and Placebo

. . . The patient's weight at ~~screening~~ *baseline* will be used to determine the actual dose of onartuzumab. . . .

SECTION 4.3.2.2: mFOLFOX6

. . . Oxaliplatin will be administered as an 85 mg/m^2 IV infusion over 2 hours (Day 1 every 14 days) in combination with 400 mg/m^2 folinic acid (or 200 mg/m^2 levofolinic acid if folinic acid is not available), followed by 400 mg/m^2 5-FU bolus, and then 2400 mg/m^2 5–FU as a continuous IV infusion over 46–48 hours. *In lieu of the suggested dosing and administration schedule, folinic acid (or levofolinic acid) may be prescribed and administered as deemed appropriate by the investigator in accordance with institutional standards of care.*

SECTION 4.3.3: ~~Additional Required Medication~~ *Supportive Care*

Patients should receive anti-emetic and other prophylactic treatments according to the local standard of care and manufacturer's instruction.

~~Patients may be pre-medicated with 5-hydroxytryptamine3 (5-HT$_3$) receptor antagonists or other standard-of-care methods to control nausea and vomiting. For symptoms of diarrhea and/or abdominal cramping, patients should be instructed to begin taking loperamide (2 mg) at the time of the first liquid stool and continue taking 2 mg approximately every 2 hours until at least 12 hours after the last liquid stool, with oral rehydration.~~

Patients should receive full supportive care, including epoetin and other hematopoietic growth factors, transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate.

SECTION 4.4.2: Prohibited Therapy

Live Vaccines

Vaccination with a live vaccine should be avoided in patients receiving 5-FU because of the potential for serious or fatal infections.

SECTION 4.5.1.6: *Electrocardiogram (ECG)*

An ECG is required at baseline. Additional ECGs may be performed during the study as clinically indicated. For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site.

SECTION 4.5.1.8: Tumor and Response Evaluations

. . . CT or MRI of the chest, ~~and~~ abdomen, *and pelvis* should be performed using contrast media unless clinically contraindicated. *CT scans of the neck should be included if clinically indicated.* Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease is suspected. . . .

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 6 weeks ± 7 days (during the last week of every third cycle) *for the first 12 months and then every 12 weeks ± 14 days (during the last week of every sixth cycle)* during treatment, and at the time of treatment discontinuation, if disease progression has not already been documented. . . .

SECTION 4.5.1.9: Laboratory Assessments

- PT and INR *(required for all patients at baseline)*

  Ongoing evaluation should be continued for patients who are receiving therapeutic anticoagulation according to ~~the~~ local standard of care

SECTION 4.5.1.11: Tumor Tissue Samples for Patient Stratification and Exploratory Biomarkers

For enrolled patients only, part of the available tumor tissue from the tissue submitted will be used to assess exploratory biomarkers. Tissue assessments will include testing of protein expression, activation status, somatic mutations, and/or gene amplification ~~of Met, HER2, EGFR, VEGFR~~ *related to angiogenesis, tumorigenesis*, inflammation, and other exploratory markers related to onartuzumab and to gastric cancer biology. *Since the identification of new markers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of analyses remains to be determined; however, it will include the following markers: Met amplification, HGF, MACC1, ROS1, HER3, PTEN, KRAS, EGFR, PI3K. Such analysis is exploratory by nature and will be performed retrospectively after the main study analysis is completed.* These assessments will be performed by the Sponsor at a central laboratory or by a Sponsor-selected vendor. The remaining tumor tissue block will be returned to the site upon request.

SECTION 4.5.1.12: Blood Samples for Exploratory Biomarkers

Samples will be sent to one or more central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The remainder of these samples will be destroyed no later than 5 years after the end of the study ~~unless the patient gives specific consent for them to be stored for optional future research~~ *or earlier depending on local regulations*. If the patient provides consent for optional future research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

SECTION 4.5.2.2: Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). . . . *Patients must receive their first dose of study drug within 3 days after being randomized.*

SECTION 5.1.1.1: Dose Modification Due to Toxicity

General Notes Regarding Dose Modifications

- *If oxaliplatin requires discontinuation because of toxicity, 5-FU, folinic acid (or levofolinic acid), and onartuzumab or placebo should be continued per the study protocol.*
- *Following either completion of or discontinuation from chemotherapy, onartuzumab or placebo should be continued until disease progression or unacceptable toxicity if clinically appropriate.*
- When a treatment cycle is temporarily interrupted because of toxicity caused by one component of the regimen, the treatment cycles will be re-started such that study drug infusions remain synchronized with the chemotherapy. The tumor assessment schedule will not be altered if chemotherapy is delayed. Tumor assessments will be performed every 6 weeks (± 7 days) *during the first 12 months and then every 12 weeks (±14 days) until disease progression*.
- Patients who require chemotherapy dose reductions will receive the reduced dose for the remainder of the study. The only exception to this practice will be in the case of nausea/vomiting. If nausea and/or vomiting occur despite anti-emetic therapy, the chemotherapy dose should be reduced by 25% for the next dose. If tolerated, an increase back to a 100% dose may be allowed at the treating physician's discretion. ~~Any patient who required two dose reductions and experienced persistent toxicity with a third dose reduction will be discontinued from all chemotherapy.~~ Chemotherapy cycles may be delayed to manage toxicity. Cycle delays of up to 28 days are permitted. Any delay longer than 28 days will require permanent discontinuation of all chemotherapy.

SECTION 5.1.1.1.1: Onartuzumab/Placebo

. . . Any toxicities associated or possibly associated with onartuzumab treatment should be managed according to standard medical practice. ~~If a cycle of chemotherapy is delayed, onartuzumab or placebo should also be delayed.~~ Patients who discontinue treatment for onartuzumab toxicity in the absence of disease progression may continue on trial until a PFS event occurs. . . .

SECTION 5.1.1.1.2: mFOLFOX6

Dose adjustments at the start of each 14-day cycle will be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Dose level adjustments for oxaliplatin, 5-FU bolus, and 5-FU infusion will be reduced according to Table 3 after determining the appropriate hematologic criteria in Table 4 or non-hematologic criteria in Table 5. Once a dose reduction is made, the dose will not be re-escalated during subsequent cycles. *For each agent,* no more than two dose reductions will be allowed for any patient *(see Table 3). Dose adjustments of each agent may*

be made independently based on the specific types of toxicities observed. If a dose reduction beyond −2 dose levels for any agent is required, that agent should be discontinued.

. . .

Folinic acid ~~will stay at a fixed dose of~~ *(*400 mg/m^2 ~~and~~ *or as deemed appropriate by the investigator)* will be given prior to each 5-FU dose. If 5-FU is delayed, folinic acid will be delayed. If folinic acid is not available, levofolinic acid (200 mg/m^2 *or as deemed appropriate by the investigator*) may be administered. Folinic acid or levofolinic acid may be omitted from study treatment in the event that they are both unavailable.

Table 3 Dose Adjustment Levels for ~~FOLFOX6~~*Oxaliplatin and 5-FU*

	Oxaliplatin (mg/m^2)	5-FU (mg/m^2)	
		Bolus	Infusion
Starting Dose	85	400	2400
–1 Dose Level	65	320	1900
–2 Dose Levels	50	260	1500

. . .

mFOLFOX6: Dose Modification for Hematologic Toxicity

Table 4 shows the dose modifications for hematological toxicity, which apply for 5-FU, folinic acid, and oxaliplatin. ~~The patient may begin a new 2-week treatment cycle without dose modification if the absolute neutrophil count (ANC) is > 1.5 × 10^9/L and the platelet count is > 75 × 10^9/L at the start of each cycle. Otherwise,~~ Treatment ~~will~~ *should* be dose-modified or delayed until recovery of hematological parameters as stated in Table 4. If recovery has not occurred after a delay of 28 days, the patient should stop chemotherapy permanently.

SECTION 5.1.1.1.3: Oxaliplatin-Induced Neurotoxicity

If a patient experiences Grade 1 or 2 allergic reaction to oxaliplatin, pre-medication *should be given according to institutional practice* ~~with the following is suggested 30 minutes~~ prior to ~~subsequent~~ *further* study drug administration~~: dexamethasone 20 mg IV, diphenhydramine 50 mg IV, and one of the following: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV~~. If Grade 1–2 allergic reaction persists into the next cycle, ~~premedication with 50 mg oral dexamethasone 12 hours and 6 hours should be added~~ *appropriate premedication should be given according to institutional practice* prior to administration of oxaliplatin.

SECTION 5.3.5.3: Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. ~~Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to~~

~~reflect this.~~ *Initial adverse event intensity should be recorded at the time the event is reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded in the Adverse Event eCRF. Example: Headache, Grade 1 headache increases to Grade 2 headache. At the time of the intensity change, the Grade 2 intensity should be recorded in the Adverse Event eCRF in the most extreme intensity data field.*

A recurrent adverse event is one that *occurs and* resolves between patient evaluation timepoints and subsequently recurs. ~~Each recurrence of an adverse event~~ *All recurrent adverse events* should be recorded separately on ~~the~~ *an* Adverse Event eCRF.

If a change in intensity of an adverse event qualifies it as an SAE per the seriousness criteria (refer to Section 5.2.2), the event should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor following the SAE reporting procedure outlined in Section 5.4.2.

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information (for medical inquiries or patient-specific discussions)

~~Sites in the United States and Europe:~~

Medical Monitor: Steve Hack, M.D., Ph.D. *(based in South San Francisco, CA, U.S.A.)*

Telephone No.: +1 650 467 2063

~~Sites in the Asia-Pacific Region:~~

~~Medical Monitor: Alice Kang, M.D., Ph.D.~~

~~Telephone No.: +86 10 8507 5275~~

SECTION 6.4: EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients (ITT population) and the Met IHC 2+/3+ subgroup, with patients grouped according to the treatment assigned at randomization. The same analysis methods for primary and secondary analyses will be applied to both the ITT and Met 2+/3+ populations. ~~Objective response rate will be analyzed using all randomized patients who have measurable disease at baseline~~.

SECTION 6.4.1: Co-Primary Efficacy Endpoints

The two treatment comparisons of OS will be based on a stratified log-rank test at: 1) a one-sided significance level of 0.00577 for the Met 2+/3+ subgroup (see Section 6.1), and 2) a one-sided significance level of 0.02 for the ITT population. The stratification factors are Met expression (~~1+ vs. 2+/3+, for ITT comparison only~~ *level I, II, III, IV, or V*), world region (Asia-Pacific vs. other), ~~primary tumor location (GEJ vs. stomach),~~ and prior gastrectomy (yes vs. no).

SECTION 6.4.2: Secondary Efficacy Endpoints

Objective Response Rate. Objective response is defined as a CR or PR assessed by the investigator based on RECIST v1.1. Patients without a post-baseline tumor assessment will be considered as non-responders. The analysis population for ORR will be all randomized patients ~~with measurable disease at baseline~~. . . .

SECTION 10: REFERENCES

The reference list has been updated.

APPENDIX 1: Schedule of Assessments

Appendix 1 has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule for Collection of Blood Samples for Pharmacokinetics, Anti-Therapeutic Antibodies, and Exploratory Biomarkers

Appendix 2 has been revised to reflect the changes to the protocol.

APPENDIX 4: Examples of Patient Assignment to Met IHC Stratification Levels (I–V)

Appendix 4 has been added. Subsequent appendices have been renumbered accordingly.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ONARTUZUMAB (MetMAb) IN COMBINATION WITH 5-FLUOROURACIL, FOLINIC ACID, AND OXALIPLATIN (mFOLFOX6) IN PATIENTS WITH METASTATIC HER2-NEGATIVE, MET-POSITIVE GASTROESOPHAGEAL CANCER**
PROTOCOL NUMBER:	YO28322
VERSION NUMBER:	2
EUDRACT NUMBER:	2012-001402-23
IND NUMBER:	115018
TEST PRODUCT:	Onartuzumab (MetMAb, RO5490258, PRO143966)
MEDICAL MONITOR:	Steve Hack, M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of the signed form to a Roche representative.

Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, PHASE III, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF ONARTUZUMAB (MetMAb) IN COMBINATION WITH 5-FLUOROURACIL, FOLINIC ACID, AND OXALIPLATIN (mFOLFOX6) IN PATIENTS WITH METASTATIC HER2-NEGATIVE, MET-POSITIVE GASTROESOPHAGEAL CANCER**		
PROTOCOL NUMBER:	YO28322	**VERSION NUMBER:**	2
EUDRACT NUMBER:	2012-001402-23	**IND NUMBER:**	115018
TEST PRODUCT:	Onartuzumab (MetMAb, RO5490258, PRO143966)		
PHASE:	III		
INDICATION:	Metastatic gastroesophageal cancer (HER2-negative)		
SPONSOR:	F. Hoffmann-La Roche Ltd		

Objectives

Co-Primary Objectives

The co-primary objectives for this study are as follows:

- To evaluate the efficacy of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 as measured by overall survival (OS) in patients with previously untreated HER2–negative metastatic gastroesophageal cancer (GEC) classified as Met-IHC 2+ or 3+ (Met 2+/3+ subgroup)
- To evaluate the efficacy of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 as measured by OS in patients with previously untreated HER2-negative metastatic GEC classified as Met-IHC 1+, 2+, or 3+ (intent-to-treat [ITT] population)

Secondary Objectives

The secondary objectives for this study are as follows:

- To evaluate the efficacy of onartuzumab + mFOLFOX6 relative to placebo + mFOLFOX6 as measured by PFS and ORR in the Met 2+/3+ subgroup and in the ITT population
- To evaluate the safety of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 in patients with *metastatic* HER2-negative, *Met-positive* GEC, focusing on all adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities
- To compare patient-reported outcomes (PROs) following treatment with onartuzumab + mFOLFOX6 relative to placebo + mFOLFOX6, as measured by the EORTC QLQ-C30 and its gastric cancer module (the QLQ-STO22)
- To characterize the pharmacokinetics of onartuzumab when given with mFOLFOX6
- To evaluate serum levels and incidence of anti-therapeutic antibodies (ATAs) against onartuzumab

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the potential association of exploratory tissue, serum, and plasma biomarkers and inflammatory markers with study drug response, including efficacy and/or adverse events, and to increase knowledge and understanding of gastric cancer biology.

- To compare PROs of health status, as measured by the EuroQol EQ-5D instrument, of the two treatment arms in the Met 2+/3+ subgroup and in the ITT population
- To evaluate and compare disease control rate (DCR) and duration of response (DOR) in the Met 2+/3+ subgroup and in the ITT population.

Study Design

Description of Study

Study YO28322 is a randomized, Phase III, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of onartuzumab in combination with mFOLFOX6 as compared with treatment with mFOLFOX6 alone in patients with metastatic adenocarcinoma of stomach or gastroesophageal junction that is classified as both HER2 negative and Met positive.

Male and female patients aged ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have received no prior chemotherapy for metastatic HER2-negative GEC will be eligible. Tumor specimens from patients meeting eligibility criteria will be prospectively tested by *a* central laboratory to determine Met *expression status* using the Ventana® anti-Total c-MET (SP44) rabbit monoclonal antibody IHC assay, HER2 status, and Lauren histologic subtype. Only patients with Met–positive tumors will be enrolled (i.e., those with tumor samples *with ≥ 50% of tumor cells showing weak, moderate, and/or strong staining intensity*). Eligible patients will be stratified *according to the following stratification factors:*

- Met expression *by IHC (level I, II, III, IV, or V)*
- World region (Asia-Pacific vs. other)
- Prior gastrectomy (yes vs. no).

Patients will be randomized in a 1:1 ratio to receive either onartuzumab + mFOLFOX6 or placebo + mFOLFOX6. *Patients must receive their first dose of study drug within 3 days after being randomized.* Patients will receive a maximum of 12 cycles (each cycle is 14 days) of mFOLFOX6 with either placebo or onartuzumab. Patients whose disease has not progressed after 12 cycles of mFOLFOX6 with placebo or onartuzumab will continue treatment with either onartuzumab or placebo until disease progression, unacceptable toxicity, or death.

Tumor response evaluations will occur every 6 weeks (± 7 days) *during the first 12 months and then every 12 weeks (±14 days) until disease progression*. Response will be based on the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Tumor response data collection will continue if treatment is stopped prior to disease progression. Follow-up data capture, including subsequent anti-cancer therapies, will continue for each patient until patient death or study closure.

Tissue and blood samples will also be collected during the course of the study to evaluate exploratory prognostic and/or predictive biomarkers, including biomarkers related to HGF/Met pathway signaling, inflammation, and gastric cancer pathophysiology.

The pharmacokinetic (PK) and anti-therapeutic antibody (ATA) profile of onartuzumab will be assessed in patients at selected centers. Centers will be selected based their ability and willingness to execute PK/ATA sampling.

An independent Data Monitoring Committee (IDMC) will monitor all accumulating patient safety data approximately every 6 months during the course of the study.

One interim analysis for efficacy and futility for the Met 2+/3+ subgroup is planned once approximately 67% of the total OS events (79 deaths) have been observed in that subgroup. The Sponsor will examine the unblinded results and make the final decision regarding continuation of the study for the Met 2+/3+ subgroup. By this time, a sufficient number of events (449 deaths) in the ITT population for final analysis should have occurred; therefore, the single, final ITT analysis will likely coincide with the interim analysis of the Met 2+/3+ subgroup.

Number of Patients

The study will enroll approximately 800 patients at approximately 140 study sites.
The enrollment of Met IHC 1+ patients will be capped at 600 to ensure that at least 200 Met IHC 2+/3+ patients will be enrolled.

Target Population

Patients must meet the following criteria for study entry:

- Ability and willingness to provide written informed consent and to comply with the study protocol
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Life expectancy > 3 months
- Histologically confirmed adenocarcinoma of the stomach or GEJ with inoperable metastatic disease not amenable to curative therapy
- Adequate archival or newly obtained formalin-fixed paraffin-embedded (FFPE) tissue for central IHC assay of Met receptor and HER2 status
- Tumor (either primary or metastatic lesion) defined as Met positive by IHC (≥ 50% of tumor cells with membrane and/or cytoplasmic staining at weak, moderate, or high intensity)
- Measurable disease or non-measurable but evaluable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

  Patients with peritoneal disease would generally be regarded as having evaluable disease and be allowed to enter the trial.
- For women who are not postmenopausal (12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to use an adequate method of contraception (a method with a failure rate of < 1% per year, such as hormonal implants, combined oral contraceptives, or a vasectomized partner) during the treatment period and for at least 90 days after the last dose of onartuzumab/placebo and 6 months after the last dose of oxaliplatin
- For men: agreement to use a barrier method of contraception during the treatment period and for at least 90 days after the last dose of onartuzumab/placebo and 6 months after the last dose of oxaliplatin

Patients who meet any of the following criteria will be excluded from study entry:

<u>Cancer-Related Criteria</u>

- HER2-positive tumor (primary tumor or metastasis)

  HER2-positivity is defined as either IHC 3+ or IHC 2+/ISH+; ISH positivity is defined as a HER2:CEP17 ratio of ≥ 2.0.
- Previous chemotherapy for locally advanced or metastatic gastric carcinoma

  Patients may have received either neoadjuvant or adjuvant chemotherapy as long as it was completed at least 6 months prior to randomization.
- Prior exposure to experimental treatment targeting either the HGF or Met pathway
- History of another malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, *localized prostate cancer that has been treated surgically with curative intent and presumed cured,* or other malignancies with an expected curative outcome

<u>Hematologic, Biochemical, and Organ Function</u>

- Granulocyte count < 1500/mm^3, platelet count < 100,000/mm^3, and hemoglobin < 9.0 g/dL within 7 days prior to enrollment
- Partial thromboplastin time (PTT), international normalized ratio (INR), or prothrombin time (PT) > 1.5 x the upper limit of normal (ULN), except for patients receiving anticoagulation therapy
- AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP) ≥ 2.5 × ULN (≥ 5 × ULN with liver metastases)
- Total bilirubin ≥ 1.5 × ULN (except in patients diagnosed with Gilbert's disease)

- Serum calcium > ULN (corrected for low serum albumin concentrations)

  Corrected calcium (mg/dL) = serum Ca^{2+} + [(4.0–measured serum albumin) x 0.8]

  Corrected calcium (mmol/L) = serum Ca^{2+} + 0.02 × (40–serum albumin)
- Serum creatinine > 1.5 × ULN or calculated creatinine clearance < 60 mL/min (Cockcroft and Gault 1976)
- Uncontrolled diabetes as evidenced by fasting serum glucose level > 200 mg/dL

General

- Pregnancy or lactation
- Receipt of an investigational drug within 28 days prior to initiation of study drug
- Clinically significant gastrointestinal abnormalities, apart from gastric cancer, including uncontrolled inflammatory gastrointestinal diseases (Crohn's disease, ulcerative colitis, etc.)
- Significant history of cardiac disease (i.e., unstable angina, congestive heart failure, as defined by the New York Heart Association [NYHA] as Class II, III, or IV) within 6 months prior to Day 1 of Cycle 1, myocardial infarction within the previous year, or current cardiac ventricular arrhythmias requiring medication
- Significant vascular disease (such as aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- Serious (Grade ≥ 3) active infection at the time of randomization, or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment
- Known active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV), or known HIV-seropositivity.
- Radiotherapy within 4 weeks before start of study treatment (2-week interval allowed following palliative radiotherapy given to peripheral bone metastatic site and patient has recovered from all acute toxicities)
- Major surgery within 4 weeks before start of study treatment, without complete recovery
- Any condition (e.g., psychological, geographical, etc.) that does not permit compliance with study and follow-up procedures
- Peripheral neuropathy (NCI CTCAE v4.0, Grade > 1)
- Absence of deep tendon reflexes as the sole neurologic abnormality does not render the patient ineligible.
- Prior unanticipated severe reaction to fluoropyrimidine therapy (with or without documented dihydropyrimidine dehydrogenase [DPD] deficiency) or patients with known DPD deficiency
- Known sensitivity *or contraindication* to any component of study treatment
- Active (significant or uncontrolled) gastrointestinal bleeding

Length of Study

The total study duration, from the first patient recruited to the time of the primary analysis, is approximately 38 months: approximately 32 months of recruitment and approximately 6 months of follow-up for the last patient recruited.

End of Study

The final analysis for the ITT population will occur after 449 deaths have been observed (expected 29 months after first patient in [FPI]), while the final analysis for the Met 2+/3+ subgroup will occur after 118 deaths in the Met 2+/3+ subgroup have been observed (expected 38 months after FPI). Follow-up for survival will continue until all patients have either died, or are lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

Efficacy Outcome Measures

The efficacy outcome measures are as follows:

- OS, defined as the time from randomization to death from any cause
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first
- ORR, defined as partial response (PR) plus complete response (CR), as determined by the investigator using RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression (as determined by the investigator using RECIST v1.1) or death from any cause during the study
- DCR, defined as the rate of PR + CR + stable disease for at least 6 weeks, as defined by the investigator using RECIST v1.1

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, including serious adverse events
- Changes in clinical laboratory results during and following study drug administration
- Incidence and serum levels of ATAs to onartuzumab

Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are as follows:

- Pre-dose serum onartuzumab concentration (C_{min}) on Day 1 of Cycles 1, 2, and 4 and at study termination
- Post-dose serum onartuzumab concentration (C_{max}) on Day 1 of Cycle 1

Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- EORTC QLQ-C30
- EORTC QLQ-STO22
- EuroQol EQ-5D

Investigational Medicinal Products

Test Product

Onartuzumab (10 mg/kg IV) every 2 weeks until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death

Comparator

Placebo (0.9% normal saline solution; same dose, route, and regimen as described above for onartuzumab)

Non-Investigational Medicinal Products

mFOLFOX6 every 2 weeks:

Oxaliplatin (85 mg/m² IV)

Folinic acid (400 mg/m^2 *or as deemed appropriate per investigator*), or levofolinic acid (200 mg/m^2 *or as deemed appropriate per investigator*) if folinic acid unavailable

5-FU (400 mg/m^2 IV bolus followed by 2400 mg/m^2 continuous IV infusion over 46–48 hours)

Statistical Methods

The primary and secondary efficacy analyses will include all randomized patients (ITT population) and the Met IHC 2+/3+ subgroup, with patients grouped according to the treatment assigned at randomization. The same analysis methods for primary and secondary analyses will be applied to both the ITT and Met 2+/3+ populations.

Primary Analysis

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive.

The two treatment comparisons of OS will be based on a stratified log-rank test at: 1) a one-sided significance level of 0.00577 for the Met 2+/3+ subgroup, and 2) a one-sided significance level of 0.02 for the ITT population. The stratification factors are Met expression (*level I, II, III, IV, or V*), world region (Asia-Pacific vs. other), and prior gastrectomy (yes vs. no).

Results from an unstratified log-rank test will also be presented. Kaplan–Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan–Meier curve will be constructed to provide a visual description of the difference between the treatment arms. Estimates of the treatment effect will be expressed as HRs using a stratified Cox model, including 95% confidence intervals (CIs).

Determination of Sample Size

This Phase III trial is designed to further assess the efficacy and safety of onartuzumab in combination with mFOLFOX6 chemotherapy in patients with previously untreated metastatic GEC in HER2 negative and Met-positive populations (Met 1+, 2+, or 3+, or Met 2+/3+ only).

The study will enroll approximately 800 patients, with recruitment of Met 1+ patients capped at 600. Estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- One-sided significance level of 0.025 (accounting for the correlation between the two populations, the nominal alpha is 0.00577 for the Met 2+/3+ subgroup and 0.02 for the ITT population)
- Ninety-one percent power to detect an HR of onartuzumab + mFOLFOX6 versus placebo + mFOLFOX6 of 0.49, corresponding to an improvement in median OS from 9 months to 18 months, in the Met 2+/3+ subgroup
- Ninety percent power to detect an HR of onartuzumab + mFOLFOX6 versus placebo + mFOLFOX6 of 0.73, corresponding to an improvement in median OS from 9 months to 12.3 months, in the ITT population
- Dropout rate of 5% per year
- One interim efficacy and futility analysis planned for the Met 2+/3+ subgroup occurring at the time of the ITT final analysis, which is triggered by obtaining 67% of total OS information (79 events) from the Met 2+/3+ subgroup and 449 events from the ITT population
- Final efficacy analysis for the 2+/3+ subgroup triggered by 118 OS events (this will likely occur after the final analysis of the ITT population)

With these assumptions, the interim analysis of the Met 2+/3+ subgroup and the final analysis of the ITT population will occur approximately 29 months after the first patient has been enrolled. The final analysis of the Met 2+/3+ subgroup will occur approximately 38 months after the first patient is enrolled.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
ALP	alkaline phosphatase
ALT (SGPT)	alanine transaminase (serum glutamic pyruvic transaminase)
AST (SGOT)	aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATA	anti-therapeutic antibody
C_{max}	maximum concentration observed
C_{min}	minimum concentration observed
CNG	copy number gain
CNS	central nervous system
CR	complete response
CSF	colony-stimulating factor
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of objective response
DPD	dihydropyrimidine dehydrogenase
EC	ethics committee
ECG	*electrocardiogram*
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	standardized measure of health status developed by EuroQol in order to provide a simple, generic measure of health for clinical and economic appraisal
ESA	erythropoiesis-stimulating agent
ESMO	European Society for Medical Oncology
EuroQol	network of international multidisciplinary researchers devoted to the measurement of health status
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GEC	gastroesophageal cancer
GEJ	gastroesophageal junction

Abbreviation	Definition
HEENT	head, eye, ear, nose, and throat
HBV	hepatitis B virus
HCV	hepatitis C virus
HGF	hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	institutional review board
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice/web response system
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MetMAb	monoclonal antibody directed against Met receptor
mFOLFOX6	modified 5-fluorouracil, folinic acid (leucovorin), and oxaliplatin
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PVC	polyvinyl chloride
q14d	every 14 days
QLQ-C30	EORTC core quality-of-life questionnaire (30-item version)
QLQ-STO22	EORTC gastric cancer–specific quality-of-life questionnaire
QOL	quality of life

Abbreviation	Definition
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SDDV	study drug discontinuation visit
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

1. BACKGROUND

1.1 CANCER OF THE STOMACH AND GASTROESOPHAGEAL JUNCTION

1.1.1 Epidemiology of Gastroesophageal Carcinoma

Gastroesophageal cancer (GEC) represents a challenging global health problem. GEC is the fourth most common malignancy behind lung, breast, and colorectal cancers, with approximately 1 million cases per year occurring around the world. GEC is the second leading cause of cancer death globally, and it is estimated that in excess of 700,000 patients will die from the disease annually. There are significant geographic variations in the incidence of GEC; it is far more common in East Asia, Eastern Europe, and parts of Central and South America than it is in the United States or Western Europe. Almost 70% of cases arise in developing countries, with ~40% of cases occurring in China alone.

There are clear epidemiologic differences between cancer localized to the gastric cardia (gastroesophageal junction [GEJ]) and that localized to the rest of the stomach. Cancer of the cardia accounts for 39% of gastric cancer cases in Caucasian men in the United States but only in 4% of gastric cancers in men in Japan. For reasons that are not clear, the incidence of cancer of the gastric cardia and lower esophagus has increased rapidly in developed countries since the 1970s.

1.1.2 Histologic Classification, Etiology, and Molecular Subtyping

The vast majority of malignant tumors of the stomach (> 90%) are adenocarcinomas, and GEC can have different outcomes depending on anatomic location. More proximal GEJ and cardia tumors tend to have a worse prognosis compared with distal pyloric, antral, and curvature cancers.

The histology of GEC falls into two broad subtypes based on microscopic features observed in gastric tumors, namely intestinal or diffuse, according to Lauren's classification (Lauren 1965). Intestinal-type tumors tend to arise in the antrum or antral-corpus junction. Intestinal-type cancers are classically characterized by glandular differentiation on a background of gastric atrophy or intestinal metaplasia, whereas diffuse cancers typically appear as rows of single mononuclear "signet ring" cells with little cell adhesion. These apparently distinct features, however, are not always discernable in clinical samples, where inter-observer variation and unclassifiable or "mixed" subtypes are not uncommonly reported. Intestinal-type tumors are significantly more common than the diffuse type and tend to be associated with intestinal metaplasia and chronic inflammation (e.g., atrophic gastritis), often as a result of chronic *Helicobacter pylori* infection. By contrast, diffuse tumors do not generally develop on a background of intestinal metaplasia and inflammation is characteristically absent (Shah et al. 2011).

Histologic subtypes of GEC may be associated with distinct molecular features, clinical outcomes, and response to chemotherapeutic drugs (Tan et al. 2011). Expression of tumor suppressor genes such as phosphatase and tensin homology deleted from human chromosome 10 (PTEN), p53, and matrix metalloproteinase (MMP) is increased in intestinal-type carcinomas compared with the diffuse type (Zheng et al. 2007). Angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) may also be more commonly expressed in intestinal-type tumors than in diffuse-type cancers (Chen et al. 2004; Oh et al. 2008). Met overexpression may also correlate with histologic subtype (Power et al. 2010; Tan et al. 2011). The robustness and exact nature of the correlation between Met overexpression and histologic subtype is unclear at present; some studies suggest that Met overexpression is more commonly associated with intestinal-type tumors (Janjigian et al. 2011; Zhao et al. 2011b), whereas others indicate a stronger association with diffuse-type disease (Kuniyasu et al. 1992; Wu et al. 1997; Tahara 2004).

1.1.3 Prognosis

Survival rates from GEC have improved over the last few decades. Five-year overall survival (OS) in the Western world is estimated at ~20% (van Cutsem et al. 2011). In the West, fewer patients are referred for surgery compared with Asia, but those who undergo resection have a higher survival rate, which reaches 50%, possibly because of more accurate preoperative staging and improved imaging techniques. In large-scale screening programs in Asia, detection at earlier stages and more aggressive surgical approaches, including more frequent D2 lymph node resection, contribute to higher OS rates of ~60%. The median OS among patients with late-stage GEC is ~14 months in patients with locally advanced disease and 9 months in patients with metastatic disease (Cunningham et al. 2008).

1.2 SYSTEMIC TREATMENT FOR ADVANCED GASTROESOPHAGEAL CANCER

For patients with unresectable, metastatic disease, the main therapeutic option is chemotherapy. Chemotherapy has been shown to increase survival and quality of life (QOL) in patients with advanced GEC in several randomized trials and meta-analyses (De Vivo et al. 2000). It is evident that combination therapy outperforms single-agent (mainly 5-fluorouracil [5-FU]) therapy (hazard ratio [HR] = 0.83; 95% CI: 0.74, 0.93) (Wagner et al. 2010). Median survival for patients with metastatic disease treated with chemotherapy is approximately 8–11 months.

Despite intensive evaluation of multiple chemotherapy regimens, no international consensus exists regarding the optimal first-line regimen in advanced GEC. In Western countries and in Asia, the reference chemotherapy regimen for the first-line treatment of metastatic GEC is a fluoropyrimidine (5-FU or capecitabine) in combination with a platinum agent (either cisplatin or oxaliplatin) with or without a third cytotoxic drug (usually epirubicin or docetaxel) (van Cutsem et al. 2011). Based on several Phase III studies and meta-analyses, oxaliplatin and capecitabine have both been shown to be non-inferior to cisplatin and 5-FU, respectively (Al-Batran et al. 2008; Cunningham et al. 2010; Wagner et al. 2010; Montagnani et al. 2011). National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend that a fluoropyrimidine (either 5-FU or capecitabine) combined with either cisplatin or oxaliplatin are appropriate standards of care in the first-line setting (Ajani et al. 2010; van Cutsem et al. 2011).

The use of three-drug "triplet" chemotherapy remains controversial. The addition of a taxane or an anthracycline to a platinum-based doublet is associated with an incremental improvement in survival of ~1 month for patients with metastatic GEC (Wagner et al. 2010); however, this marginal survival benefit is countered by significant treatment-associated toxicity (van Cutsem et al. 2011). Triplet regimens such as docetaxel, cisplatin, and 5-FU (DCF); epirubicin, cisplatin, and 5-FU (ECF); or epirubicin, oxaliplatin, and capecitabine (EOX) are considered appropriate for highly functioning patients with minimal comorbidities (Shah and Kelsen 2010), but their systematic use is not generally recommended in treatment guidelines (van Cutsem et al. 2011).

1.2.1 Comparison of Cisplatin- and Oxaliplatin-Based Regimens

The mechanism of action of oxaliplatin is similar to that of cisplatin and other platinum compounds. Oxaliplatin demonstrates a broad spectrum of in vitro cytotoxic and in vivo antitumor activity and is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin. In addition, oxaliplatin in combination with 5-FU leads to synergistic antiproliferative activity in several in vivo tumor models (Raymond et al. 1998). The in vitro activity of cisplatin and oxaliplatin has been well investigated, and it is thought that oxaliplatin induces more double-strand breaks in DNA adducts compared with cisplatin, with increased cytotoxicity (Chaney et al. 2005).

Oxaliplatin and cisplatin are both widely accepted as part of the treatment armamentarium for advanced and metastatic GEC (NCCN Guidelines 2011; van Cutsem et al. 2011). In countries such as China and South Korea, where GEC is endemic, oxaliplatin-based combinations are the most commonly selected first-line palliative treatment regimen (Roche data on file; Zhang et al. 2011). Numerous studies have compared the efficacy and safety of cisplatin- and oxaliplatin-based regimens. In general, oxaliplatin-based regimens are associated with comparable efficacy, less toxicity, and better tolerability compared with cisplatin-based

combinations (Al-Batran et al. 2008; Cunningham et al. 2008; Starling et al. 2009; Montagnani et al. 2011).

A randomized German Phase III trial compared the efficacy and safety profile of fluorouracil, folinic acid, and oxaliplatin (FLO) with fluorouracil, folinic acid, and cisplatin (FLP) in 220 patients with advanced GEC (Al-Batran et al. 2008). FLO was associated with significantly less (any grade) anemia (54% vs. 72%), nausea (53% vs. 70%), vomiting (31% vs. 52%), alopecia (22% vs. 39%), fatigue (19% vs. 34%), renal toxicity (11% vs. 34%), thromboembolic events (0.9% vs. 7.8%), and treatment-related serious adverse events (9% vs. 19%). FLP was associated with significantly less peripheral neuropathy (22% vs. 63%). There was a trend toward improved median PFS with FLO versus FLP (5.8 vs. 3.9 months, respectively; $p = 0.077$) and no significant difference in median OS (10.7 vs. 8.8 months, respectively). However, in patients older than 65 years (n = 94), treatment with FLO resulted in significantly superior response rates (41.3% vs. 16.7%; $p = 0.012$), time to treatment failure (5.4 vs. 2.3 months; $p < 0.001$), and PFS (6.0 vs. 3.1 month; $p = 0.029$) and an improved OS (13.9 vs. 7.2 months) as compared with FLP.

A recent meta-analysis of data from randomized trials involving a total of 1294 patients demonstrated that oxaliplatin was associated with significantly improved progression-free survival (PFS) (HR = 0.88, $p = 0.02$) and OS (HR = 0.88, $p = 0.04$) compared with cisplatin. Oxaliplatin was associated with less neutropenia (OR = 0.53, $p < 0.01$) and fewer thromboembolic events (odds ratio [OR] = 0.42, $p < 0.01$), but was associated with increased neurotoxicity (OR = 6.91, $p < 0.01$) (Montagnani et al. 2011). In addition to a favorable safety profile, oxaliplatin can be given as a simple 2-hour intravenous infusion in contrast to cisplatin, which requires protracted intravenous (IV) hydration to prevent drug-related nephrotoxicity.

1.2.2 Targeted Agents in Advanced Gastric Cancer

It is generally accepted that cytotoxic chemotherapy, though important for effective cytoreduction of tumor burden, will not by itself significantly improve survival outcomes for patients with gastric cancer. Over the past decade, significant advances have been made in understanding the biological underpinnings of cancer, resulting in the development of several novel targeted agents.

To date, the trastuzumab for gastric cancer (ToGA) trial is the only positive Phase III study of a targeted agent in first-line GEC. In ToGA, the addition of trastuzumab to chemotherapy was found to be superior to chemotherapy alone in terms of OS, the primary endpoint, in patients with HER2-positive advanced gastric or GEJ cancer (Bang et al. 2010). Trastuzumab in combination with chemotherapy is now considered as a standard option for patients with HER2-positive advanced GEC.

The anti-VEGF (vascular endothelial growth factor) monoclonal antibody bevacizumab was recently evaluated in a Phase III trial (AVAGAST; Ohtsu et al. 2011). Patients were

randomized to receive cisplatin/capecitabine (or 5-FU) with or without bevacizumab. The difference in OS was not statistically significant, and therefore the trial failed to meet the primary endpoint (HR = 0.87; p = 0.1) (Ohtsu et al. 2011). A confirmatory Phase III study in a Chinese population (AVATAR) with a design identical to AVAGAST also failed to meet a primary endpoint of OS (Shen et al. 2012).

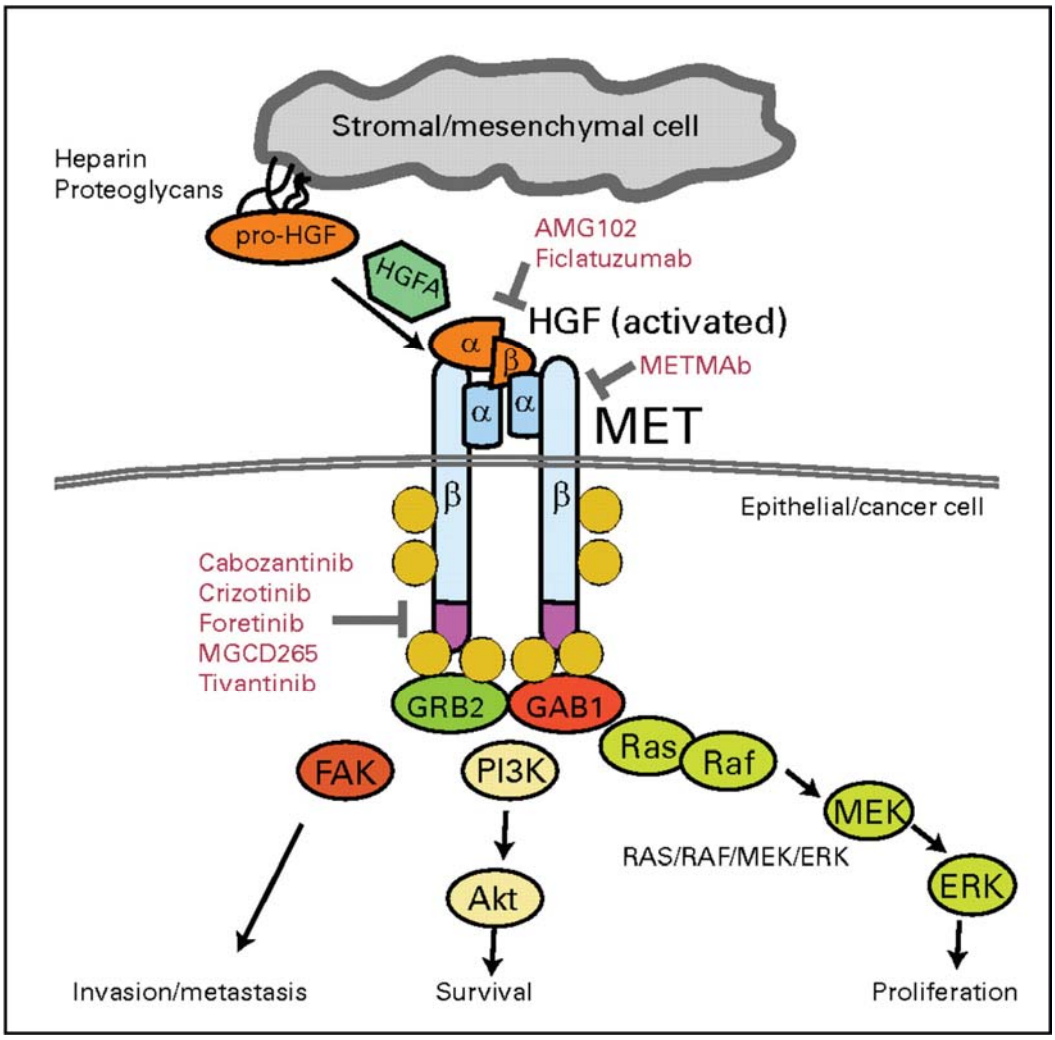
The REAL-3 trial evaluated the addition of panitumumab (an anti-EGFR antibody) to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced GEC (Waddell et al. 2012). The addition of panitumumab to EOC chemotherapy was associated with worsening of OS (the primary endpoint) in an unselected population with advanced GEC (HR = 1.37 [95% CI: 1.07, 1.76]; p = 0.013).

1.3 MET BIOLOGY AND ONARTUZUMAB

1.3.1 Met Signaling

The Met protooncogene, located on the 7q31 locus, encodes the receptor tyrosine kinase Met, also known as the Met or hepatocyte growth factor (HGF) receptor. The binding of HGF to the Met receptor results in C-terminus receptor tyrosine phosphorylation and receptor activation. HGF (also known as scatter factor) and its receptor Met promote cell proliferation, motility, invasion, survival, and morphogenic changes that can stimulate tissue repair and regeneration in normal tissue but can stimulate growth, invasion, and survival in tumor cells (Stoker et al. 1987; Miyazawa et al. 1989; Nakamura et al. 1989; Zarnegar and Michalopoulos 1989; Gherardi and Stoker 1990; Bottaro et al. 1991; Weidner et al. 1991; Ma et al. 2003). Met pathway activation promotes proliferative and antiapoptotic activities common to many growth factors; however, Met activation seems to particularly stimulate cell-cell detachment, migration, and tumor invasiveness (Trusolino et al. 2010). Dysregulation of the HGF/Met pathway in cancer can occur by several mechanisms, including aberrant paracrine and autocrine activation via inappropriate ligand production, activating mutation, genomic amplification, increased transcription, or Met receptor overexpression.

Figure 1 Met Signaling Pathway



ERK = extracellular signal–regulated kinase; FAK = focal adhesion kinase; MEK = mitogen-activated protein kinase/ERK kinase; PI3K = phosphoinositide 3-kinase.

Hepatocyte growth factor (HGF)/MET signaling pathway transduces invasive growth signals from mesenchymal to epithelial cells. HGF precursor secreted by mesenchymal cells is activated by HGFA and binds to MET receptor on epithelial cells. MET kinase activation results in trans-autophosphorylation and binding of adaptor proteins such as growth factor receptor–bound protein 2 (GRB2) and GRB2-associated binding protein 2 (GAB2), which form scaffolds for recruitment and activation of signaling proteins. Signals generated from these assembled structures lead to changes in gene expression and cell behavior, with increased proliferation, survival, motility, invasiveness, and stimulation of angiogenesis. Amplification or activation of MET can result in transformation, and inhibitors of MET pathway components are being developed as cancer therapies.

Source: Appleman LJ. MET signaling pathway: a rational target for cancer therapy. J Clin Oncol 2011;29:4837–8.

Met is also known to be expressed on endothelial and lymphendothelial cells, and therefore has been implicated in the initiation, modulation, and/or maintainance of angiogenesis and/or lymphangiogenesis (Zhao et al. 2011a). Therefore, the mechanism of action of Met inhibitors such as onartuzumab may include both anti-tumor effects as well as anti-angiogenic and/or anti-lymphangiogenic effects.

1.3.2 Met Pathway Aberrations in Gastric Cancer

Met pathway dysregulation is known to occur in gastric carcinomas and is associated with a more aggressive phenotype (Wu et al. 1998; Nakajima et al. 1999; Huang et al. 2001; Amemiya et al. 2002; Inoue et al. 2004; Toiyama et al. 2012).

Met mutations appear to be exceedingly rare in GEC (Lee et al. 2000; Chen et al. 2001; Kim et al. 2003; Asaoka et al. 2010).

The *MET* oncogene is amplified in a fraction of human gastric carcinoma cell lines and clinical cases (Smolen et al. 2006; Lee et al. 2011; Lennerz et al. 2011). *MET* amplification has been mainly studied in Asian patients thus far, and different methods have been used for its assessment. Earlier studies using Southern blot analysis found *MET* amplification in 10% of GEC specimens (Tsugawa et al. 1998; Nakajima et al. 1999), whereas Hara et al. (1998) reported an amplification rate of 4% using fluorescence in situ hybridization (FISH). More recently, Lee et al. (2011), using quantitative PCR, showed *MET* gene copy number gain (CNG) more than 4 copies in 21% of Korean clinical cases. Met CNG (≥ 5 copies) was reported in 21/216 (10%) of stage II/III GEC cases in an Italian cohort with CNG ≥ 5 associated with significantly worse prognosis (Graziano et al. 2011). The seemingly lower detection rate with FISH was confirmed by two recent studies reporting either a zero or 2% incidence of *MET* amplification by FISH in Western populations (Graziano et al. 2011; Janjigian et al. 2011). Taken together, the reported frequencies of *MET* amplification indicate that genomic activation of the pathway may be less frequent than previously thought and may occur less commonly in Western populations. *MET* gene amplification may confer exquisite sensitivity to small molecule Met pathway inhibitors in gastric cancer cell lines (Smolen et al. 2006; Lee et al. 2011).

HGF/Met co-expression, suggestive of either autocrine or paracrine signaling, has been reported in gastric cancer cell lines and tumor specimens (Park et al. 2000; Toiyama et al. 2012). High co-expression of both HGF and Met are correlated with both diminished median survival times and the development of peritoneal metastases. Preclinical HGF/Met autocrine tumor models have demonstrated exquisite sensitivity to Met inhibitors in vitro and in vivo (Jin et al. 2008). Serum HGF is elevated in patients with gastric cancer and circulating HGF levels decline following gastrectomy (Beppu et al. 2000; Tanaka et al. 2004; Han et al. 2005).

Overexpression of Met receptor protein is the most common mechanism by which the Met pathway is unregulated in cancer. Met overexpression, as assessed by

immunohistochemistry (IHC), has been shown to occur in 40%–60% of GECs (Iveson et al. 2011; Janjigian et al. 2011; Lee et al. 2011; Zhao et al. 2011b) and is associated with more aggressive tumor biology and worsened clinical outcomes.

1.3.3 Onartuzumab

Onartuzumab is a recombinant, fully humanized, monovalent monoclonal anti-Met antibody based on the human IgG1κ (kappa) framework sequence. It binds in the Sema domain of Met within the extracellular domain, where it acts to inhibit HGF binding and initiation of receptor activation. This monovalent (or "one-armed") antibody is composed of a full-length heavy chain, a light chain, and a truncated heavy chain that consists only of the C_H2 and C_H3 domains. The molecule is not glycosylated and has a molecular mass of approximately 99 kDa.

The unique monovalent design of onartuzumab eliminates the potential for Met activation via antibody-driven receptor dimerization, which can occur with a bivalent antibody against Met (Prat et al. 1998).

See the Onartuzumab (MetMAb) Investigator Brochure for details on nonclinical studies.

1.3.4 Clinical Phase I

Study OAM4224g was a sequential dose-escalation study of onartuzumab administered by IV infusion every 3 weeks until disease progression in patients with advanced cancer. Using standard "3 + 3" escalation cohorts, a total of 21 patients were treated at dose levels of 1 mg/kg (n = 3), 4 mg/kg (n = 6), 10 mg/kg (n = 3), 20 mg/kg (n = 3), or 30 mg/kg (n = 6) mg/kg given every 3 weeks as a single agent. A single dose-limiting toxicity (DLT) of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 pyrexia occurred at a dose level of 4 mg/kg. A dose of 15 mg/kg every 3 weeks was subsequently selected to provide an exposure level consistent with that required for efficacy in nonclinical models ($C_{min} \geq 15$ µg/mL), and an additional 13 patients received single-agent onartuzumab on that dosing regimen.

Patients in this study ranged from 29 to 85 years of age. Tumor types included non–small cell lung, colorectal, gastric, adrenal, head and neck, cervical, liver, ovarian, pancreatic, thyroid, uterine, renal, and ampulla of Vater cancers, as well as melanoma, mesothelioma, and sarcoma. Met expression on tumor tissue was not evaluated in this study. Most patients had received multiple prior anti-cancer therapies.

The most frequently reported adverse events (AEs) occurring in ≥ 20% of patients treated with single-agent onartuzumab included fatigue (56%), peripheral edema (35%), decreased appetite (32%), constipation (29%), nausea (27%), vomiting (24%), and hypoalbuminemia (24%). There was no consistent relationship between AEs and dose level. Grade 1–2 (according to the NCI CTCAE) treatment-related AEs included fatigue (38%), peripheral edema (18%), hypoalbuminemia (12%), nausea (12%), vomiting (9%), anorexia (9%), and muscle spasms (9%). Treatment-related Grade 3 AEs included

peripheral edema in 3 patients (9%), and abdominal pain, AST increase, fever, and hyponatremia in 1 patient each. There were no Grade 4 AEs reported in the patients receiving Onartuzumab as a single agent.

Six onartuzumab-treated patients were determined to be positive for anti-therapeutic antibodies (ATAs) to onartuzumab; however, the titers were low, did not increase over time, and did not correlate with onartuzumab drug levels or any changes in the nature or time course of adverse effects.

Onartuzumab was generally safe and well tolerated. The maximum tolerated dose was not reached either in single-agent dose escalation. The majority of adverse events were Grades 1 or 2. With the exception of peripheral edema, no obvious dose relationship associated with the adverse events was demonstrated.

Onartuzumab showed linear pharmacokinetics in the dose range from 4 to 30 mg/kg, with mean clearance values with a range of 6.7–8.3 mL/day/kg. The 1 mg/kg dose had faster clearance (approximately 2-fold) compared with the other dose groups. The observed onartuzumab clearance at doses ≥ 4 mg/kg is slightly faster than that for standard bivalent antibodies. The AUC and C_{max} increase proportionally with dose, further suggesting that the pharmacokinetics of onartuzumab are linear in this dose range. The half-life is approximately 10 days.

1.3.5 Clinical Phase II

The first proof-of-concept study supporting the therapeutic value of Met inhibition with onartuzumab was a randomized, placebo-controlled Phase II trial evaluating erlotinib + placebo versus erlotinib + onartuzumab in patients who had received one to two prior treatments for metastatic NSCLC (Study OAM4558g; Spigel et al. 2011). The results of this study in the intent-to-treat (ITT; i.e., as-randomized) population demonstrated no incremental benefit when onartuzumab was added to erlotinib. However, in patients who had Met-positive tumors (≥ *50% of tumor cells with moderate or strong Met staining intensity*), the addition of onartuzumab to erlotinib treatment resulted in clinically meaningful and statistically significant improvements in PFS and OS. The stratified PFS HR of the onartuzumab + erlotinib arm relative to the placebo + erlotinib arm was 0.529 (95% CI: 0.284, 0.986; log-rank p = 0.04), with median PFS of 2.9 months versus 1.5 months, respectively. The stratified OS HR of the onartuzumab + erlotinib arm relative to the placebo + erlotinib arm was 0.374 (95% CI: 0.193, 0.722; log-rank p = 0.002), with median OS of 12.6 months versus 3.8 months, respectively. In the Met-negative population, patients treated with onartuzumab + erlotinib had a shorter duration of PFS (HR = 1.82; 95% CI: 0.99, 3.32; log-rank p = 0.05) and OS (HR = 1.78; 95% CI: 0.79, 3.99; log-rank p = 0.16) compared with those treated with placebo + erlotinib. The reason for the poor outcomes in this subset of patients cannot be explained using known clinical variables.

The combination of onartuzumab + erlotinib did not substantially alter the safety profile of erlotinib. Although there was worse OS in the Met-negative group of NSCLC patients

treated with onartuzumab in combination with erlotinib, the overall AE profile for onartuzumab in this population was not substantially different from that seen in the Met–positive population, and the number of adverse events that resulted in death was the same in each treatment arm. Although a higher rate of Grade ≥ 3 AEs and SAEs was observed in the onartuzumab treatment arm of the Met-negative population, this rate was not different from the rates seen in either study arm of the Met-positive population. A clinical review of the AE-related deaths that occurred on the onartuzumab arms in both Met diagnostic populations shows primarily NSCLC-associated events. The poorer OS outcome of onartuzumab-treated patients with Met–negative tumors does not appear to be related to drug-related toxicity. There were no laboratory abnormalities that could be attributed to the administration of onartuzumab.

The comprehensive safety data collected in this trial suggest onartuzumab in combination with erlotinib has an acceptable safety profile. The most common AEs associated with the administration of onartuzumab included peripheral edema, asthenia, insomnia and pyrexia. These events were commonly NCI CTCAE Grade 1–3 in severity and not dose limiting in the majority of patients.

The incidence of adverse events associated with the administration of erlotinib (e.g., diarrhea, rash, and acneiform dermatitis) was not increased with the addition of onartuzumab. Onartuzumab does not appear to be associated with immune adverse events resulting from ATA formation, as only 1 patient at one timepoint in the study had a positive ATA result, with no clinical sequelae.

The efficacy and safety data from this trial suggest a favorable benefit–risk profile for the combination of onartuzumab + erlotinib in patients with Met-positive NSCLC. The results by Met diagnostic status suggest that the Met status may be predictive for onartuzumab efficacy.

The average peak and trough concentrations of onartuzumab at Cycle 1 were 388 (± 77) and 40 (± 15) μg/mL, respectively. Following multiple doses of onartuzumab, a moderate drug accumulation (~1.5-fold) was observed. At Cycle 3, approaching the steady state, the peak and trough concentrations were 500 (± 183) and 70 (± 32) μg/mL, respectively. All patients achieved steady-state trough concentrations above 15 μg/mL.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.4.1 Met Pathway Upregulation, GEC Prognosis, and Response to Treatment

Aberrant upregulation of the Met/HGF pathway has been associated with poor prognosis in multiple human malignancies, including GEC. Study YO28322 is part of a clinical development plan that aims to evaluate the clinical utility of onartuzumab in patients with metastatic GEC. In GEC, dysregulation of the HGF/Met pathway has been linked to more aggressive tumor biology, adverse treatment outcomes, and poor overall prognosis (Graziano et al. 2011; Lee et al. 2011; Lennerz et al. 2011; Zhao et al.

2011b; Toiyama et al. 2012). A number of studies have also shown that aberrant HGF/Met signaling is a mediator of resistance to DNA-damaging chemotherapeutics, including platinum agents (Bowers et al. 2000; Chen et al. 2008). In preclinical models, inhibition of HGF/Met signaling can bring about an increase in sensitivity to platinum drugs (Bowers et al. 2000; Bu et al. 2011; *Catenacci et al. 2011a*). Based on these data, it is plausible that inhibition of Met signaling with onartuzumab may increase the effectiveness of platinum-based chemotherapy when administered to patients with metastatic GEC.

1.4.2 Activity of Met-Directed Drugs in Advanced GEC

Preliminary data from Phase I and Phase II studies indicate that Met-targeted agents, including onartuzumab, are active in GEC (Moss et al. 2010; Catenacci et al. 2011b; Lennerz et al. 2011; Yap et al. 2011).

A durable complete response (CR) was observed in 1 of 5 patients with treatment-refractory gastroesophageal carcinoma in a Phase I study that evaluated onartuzumab monotherapy in patients with solid tumors refractory to standard treatment (Moss et al. 2010; Catenacci et al. 2011b). A 48-year-old female patient with chemotherapy-refractory GEC with metastasis to the liver was enrolled into the study. MetMAb was administered intravenously every 3 weeks beginning in March 2008 for 10 doses. A CR was observed in June 2008, after the patient had received 4 doses of MetMAb, which was subsequently confirmed by MRI in September 2008. Toxicities reported included Grade 2 anasarca and Grade 2 hypoalbuminemia. The CR persisted for ~2.5 years before a new asymptomatic lesion in the transverse colon was noted along with a new metastatic deposit at the gastrohepatic ligament in October 2010. To further evaluate the complete radiologic response observed after treatment with onartuzumab, additional correlative studies were conducted. There was no evidence of high-level, focal *MET* gene amplification, which has been identified in approximately 2%–20% of gastroesophageal adenocarcinomas (Lee et al. 2011; Lennerz et al. 2011). However *MET* gene polysomy was noted, indicating some degree of genomic Met upregulation. Immunohistochemical analysis of Met and HGF (the only known ligand for Met) indicated evidence consistent with an autocrine signaling loop. Evidence of HGF/Met autocrine signaling has been noted previously in cases of GEC and maybe associated with peritoneal metastases and poor prognosis (Park et al. 2000; Toiyama et al. 2012). The HGF serum level was extremely high before treatment with onartuzumab and precipitously decreased immediately after drug exposure. Serum HGF levels remained low, even at the time of widespread recurrence of disease (Catenacci et al. 2011b). Elevated levels of serum HGF have been noted in ~30% of patients with GEC (Taniguchi et al. 1997; Niki et al. 1999; Tanaka et al. 2004).

Rilotumumab (AMG-102), an anti-HGF antibody, has recently been shown in a randomized Phase II study to improve PFS (HR = 0.64; 80% CI: 0.48, 0.85) and OS (HR = 0.73; 80% CI: 0.53, 1.01) in patients with advanced GEC when combined with triplet (ECX)

chemotherapy (Iveson et al. 2011). The incidence of peripheral edema, hematologic toxicities, and thromboembolic events was higher in the experimental arms. Of note, the treatment effect of rilotumumab was magnified (OS HR = 0.29; 80% CI: 0.11, 0.76) in patients with high levels of Met protein expression as assessed by IHC (defined as > 50% of tumor cells positive for Met), indicating that Met expression by IHC may be a valid biomarker in the setting of GEC.

Tumor regression has also been seen in patients with advanced, refractory GEC following treatment with small molecule Met inhibitors (Lennerz et al. 2011; Yap et al. 2011).

Together these data provide evidence that the Met pathway is a valid target in advanced GEC.

1.4.3 Onartuzumab Studies in Other Tumor Types

To date, onartuzumab has been studied in one Phase I trial (OAM4224g) and one randomized Phase II trial (OAM4558g). Randomized Phase II trials are currently ongoing in triple-negative metastatic breast cancer (OAM4861g), first-line metastatic colorectal cancer (GO27827/SCRI GI155), *relapsed glioblastoma (GO27819)*, and first-line non–small cell lung cancer (squamous and non-squamous [GO27820 and GO27821, respectively]). A Phase III study in second/third-line NSCLC (OAM4971g) is open to enrollment.

GO27827/SCRI GI155 is currently randomizing eligible patients to mFOLFOX6/bevacizumab ± onartuzumab. No new safety signals were found following the initial safety data review of 12 randomized patients and the study remains open to enrollment.

Overall, these data support further clinical development of onartuzumab in combination with standard-of-care treatment in patients with metastatic GEC.

2. OBJECTIVES

2.1 CO-PRIMARY OBJECTIVES

The co-primary objectives for this study are as follows:

- To evaluate the efficacy of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 as measured by OS in patients with previously untreated HER2–negative metastatic GEC classified as Met-IHC 2+ or 3+ (Met 2+/3+ subgroup)
- To evaluate the efficacy of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 as measured by OS in patients with previously untreated HER2-negative metastatic GEC classified as Met-IHC 1+, 2+, or 3+ (intent-to-treat [ITT] population)

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To evaluate the efficacy of onartuzumab + mFOLFOX6 relative to placebo + mFOLFOX6 as measured by PFS and ORR in the Met 2+/3+ subgroup and in the ITT population
- To evaluate the safety of onartuzumab + mFOLFOX6 compared with placebo + mFOLFOX6 in patients with *metastatic* HER2-negative, *Met-positive* GEC, focusing on all adverse events, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0) Grade ≥ 3 adverse events, and Grade ≥ 3 laboratory toxicities
- To compare patient-reported outcomes (PROs) following treatment with onartuzumab + mFOLFOX6 relative to placebo + mFOLFOX6, as measured by the EORTC QLQ-C30 and its gastric cancer module (the QLQ-STO22)
- To characterize the pharmacokinetics of onartuzumab when given with mFOLFOX6
- To evaluate serum levels and incidence of anti-therapeutic antibodies (ATAs) against onartuzumab

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the potential association of exploratory tissue, serum, and plasma biomarkers and inflammatory markers with study drug response, including efficacy and/or adverse events, and to increase knowledge and understanding of gastric cancer biology
- To compare PROs of health status, as measured by the EuroQol EQ-5D instrument, of the two treatment arms in the Met 2+/3+ subgroup and in the ITT population
- To evaluate and compare disease control rate (DCR) and duration of response (DOR) in the Met 2+/3+ subgroup and in the ITT population

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview

Study YO28322 is a randomized, Phase III, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of onartuzumab in combination with mFOLFOX6 as compared with treatment with mFOLFOX6 alone in patients with metastatic adenocarcinoma of stomach or gastroesophageal junction that is classified as both HER2 negative and Met positive.

Male and female patients aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who have received no prior chemotherapy for metastatic HER2-negative GEC will be eligible. Tumor specimens from patients meeting eligibility criteria will be prospectively tested by *a* central laboratory to determine Met

expression status using the Ventana® anti-Total c-MET (SP44) rabbit monoclonal antibody IHC assay (see Appendix 3), HER2 status, and Lauren histologic subtype. Only patients with Met–positive tumors will be enrolled (i.e., those with tumor samples *with ≥ 50% of tumor cells showing weak, moderate, and/or strong staining intensity*; see Appendix 3). Eligible patients will be stratified *according to the following stratification factors:*

- Met expression *by IHC (level I, II, III, IV, or V; see Table 1 in Section 3.3.4.1)*
- World region (Asia-Pacific vs. other)
- Prior gastrectomy (yes vs. no)

Patients will be randomized in a 1:1 ratio to receive either onartuzumab + mFOLFOX6 or placebo + mFOLFOX6. *Patients must receive their first dose of study drug within 3 days after being randomized.* Patients will receive a maximum of 12 cycles (each cycle is 14 days) of mFOLFOX6 with either placebo or onartuzumab. Patients whose disease has not progressed after 12 cycles of mFOLFOX6 with placebo or onartuzumab will continue treatment with either onartuzumab or placebo until disease progression, unacceptable toxicity, or death. The study schema is shown in Figure 2.

Tumor response evaluations will occur every 6 weeks (± 7 days) *during the first 12 months and then every 12 weeks (±14 days) until disease progression*. Response will be based on the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Tumor response data collection will continue if treatment is stopped prior to disease progression. Follow-up data capture, including subsequent anti-cancer therapies, will continue for each patient until patient death or study closure.

Tissue and blood samples will also be collected during the course of the study to evaluate exploratory prognostic and/or predictive biomarkers, including biomarkers related to HGF/Met pathway signaling, inflammation, and gastric cancer pathophysiology.

The PK and ATA profile of onartuzumab will be assessed in patients at selected centers. Centers will be selected based their ability and willingness to execute PK/ATA sampling.

An independent Data Monitoring Committee (IDMC; see Section 3.1.2) will monitor all accumulating patient safety data approximately every 6 months during the course of the study.

One interim analysis for efficacy and futility for the Met 2+/3+ subgroup is planned once approximately 67% of the total OS events (79 deaths) have been observed in that subgroup. The Sponsor will examine the unblinded results and make the final decision regarding continuation of the study for the Met 2+/3+ subgroup. By this time, a sufficient number of events (449 deaths) in the ITT population for final analysis should have occurred; therefore, the single, final ITT analysis will likely coincide with the interim analysis of the Met 2+/3+ subgroup.

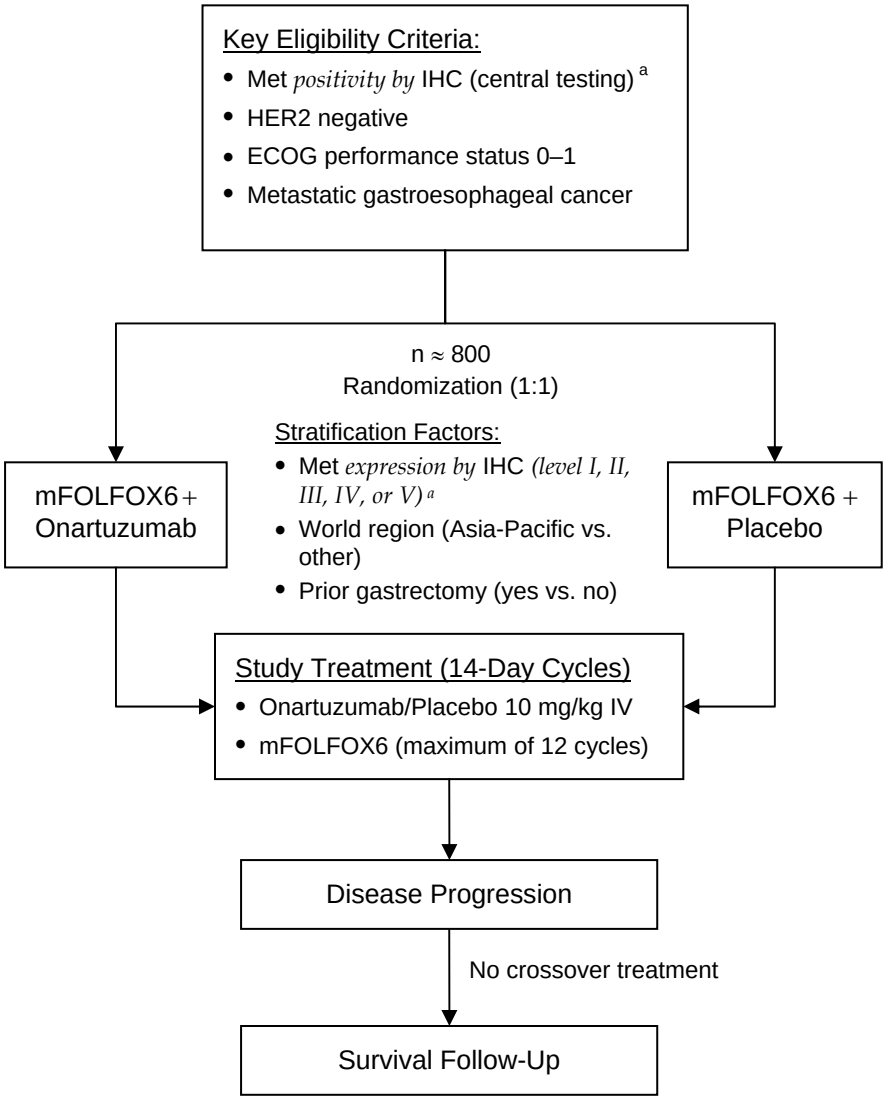
PLANNED TOTAL SAMPLE SIZE

The study will enroll approximately 800 patients at approximately 140 study sites. The enrollment of Met IHC 1+ patients will be capped at 600 to ensure that at least 200 Met IHC 2+/3+ patients will be enrolled.

STUDY DURATION

The total study duration, from the first patient recruited to the time of the primary analysis, is approximately 38 months: approximately 32 months of recruitment and approximately 6 months of follow-up for the last patient recruited.

Figure 2 Study Design



[a] *Eligibility based on Met staining in 50% or more tumor cells.*
[b] *See Section 3.3.4.1 for description of Met IHC levels.*

A schedule of assessments is provided in Appendix 1.

3.1.2 Independent Data Monitoring Committee

The IDMC will consist of independent experts not involved in the study, including oncologists and a biostatistician. The role of the IDMC and the decision-making process will be documented in a separate IDMC charter.

An IDMC will monitor all accumulating patient safety data approximately every 6 months during the course of the study.

Safety data provided to the IDMC will include demographic data, adverse events, serious adverse events (including copies of the serious adverse event forms received), laboratory abnormalities (hematology and biochemistry), and Met status; further information will be provided on request.

All safety data summaries/analyses by treatment arm for the IDMC's review will be prepared by an independent data-coordinating center (IDCC), an external statistical service provider that will assist the IDMC with the interim data reviews. The IDCC is independent of the Sponsor's study management team and will not disseminate unblinded safety data results to anyone except IDMC members.

3.1.3 Data Review at Interim Analysis

For analysis of the efficacy endpoint of OS, the Sponsor will review the unblinded results at the prespecified interim analysis for the Met 2+/3+ subgroup (67% deaths, coincident with the final analysis in the ITT population), and the final decision regarding study continuation in this subgroup will rest with the Sponsor.

3.2 END OF STUDY

The final analysis for the ITT population will occur after 449 deaths have been observed (expected 29 months after first patient in [FPI]), while the final analysis for the Met 2+/3+ subgroup will occur after 118 deaths in the Met 2+/3+ subgroup have been observed (expected 38 months after FPI). Follow-up for survival will continue until all patients have either died, or are lost to follow-up, or the Sponsor decides to end the trial, whichever occurs first.

3.3 RATIONALE FOR STUDY DESIGN

The aim of this study is to compare efficacy and safety of onartuzumab versus placebo in combination with an accepted standard therapy mFOLFOX6 in previously untreated patients with metastatic gastric cancer that is classified as both HER2 negative and Met positive.

3.3.1 Rationale for Test Product Dosage

The proposed dose of onartuzumab in this study is 10 mg/kg given intravenously every 14 days. This dose was proposed on the basis of nonclinical pharmacokinetic and pharmacodynamic data, which suggest a target concentration associated with efficacy of

15 μg/mL (Salgia et al. 2008). Based on the Phase I (OAM4224g) and Phase II (OAM4558g) data, a dose of 10 mg/kg given every 14 days is expected to maintain the desired minimum serum concentration of 15 μg/mL in ≥ 90% of patients and hence anticipated to achieve clinical tumor response. Additionally, as mFOLFOX6 is administered every 2 weeks, the administration of onartuzumab every 2 weeks offers patient convenience.

The doses of 5-FU, folinic acid, and oxaliplatin are based on the literature and treatment guidelines described in Section 1.2.

3.3.2 Rationale for Patient Population

Patients with metastatic GEC will be enrolled into this trial. Historically, this patient population has a poor prognosis, with 5-year OS rates of approximately 20% (van Cutsem et al. 2011). *This prognosis is likely to be further worsened as a result of Met overexpression (Amemiya et al. 2002; Drebber et al. 2008; Toiyama et al. 2012).* Data from randomized Phase II *studies in* refractory NSCLC (OAM4558g; see Section 1.3.5) *and advanced GEC* provide proof of concept that blocking Met signaling may be efficacious in patients with Met-positive tumors (Spigel et al. 2011; *Iveson et al. 2011; Oliner et al. 2012*).

It is probable that the benefit of onartuzumab will only be seen in patients with tumors expressing the Met receptor at or above physiological levels. As a result, eligible patients with Met-positive metastatic GEC will be enrolled into this Phase III study (YO28322). An IHC assay will be used to measure Met receptor expression and to prospectively screen and enroll patients with Met-positive GEC. Tumor samples from eligible patients will be considered Met-positive if ≥ 50% of malignant cells stain positive for Met at weak, moderate, and/or strong intensity levels (see Appendix 3).

This IHC-based diagnostic definition of Met positivity is based on published data suggesting that the efficacy of HGF/Met axis inhibition is maximized in cases where the majority of tumor cells (≥ 50%) within a sample are found to be Met positive (Iveson et al. 2011; Oliner et al. 2012).

3.3.3 Rationale for Control Group

There is no single standard, globally accepted first-line reference chemotherapeutic regimen for advanced gastric cancer. A fluoropyrimidine (5-FU or capecitabine) in combination with platinum agent (cisplatin or oxaliplatin) is an accepted standard of care in both Western and Asian countries (Kim et al. 1993; Ajani 2000; Ohtsu et al. 2003; Ajani et al. 2010; NCCN 2011). *Both classes of agent* are considered to be interchangeable according to NCCN and ESMO treatment guidelines. The control group in this study will receive the combination of 5-FU, folinic acid, and oxaliplatin (mFOLFOX6), which is a globally accepted standard-of-care treatment for patients with metastatic GEC. The safety of this combination regimen is well documented. Oxaliplatin was chosen as the platinum agent for the following reasons:

- The FOLFOX regimen using biweekly oxaliplatin and continuous infusion 5-FU/folinic acid has shown both safety and efficacy advantages compared with 5-FU/cisplatin in a randomized Phase III study (Al-Batran et al. 2008).
- Oxaliplatin is associated with lower levels of myelotoxicity, albeit at the expense of more sensory neuropathy (Montagnani et al. 2011). Preliminary data in GEC suggest that Met pathway inhibition in combination with cisplatin-based chemotherapy (ECX) results in accentuated myelotoxicity compared with ECX alone (Grade 3/4 neutropenia 44% vs. 28%; thrombocytopenia 6% vs. 0%) (Iveson et al. 2011). This may be due to the involvement of the HGF/Met pathway in maturation of bone marrow progenitor cells (Galimi et al. 1994). The use of oxaliplatin rather than cisplatin in this study may result in a combination regimen with minimal additional bone marrow toxicity.
- Unlike cisplatin, patients receiving oxaliplatin do not require pre-infusion hydration, making the drug easier to administer in a routine clinical setting.
- The combination of onartuzumab with 5-FU and oxaliplatin is not expected to have overlapping toxicity, based on the safety data collected in the Phase I and II onartuzumab clinical trials. Onartuzumab is currently being combined with mFOLFOX6 plus bevacizumab as part of a randomized Phase II study in first-line metastatic colorectal cancer (mCRC). An initial blinded safety review was undertaken after 12 patients had been randomized and treated with at least 2 cycles of study treatment. The safety cohort comprised 5 females and 7 males with an average age of 59 years. Three of the 12 patients (25%) were found to have Met 2+/3+ tumors, with the remainder classified as Met 1+. The most common toxicities were grade 1/2 neuropathy (9/12; 75%), grade 1/2 fatigue (6/12; 50%), grade 3/4 neutropenia (2/12; 17%), grade 3 hypertension (1/12; 8%) and grade 3 pulmonary embolism (1/12; 8%). The Medical Monitor and Study Chair determined that no unexpected safety signals were apparent, and the study remains unchanged and open to enrollment.

Given onartuzumab has not been administered in combination with chemotherapy to patients with metastatic GEC, safety data from all patients will be reviewed by the IDMC, as described in Section 3.1.2.

A placebo control will be administered with the chemotherapy to avoid any observational or other potential bias in the assessment of both efficacy and safety of the study treatment. This control group will be instrumental in assessing the relative benefit or risk of adding onartuzumab to chemotherapy.

3.3.4 Rationale for Stratification

To balance the disease-related risk factors across the treatment arms, patients will be stratified at study entry. A permuted-block randomization scheme will be used to ensure an approximately equal sample size and a similar distribution of stratification factors for the two treatment arms. Patients will be stratified by the following:

- Met *expression by* IHC *(level I, II, III, IV, or V; see Section 3.3.4.1 below)*
- World region (Asia-Pacific vs. other)
- Prior gastrectomy (yes vs. no)

3.3.4.1 Met Expression *by IHC*

Met receptor overexpression is thought to be associated with poor prognosis in advanced GEC. The level of Met protein overexpression as determined by IHC may be correlated with the degree of clinical benefit associated with treatment with Met pathway inhibitors (Spigel et al. 2010; Iveson et al. 2011; *Oliner et al. 2012*). *As a result,* patients *with higher Met expression* may derive more benefit from treatment with onartuzumab compared with those *with weaker levels of Met expression*.

The IHC scoring system used to select and stratify patients with Met-positive GEC is a composite algorithm that encompasses both staining intensity (weak, moderate, or strong) and percentage of cells staining positive for Met (see Appendix 3). Patients are considered to be Met positive and eligible for the study if the majority (≥ 50%) of malignant cells in a specimen are found to express Met at weak, moderate, or strong intensity.

It is possible that a more stringent proportional cutoff in which ≥90% tumor cells are Met positive could better select patients for treatment with onartuzumab. To account for this possibility, both a 50% and 90% cutoff for percentage of cells staining positive for Met will be used for stratification. Stratification levels for Met IHC status are defined by a composite of both the 50% and 90% cutoff, leading to a total of five stratification levels (I, II, III, IV, and V; see Table 1).

Table 1 Met IHC Stratification Levels Defined According to ≥ 50% and ≥ 90% Cutoffs

		Met IHC by 90% Cutoff		
	Score	*2+/3+*	*1+*	*0*
Met IHC by 50% Cutoff	*2+/3+*	***I*** *≥50% m+s* *and ≥90% m+s*	***II*** *≥50% m+s* *and ≥90% w+m+s* *but <90% m+s*	***III*** *≥50% m+s* *and <90% w+m+s*
	1+	*Not applicable*	***IV*** *≥50% w+m+s* *but <50% m+s* *and ≥90% w+m+s* *but <90% m+s*	***V*** *≥50% w+m+s* *but <50% m+s* *and <90% w+m+s*

w=weak staining intensity; m=moderate staining intensity; s=strong staining intensity.

The randomization schema incorporating these five Met IHC stratification levels will increase the likelihood that the baseline demographic characteristics and disease-related risk factors remain well balanced across both treatment arms in the analysis populations as defined by a cutoff of either 50% or 90%.

See Appendix 4 for examples of how eligible patient assignments to the five Met IHC stratification levels (I–V; see Table 1 above) will be conducted during the trial.

3.3.4.2 World Region

Although gastric cancer is a global disease, there is significant heterogeneity *with respect to survival outcomes between Eastern and Western populations, with better OS reported in Eastern series. These differential outcomes may be driven by variations in initial staging, biology, or treatment practice (Bickenback and Strong 2012)*. Given the significant geographic heterogeneity in GEC, this study will stratify randomization according to world region (Asia-Pacific vs. other) in order to prevent an imbalance in study arms.

3.3.4.3 Prior Gastrectomy

Patients will be stratified based on history of prior gastric resection (gastrectomy) because this has been shown to be a highly influential prognostic factor associated with longer OS in studies such as ToGA and AVAGAST (Bang et al. 2010; Ohtsu et al. 2011; Sawaki et al. 2011).

3.3.5 Rationale for Biomarker Assessments

In addition to the primary diagnostic marker (Met expression by IHC), a number of exploratory biomarkers will also be included in this study for evaluation as potential independent predictive biomarkers of onartuzumab activity or prognostic factors for gastric cancer.

The selection of these biomarkers was based on scientific hypotheses involving Met signaling and gastric cancer pathophysiology.

Onartuzumab functions by inhibiting the binding of HGF to the Met receptor, supporting the rationale to assess systemic HGF levels as a potential predictive marker for patient benefit with onartuzumab treatment.

High *MET* gene copy number has been observed in up to ~ 30% of gastric cancer patients, with true Met gene amplification occuring in 0 to 20% of cases (Graziano et al. 2011; Janjigian et al. 2011; Lee et al. 2011; Lennerz et al. 2011). Preclinically, gastric cancer cell lines harboring Met gene amplifications are dependent on Met signaling for growth/survival and are exceptionally sensitive to Met small molecule inhibitors. High levels of either HGF and/or Met correlate with poor prognosis in several cancer indications, including gastric cancer. This supports a rationale for evaluating the effect of Met copy number gains or amplification on patient outcome on onartuzumab and chemotherapy.

Other exploratory markers related to onartuzumab's mechanism of action and to gastric cancer biology and/or mechanism of progression will also be assessed.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures are as follows:

- OS, defined as the time from randomization to death from any cause
- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first
- ORR, defined as partial response (PR) plus CR, as determined by the investigator using RECIST v1.1
- DOR, defined as the time from the first occurrence of a documented objective response to disease progression (as determined by the investigator using RECIST v1.1) or death from any cause during the study
- DCR, defined as the rate of PR + CR + stable disease for at least 6 weeks, as defined by the investigator using RECIST v1.1

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, including serious adverse events
- Changes in clinical laboratory results during and following study drug administration
- Incidence and serum levels of ATAs to onartuzumab

3.4.3 Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are as follows:

- Pre-dose serum onartuzumab concentration (C_{min}) on Day 1 of Cycles 1, 2, and 4 and at study termination
- Post-dose serum onartuzumab concentration (C_{max}) on Day 1 of Cycle 1

3.4.4 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- EORTC QLQ-C30
- EORTC QLQ-STO22
- EuroQol EQ-5D

3.4.5 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures are as follows:

- Changes in biomarkers, and correlation of biomarkers with PFS, ORR, and OS

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients may be eligible if they have histologically confirmed inoperable, metastatic, HER2-negative adenocarcinoma of the stomach or GEJ and have received no prior treatment for metastatic gastric cancer. Patients must have tumors *defined as Met positive by IHC (≥ 50% of tumor cells with membrane and/or cytoplasmic staining at weak, moderate, or high intensity)* to be enrolled into this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability and willingness to provide written informed consent and to comply with the study protocol
- Male or female, 18 years of age or older
- ECOG performance status of 0 or 1
- Life expectancy > 3 months
- Histologically confirmed adenocarcinoma of the stomach or GEJ with inoperable metastatic disease not amenable to curative therapy

- Adequate archival or newly obtained formalin-fixed paraffin-embedded (FFPE) tissue for central IHC assay of Met receptor and HER2 status

  See Section 4.5.1.10 for tissue requirements.

- Tumor (either primary or metastatic lesion) defined as Met positive by IHC (≥ 50% of tumor cells with membrane and/or cytoplasmic staining at weak, moderate, or high intensity; see Appendix 3)
- Measurable disease or non-measurable but evaluable disease, according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

  Patients with peritoneal disease would generally be regarded as having evaluable disease and be allowed to enter the trial.

- For women who are not postmenopausal (12 months of amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to use an adequate method of contraception (a method with a failure rate of < 1% per year, such as hormonal implants, combined oral contraceptives, or a vasectomized partner) during the treatment period and for at least 90 days after the last dose of onartuzumab/placebo and 6 months after the last dose of oxaliplatin
- For men: agreement to use a barrier method of contraception during the treatment period and for at least 90 days after the last dose of onartuzumab/placebo and 6 months after the last dose of oxaliplatin

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-Related Criteria

- HER2-positive tumor (primary tumor or metastasis)

  HER2-positivity is defined as either IHC 3+ or IHC 2+/ISH+; ISH positivity is defined as a HER2:CEP17 ratio of ≥ 2.0.

- Previous chemotherapy for locally advanced or metastatic gastric carcinoma

  Patients may have received either neoadjuvant or adjuvant chemotherapy as long as it was completed at least 6 months prior to randomization.

- Prior exposure to experimental treatment targeting either the HGF or Met pathway
- History of another malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, *localized prostate cancer that has been treated surgically with curative intent and presumed cured,* or other malignancies with an expected curative outcome

Hematologic, Biochemical, and Organ Function

- Granulocyte count < 1500/mm^3, platelet count < 100,000/mm^3, and hemoglobin < 9.0 g/dL within 7 days prior to enrollment
- Partial thromboplastin time (PTT), international normalized ratio (INR), or prothrombin time (PT) > 1.5 x the upper limit of normal (ULN), except for patients receiving anticoagulation therapy

- AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP) ≥ 2.5 × ULN (≥ 5 × ULN with liver metastases)
- Total bilirubin ≥ 1.5 × ULN (except in patients diagnosed with Gilbert's disease)
- Serum calcium > ULN (corrected for low serum albumin concentrations)

  Corrected calcium (mg/dL) = serum Ca^{2+} + [(4.0–measured serum albumin) x 0.8]

  Corrected calcium (mmol/L) = serum Ca^{2+} + 0.02 × (40–serum albumin)
- Serum creatinine > 1.5 × ULN or calculated creatinine clearance < 60 mL/min (Cockcroft and Gault 1976)
- Uncontrolled diabetes as evidenced by fasting serum glucose level > 200 mg/dL

General

- Pregnancy or lactation
- Receipt of an investigational drug within 28 days prior to initiation of study drug
- Clinically significant gastrointestinal abnormalities, apart from gastric cancer, including uncontrolled inflammatory gastrointestinal diseases (Crohn's disease, ulcerative colitis, etc.)
- Significant history of cardiac disease (i.e., unstable angina, congestive heart failure, as defined by the New York Heart Association [NYHA] as Class II, III, or IV) within 6 months prior to Day 1 of Cycle 1, myocardial infarction within the previous year, or current cardiac ventricular arrhythmias requiring medication
- Significant vascular disease (such as aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- Serious (Grade ≥ 3) active infection at the time of randomization, or other serious underlying medical conditions that would impair the ability of the patient to receive protocol treatment
- Known active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV), or known HIV-seropositivity.
- Radiotherapy within 4 weeks before start of study treatment (2-week interval allowed following palliative radiotherapy given to peripheral bone metastatic site and patient has recovered from all acute toxicities)
- Major surgery within 4 weeks before start of study treatment, without complete recovery
- Any condition (e.g., psychological, geographical, etc.) that does not permit compliance with study and follow-up procedures
- Peripheral neuropathy (NCI CTCAE v4.0, Grade > 1)

  Absence of deep tendon reflexes as the sole neurologic abnormality does not render the patient ineligible.

- Prior unanticipated severe reaction to fluoropyrimidine therapy (with or without documented dihydropyrimidine dehydrogenase [DPD] deficiency) or patients with known DPD deficiency
- Known sensitivity *or contraindication* to any component of study treatment
- Active (significant or uncontrolled) gastrointestinal bleeding

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established (including tissue availability), the study site will enter demographic and baseline characteristics into the interactive voice/web response system (IxRS). For patients who are eligible for enrollment, the study site will obtain the patients' identification number and treatment assignment from the IxRS. Randomization to one of the two treatment arms will occur in a 1:1 ratio in each cohort using a permutated block randomization method. Randomization will be stratified by Met IHC (*levels I, II, III, IV, or V [see Table 1]* by central testing), world region (Asia-Pacific vs. other), and prior gastrectomy (yes vs. no). The investigator and the patient will be blinded to treatment assignment and Met diagnostic status. The dispensing pharmacist, external PK analysis vendor, and IDMC members will be unblinded to treatment assignment. The IDMC members will also be unblinded to Met diagnostic status. Unblinding for independent pharmacologic analysis of biologic samples or ongoing safety monitoring by the IDMC will be performed according to procedures in place to ensure integrity of the data.

All other individuals directly involved in this study will remain blinded until completion of the primary analysis (final analysis of the primary endpoint). Patients will not be unblinded until after final data analysis.

Treatment codes should not be broken except in emergency situations. If the investigator needs to know the study drug assignment for any reason, he or she should contact the Medical Monitor. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding because of a serious adverse event).

Data for patients who failed screening will be collected in IXRS to obtain more information on the prevalence of Met *and HER2* status in patients with GEC.

4.3 STUDY TREATMENT

All eligible patients will receive 12 cycles (14 days each) of mFOLFOX6 with either onartuzumab or placebo. On Day 1 of each cycle, all eligible patients will receive onartuzumab or placebo, followed by the mFOLFOX6 regimen. The order of study drug administration will be as follows:

Onartuzumab or placebo → oxaliplatin + folinic acid (or levofolinic acid) → 5-FU

The treatment regimen is summarized in Table 2 and detailed in Section 4.3.2. The treatment cycle length is 14 days.

Patients who experience disease progression at any time during the first 12 cycles of study treatment will discontinue all study treatment.

In the absence of disease progression after 12 cycles of mFOLFOX6 treatment, patients will discontinue mFOLFOX6 and continue treatment with onartuzumab or placebo until there is evidence of disease progression, death, or unacceptable toxicity, whichever event occurs first.

Patients should receive anti-emetic and other prophylactic treatments according to the local standard of care and manufacturer's instruction (see Section 4.3.3). Chemotherapy may be administered in accordance with local standard of care in lieu of the suggested infusion times in Table 1.

Table 2 Treatment Regimen

Study Drug	Dose/Route	Initial 12 Treatment Cycles	Cycles 13 and Beyond
Premedication	• *Premedication (e.g. anti-emetics, hydration, antihistamines, corticosteroids, etc.), should be given according to institutional standards and the respective product package insert(s)* • Prophylactic IV administration of Ca^{2+}/Mg^{2+} salts to reduce the incidence or severity of oxaliplatin-induced neuropathy is permitted at the discretion of the investigator		
Onartuzumab or placebo	10 mg/kg IV	First infusion over 60 (± 10) min, then 30 (± 10) min, on Day 1 q14d	Over 30 (± 10) min
Oxaliplatin	85 mg/m² IV	Over 2 hours on Day 1 q14d	Discontinue
Folinic acid [a]	400 mg/m^2	Over 2 hours on Day 1 q14d	Discontinue
5-FU	400 mg/m^2	Bolus	Discontinue
	2400 mg/m^2	Continuous IV infusion over 46–48 hours	Discontinue

IV = intravenous; min = minute; q14d = every 14 days.

[a] If folinic acid is unavailable, 200 mg/m^2 levofolinic acid may be used. Study treatment may be administered without either agent in the event that both are unavailable. *Folinic acid (or levofolinic acid) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care.*

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Onartuzumab and Placebo

Onartuzumab will be provided as a sterile liquid in a single-use 15-cc vial containing 600 mg *(10 mL)* or a single-use 20-cc vial containing 900 mg (*15 mL)* of onartuzumab.

Onartuzumab drug product is formulated as 60 mg/mL onartuzumab in 10 mM histidine acetate, 120 mM sucrose, 0.4 mg/mL polysorbate 20, pH 5.4.

Upon receipt, vials containing onartuzumab must be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use; do not freeze. Vials should be protected from light.

Placebo will consist of 250 mL IV 0.9% normal saline solution (NSS) and will be provided by the investigative site (see Section 4.3.2).

For further details, see the Onartuzumab (MetMAb) Investigator Brochure.

4.3.1.2 Chemotherapy

Chemotherapy may be administered in accordance with local standard of care in lieu of the suggested guidelines in Table 2, Table 3, and Table 4. If there is a significant difference between the protocol guidelines and institutional standards of care, please call the Medical Monitor to discuss. Folinic acid (or levofolinic acid), 5-FU, and oxaliplatin will be obtained from commercial sources at each participating site. Management (i.e., handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines and summaries of product characteristics (SmPCs). For countries where the Sponsor is required to provide all study drugs, including standard-of-care drugs, the Sponsor designee will provide folinic acid, 5-FU, and oxaliplatin.

For further details, see the manufacturer's prescribing information for the respective chemotherapies.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Onartuzumab and Placebo

Study treatment will be assigned by IxRS. Onartuzumab/placebo will be dosed in the clinic on Day 1 of each 14-day cycle. For patients randomized to receive onartuzumab, the dose will be 10 mg/kg in 250 mL final 0.9% NSS. The patient's weight at *baseline* will be used to determine the actual dose of onartuzumab. This dose will be administered throughout the study and will not change according to weight. Because onartuzumab clearance is not highly correlated with body weight, maintaining a flat dose of onartuzumab will not substantially change exposure to onartuzumab in the event of weight fluctuations and thus should not pose either safety or efficacy concerns.

Liquid onartuzumab should be diluted with sterile 0.9 NSS into a total volume of 250 mL. Mix the IV bag by gently inverting after injecting the study drug; do not shake. Once onartuzumab has been diluted into sterile saline, the solution should be used within 8 hours. Dextrose should not be used for dilution of onartuzumab. Any remaining solution should be discarded.

Placebo will consist of 250 mL of IV 0.9% NSS and will be provided by the investigative site.

Onartuzumab/placebo is administered as an IV infusion. The first dose of study drug should be infused over 60 ± 10 minutes. The study drug infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. Following the first dose, patients will be observed for 30–90 minutes for fever, chills, or other infusion-associated symptoms. Subsequent doses of onartuzumab may be administered over 30 ± 10 minutes, with at least a 30-minute observation period post-infusion.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one patient may not be used for any other patient.

The Sponsor recommends the use of a polyethersulphone (PES) filter. If an appropriate filter is not available or the nature of the filter is not known, it is acceptable to use no filter at all. If diluted onartuzumab needs to be transported to another facility, it should be transported at 5°C and preferably diluted in polyvinyl chloride (PVC) bags (no need to remove the headspace). Onartuzumab is stable in PVC (preferred) or polyethylene/polypropylene (PE/PP) bags. Up to 1 hour of transportation at 2°–8°C in PE/PP bags or up to 3 hours of transportation at 2°–8°C in PVC bags is acceptable.

A pharmacist who is separated from the study staff will be unblinded to onartuzumab/placebo and will prepare onartuzumab and placebo for administration.

Guidelines for dosage modification and study treatment interruption or discontinuation are provided in Section 5.1.1.1.

4.3.2.2 mFOLFOX6

Table 2 above provides suggested infusion times for the backbone chemotherapy. The cycle length is 14 days. Oxaliplatin will be administered as an 85 mg/m^2 IV infusion over 2 hours (Day 1 every 14 days) in combination with 400 mg/m^2 folinic acid (or 200 mg/m^2 levofolinic acid if folinic acid is not available), followed by 400 mg/m^2 5-FU bolus, and then 2400 mg/m^2 5–FU as a continuous IV infusion over 46–48 hours. *In lieu of the suggested dosing and administration schedule, folinic acid (or levofolinic acid) may be prescribed and administered as deemed appropriate by the investigator in accordance with institutional standards of care.*

Chemotherapy may be administered in accordance with local standard of care in lieu of the suggested infusion times in Table 2. Institutions should follow their standard administration regimens for oxaliplatin. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.1. If there is a significant difference between the protocol-specified guidelines and institutional standards of care, please call the Medical Monitor to discuss.

4.3.3 *Supportive Care*

Patients should receive anti-emetic and other prophylactic treatments according to the local standard of care and manufacturer's instruction.

Patients should receive full supportive care, including epoetin and other hematopoietic growth factors, transfusions of blood and blood products, antibiotics, anti-emetics, etc., when appropriate.

4.3.4 Investigational Medicinal Product Accountability

The investigational medicinal product (IMP) required for completion of this study (onartuzumab) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Post-Trial Access to Onartuzumab

Depending on the study's outcome, patients may be allowed to continue study treatment if they are deriving benefit, with continued safety follow-up. Benefit is defined as not meeting the study-defined criteria for progression of disease. Open-label onartuzumab may be provided only for those patients originally randomized to receive onartuzumab.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to Day 1 through the completion/early termination visit. All concomitant medications (including supportive care and treatments used to alleviate common symptoms of gastric cancer) should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

If nausea, vomiting, or diarrhea occurs, effective symptomatic treatment must be initiated (see Section 4.3.3).

Hematopoietic growth factors (i.e., G-CSF or GM-CSF) may be used according to institutional or other specific guidelines (e.g., country, regional, or oncology organizations as ASCO, etc.) to treat febrile neutropenia, but should not be used as primary or secondary prophylaxis. The use of any growth factor support must be documented in the patient's record. Growth factors must be discontinued at least 48 hours prior to initiation of the next cycle of chemotherapy.

According to NCCN 2011 guidelines (www.nccn.org), erythropoiesis-stimulating agents (ESAs) may be considered for the treatment of cancer-related anemia in patients undergoing palliative treatment. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia in cases where hemoglobin is < 11 g/dL or ≥ 2 g/dL below baseline, but only after the patient has been counseled about the risks and benefits of ESA use.

The use of prophylactic medication such as Mg^{2+}/Ca^{2+} infusions or others for prevention of oxaliplatin-induced neuropathy is at the discretion of the investigator; however, these treatments are not recommended by this protocol, as their benefits have not been clearly established.

Patients receiving bisphosphonates for a non-malignant indication are eligible for this study. Bisphosphonates or denosumab are acceptable for bone metastases if clinically indicated.

Anticoagulation for maintenance of patency of permanent indwelling IV catheters is permitted.

4.4.2 Prohibited Therapy

No other experimental or systemic anti-cancer therapy (approved or unapproved) is permitted during study treatment except for localized radiotherapy for pain control (provided that it does not compromise tumor assessments of target lesions).

Concomitant use of drugs with a potential ototoxic or nephrotoxic effect (e.g., aminoglycosides, cefalotine, furosemide, amphotericin B) should be avoided or adequately monitored.

Prophylactic use of CSFs is not permitted. American Society of Clinical Oncology (ASCO) guidelines for use of CSFs should be followed (Smith et al. 2006).

The prevention of alopecia with a cold cap or of stomatitis with iced mouth rinse is not permitted because of the risk of triggering cold-related dysesthesias.

Live Vaccines

Vaccination with a live vaccine should be avoided in patients receiving 5-FU because of the potential for serious or fatal infections.

Allopurinol

Interactions with allopurinol have been observed with 5-FU, with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with 5-FU should be avoided.

Antivirals and Antiprotozoals

5-FU should not be administered together with the antiviral drug sorivudine or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of DPD by sorivudine, has been described in the literature (Diasio 1998). This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

Metronidazole has been shown to increase the toxicity of 5-FU in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic (Martindale 2002). As it has been described in the literature, caution should be exercised.

Gastrointestinal Drugs

Pretreatment with cimetidine for 4 weeks led to increased plasma concentrations of 5-FU following IV and oral administration in 6 patients. The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen following single doses of cimetidine in 5 patients or pretreatment for just 1 week in 6 other patients. Care is required in patients taking both drugs simultaneously (Martindale 2002).

Other Anticancer Therapies

The use of other cytotoxic agents, investigational drugs, or active or passive immunotherapy for gastric cancer is not allowed during study treatment or while the patient is disease free in the follow-up phase.

Patients requiring radiotherapy (except for palliative therapy) will be considered to have had disease progression.

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer treatments and procedures and history of weight loss), disease characteristics (histologic subtype and stage of disease), smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to randomization.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.1.2 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position.

4.5.1.3 Physical Examinations

At screening, a complete physical examination should include the evaluation of head, eye, ear, nose, and throat (HEENT); cardiovascular; dermatological; musculoskeletal; respiratory; gastrointestinal; and neurological systems. Abnormalities identified at screening will be recorded as baseline conditions.

Subsequent physical examinations will be symptom directed. Changes from baseline abnormalities should be assessed at each subsequent physical examination. New or worsening abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.1.4 ECOG Performance and Weight

ECOG performance status data and weight will be recorded at baseline and throughout the study.

4.5.1.5 Chest X-Ray

The screening chest X-ray is optional for the assessment of infectious process. Additional chest X-rays may be performed during the study as clinically indicated.

4.5.1.6 *Electrocardiogram (ECG)*

An ECG is required at baseline. Additional ECGs may be performed during the study as clinically indicated. For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site.

4.5.1.7 Brain CT or MRI Scan

A computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the brain should be conducted at screening only when there is a clinical suspicion of central nervous system (CNS) metastases. Scans obtained within 6 weeks prior to randomization are acceptable for baseline assessment, unless the patient demonstrates clinical signs and symptoms of CNS disease progression.

4.5.1.8 Tumor and Response Evaluations

To be considered evaluable for complete or partial response assessment, patients must have at least one measurable lesion according to RECIST v1.1 (see Appendix 5).

All measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response assessments will be made by the investigator based on physical examinations, CT scans, or magnetic resonance imaging (MRI), using RECIST v 1.1.Within 28 days prior to randomization, the baseline disease assessment should include all areas of known and suspected disease through use of the most appropriate and reproducible radiological technique. Imaging may have been performed as part of standard of care prior to informed consent for this study. CT or MRI of the chest, abdomen, *and pelvis* should be performed using contrast media unless clinically contraindicated. *CT scans of the neck should be included if clinically indicated.* Bone scans (or focal X-ray) or brain imaging should be performed if metastatic disease is suspected. Disease must be evident by radiology; measurable lesions are preferred but not mandatory for this study. If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression prior to inclusion in the study.

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 6 weeks ± 7 days (during the last week of every third cycle) *for the first 12 months and then every 12 weeks ± 14 days (during the last week of every sixth cycle)* during treatment, and at the time of treatment discontinuation, if disease progression has not already been documented. Tumor assessments should be performed on this schedule regardless of whether study treatment has been administered or held. The imaging equipment, contrast media, and person (investigator or radiologist) performing the evaluation should be kept constant throughout a patient's course on study.

4.5.1.9 Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (hemoglobin, hematocrit, platelet count, WBC count, differential count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells])

  Reporting the differential as absolute counts is required.

- Serum chemistry (ALT, AST, ALP, bilirubin, total protein, albumin, blood urea nitrogen, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, bicarbonate, magnesium)
- Dipstick urinalysis (including specific gravity, pH, protein, glucose, blood, ketones, and bilirubin)

  Urinalysis should be performed at each study visit and at the study drug discontinuation visit (SDDV).

- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at baseline

  If clinically indicated, a urine test may be performed, but if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- PT and INR *(required for all patients at baseline)*

  Ongoing evaluation should be continued for patients who are receiving therapeutic anticoagulation according to local standard of care

Samples for the following laboratory tests will be sent to one or more central laboratories or to Roche for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Serum samples for determination of onartuzumab concentrations
- Serum samples for determination of ATAs to onartuzumab

4.5.1.10 Patient-Reported Outcomes

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of onartuzumab. The following PRO instruments will be used:

- EORTC QLQ-C30 (Aaronson et al. 1993; Fayers and Bottomley 2002) (see Appendix 6)
- EORTC QLQ-STO22 (Blazeby et al. 2004) (see Appendix 6)
- EuroQol EQ-5D (Rabin and de Charro 2001) (see Appendix 7)

The PRO instruments, translated as required in the local language, will be distributed by the study staff and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

4.5.1.11 Tumor Tissue Samples for Patient Stratification and Exploratory Biomarkers

The tissue submitted should be formalin-fixed, paraffin-embedded (FFPE) tumor specimen that enables the definitive diagnosis of gastric cancer, determination of Met diagnostic status, and assessment of HER2 status. A tissue block (preferred) or 15 serial, freshly cut, unstained slides accompanied by an associated pathology report is required for participation in this study. Tissue quality and adequate viable tumor cell content are specified in the accompanying lab manual. Cytological samples are not acceptable.

If the archival tissue is neither sufficient nor available, the patient may still be eligible, upon discussion with the Medical Monitor, with the assumption that the patient:

- Can provide sufficient tissue for Met IHC diagnostic status and HER2 status determination

  OR

- Is willing to consent to and undergo a pre-treatment biopsy of the tumor

A detailed description of tissue quality requirements and procedures for collection, handling, and shipping of the samples to the central laboratory will be provided in a separate laboratory manual.

For enrolled patients only, part of the available tumor tissue from the tissue submitted will be used to assess exploratory biomarkers. Tissue assessments will include testing of protein expression, activation status, somatic mutations, and/or gene amplification *related to angiogenesis, tumorigenesis*, inflammation, and other exploratory markers related to onartuzumab and to gastric cancer biology. *Since the identification of new markers correlating with disease activity and the efficacy or safety of treatment are rapidly evolving, the definitive list of analyses remains to be determined; however, it will include the following markers: Met amplification, HGF, MACC1, ROS1, HER3, PTEN, KRAS, EGFR, PI3K. Such analysis is exploratory by nature and will be performed retrospectively after the main study analysis is completed.* These assessments will be performed by the Sponsor at a central laboratory or by a Sponsor-selected vendor. The remaining tumor tissue block will be returned to the site upon request.

4.5.1.12 Blood Samples for Exploratory Biomarkers

The following samples will be collected from consenting patients for exploratory research:

- Serum samples for analysis of the protein levels of HGF ligands and other exploratory markers related to onartuzumab's mechanism of action and to gastric cancer biology and/or mechanism of progression.
- Plasma samples for analysis of exploratory markers related to onartuzumab mechanism of action and to gastric cancer biology and/or mechanism of progression, and for isolation of tumor DNA to analyze the activating mutation status of Met as well as other related biomarkers

Samples will be sent to one or more central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The remainder of these samples will be destroyed no later than 5 years after the end of the study *or earlier depending on local regulations*. If the patient provides consent for optional future research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.1.13 Samples for Roche Clinical Repository (Optional Future Research)

After the analysis of the study-related biomarkers and if a patient consents, a portion of the remaining tumor sample as well as any remaining plasma and serum samples will be stored for future research in the Roche Clinical Repository (RCR). The patient's participation in the RCR is optional and will not affect participation in the main study.

Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or other effects associated with medicinal products
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Optional Samples for RCR

The following samples will be used for identification of dynamic (non-inherited) biomarkers:

- Remaining serum samples
- Remaining plasma samples for protein analyses
- Tissue microarrays (TMAs) for tumor protein expression or somatic tumor-related RNA/DNA analyses

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Whole blood for DNA extraction

For all samples, dates of consent should be recorded on the associated eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the

IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. Separate, specific signatures will be required to document a patient's agreement to provide RCR specimens. Patients who decline to participate will check a “no” box in the appropriate section and will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the additional Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the appropriate Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study YO28322 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study YO28322.

Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

In addition to an internal review body, an independent Science and Ethics Advisory Group, consisting of experts in the fields of biology, ethics, sociology, and law, will advise Roche regarding the use of RCR specimens and on the scientific and ethical aspects of handling genetic information.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Baseline Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 28 days prior to Day 1, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Baseline tests and evaluations will be performed within 7 days prior to Day 1, after confirmation of other eligibility criteria, unless otherwise specified.

Please see Appendix 1 for the schedule of screening and baseline assessments and Appendix 2 for the schedule of PK, ATA, and biomarker sampling.

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments. PRO assessments should be performed prior to the completion of other study assessments. *Patients must receive their first dose of study drug within 3 days after being randomized.*

The following assessments must be performed within 7 days prior to study drug administration, so that results are available prior to dosing:

- Hematology
- Serum chemistries
- Tumor assessments according to the schedule of assessments (see Appendix 1)

Please see Appendix 1 for the schedule of assessments performed during the treatment period and Appendix 2 for the schedule of PK, ATA, and biomarker sampling.

4.5.2.3 Assessments at Study Drug Discontinuation Visit (SDDV)

When a patient discontinues all study treatment, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days (± 7 days) after the last infusion of onartuzumab for a study drug discontinuation visit (SDDV). The visit at which a response assessment showed disease progression may be used as the SDDV.

Please see Appendix 1 for the schedule of assessments performed at the SDDV, and Appendix 2 for the schedule of PK, ATA, and biomarker sampling.

4.5.2.4 Follow-Up Assessments

After the SDDV, adverse events should be followed as outlined in Sections 5.2 and 5.3.

For patients with no progressive disease after terminating study treatment, tumor assessments will be evaluated per local standard of care until disease progression is noted. Data collection every 3 months will also include study treatment–related AEs (including serious AEs), subsequent anti-cancer therapies, and date of death. Survival follow-up ends with the death or loss to follow-up of the patient, or the Sponsor's decision to end the study.

Please see Appendix 1 for the schedule of follow-up assessments.

4.5.2.5 Assessments at Unplanned Visits

Please see Appendix 1 for assessments that are required to be performed in case of an unplanned visit.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determination that it is in the best interest of the patient
- Patient non-compliance, specifically defined as missing two or more consecutive tumor assessments for unknown reasons, or receipt of non-protocol-specified anti-cancer treatment

4.6.1.1 Discontinuation from Study Drug

Patients must discontinue study drug treatment if they experience either of the following:

- Pregnancy
- Progressive disease

Patients who discontinue study drug before progressive disease is confirmed will be asked to return to the clinic for the SDDV (see Section 4.5.2.3) and should undergo follow-up assessments (see Section 4.5.2.4). The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prior to disease progression will not be replaced.

4.6.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

There are no known overlapping, significant toxicities between onartuzumab and the components of the mFOLFOX6 regimen. Drug–drug interactions have not been observed to date and are not expected to occur between mFOLFOX6 and an antibody.

All enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements (hematology, chemistry, and urinalysis). Serum samples will be drawn for determination of ATAs to onartuzumab. An IDMC has been incorporated into the trial design to carefully review the accumulating safety data for onartuzumab (please refer to the IDMC charter for detailed monitoring plan).

Patients will be evaluated for adverse events (all grades according to the NCI CTCAE v4.0), serious adverse events, and any adverse events requiring treatment interruption or discontinuation. Patients who, at time of progression, have an ongoing adverse event leading to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different anti-tumor therapy.

5.1.1 Management of Specific Adverse Events

5.1.1.1 Dose Modification Due to Toxicity

General Notes Regarding Dose Modifications

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

- Onartuzumab or placebo will not require dose adjustments for changes in body weight, as clearance of onartuzumab is not highly correlated with body weight.
- Dose modifications for chemotherapy will be performed according to the treating physician's clinical judgment using the details in this section as guidance.
- Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by more than 10% from baseline (or the newly referred body weight). Chemotherapy doses should not be modified for any body weight change of less than 10%.
- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- For toxicities that are considered by the investigator to be unlikely to develop into serious or life-threatening events, treatment may be continued at the same dose without reduction or interruption at the treating physician's discretion. In addition, dose reductions or interruptions may not be required for anemia (non-hemolytic) if satisfactorily managed by transfusions.
- If any component of the chemotherapy backbone treatment is stopped for reasons other than progressive disease during the initial 12 cycles of treatment, and a chemotherapy regimen other than that specified in the protocol is administered,

onartuzumab must be discontinued. If no other chemotherapy is given in the absence of progression, blinded onartuzumab/placebo may continue.

- Where several toxicities with different grades or severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, any observed toxicity is attributable to one drug, the dose of the other drug(s) may not require modification.
- Dose modifications for isolated abnormal hematologic laboratory values will be based on hematologic parameters at the start of a treatment cycle.
- *If oxaliplatin requires discontinuation because of toxicity, 5-FU, folinic acid (or levofolinic acid), and onartuzumab or placebo should be continued per the study protocol.*
- *Following either completion of or discontinuation from chemotherapy, onartuzumab or placebo should be continued until disease progression or unacceptable toxicity if clinically appropriate.*
- When a treatment cycle is temporarily interrupted because of toxicity caused by one component of the regimen, the treatment cycles will be re-started such that study drug infusions remain synchronized with the chemotherapy. The tumor assessment schedule will not be altered if chemotherapy is delayed. Tumor assessments will be performed every 6 weeks (± 7 days) *during the first 12 months and then every 12 weeks (± 14 days) until disease progression*.
- Patients who require chemotherapy dose reductions will receive the reduced dose for the remainder of the study. The only exception to this practice will be in the case of nausea/vomiting. If nausea and/or vomiting occur despite anti-emetic therapy, the chemotherapy dose should be reduced by 25% for the next dose. If tolerated, an increase back to a 100% dose may be allowed at the treating physician's discretion. Chemotherapy cycles may be delayed to manage toxicity. Cycle delays of up to 28 days are permitted. Any delay longer than 28 days will require permanent discontinuation of all chemotherapy.

5.1.1.1.1 Onartuzumab/Placebo

Infusion Schedule Modification

Study treatment will be administered in a setting with emergency equipment and staff who are trained to monitor for and respond to medical emergencies.
The onartuzumab/placebo infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms. If infusion-related symptoms occur, patients will be treated according to best medical practice and will be monitored until adequate resolution of signs and symptoms. Patients who experience onartuzumab/placebo infusion–associated symptoms may be pre-medicated appropriately (e.g., with NSAIDs, acetaminophen, diphenhydramine, and/or corticosteroids for subsequent infusions).

If a treatment interruption is required, onartuzumab/placebo and chemotherapy dosing may be delayed by up to one treatment cycle (dose delays longer than one cycle [14 days] may be considered pending discussion with the Medical Monitor). If a scheduled dose coincides with a holiday that precludes dosing, dosing should commence on the nearest following date and subsequent dosing can continue on a new 14-day schedule based on the infusion date, or resume on the previous 14-day schedule (provided dosing is never given earlier than 13 days from the last infusion).

Onartuzumab has a mean terminal half-life of approximately 10 days. There is no available antidote to onartuzumab. Discontinuation of onartuzumab will have no immediate therapeutic effect. Any toxicities associated or possibly associated with onartuzumab treatment should be managed according to standard medical practice. Patients who discontinue treatment for onartuzumab toxicity in the absence of disease progression may continue on trial until a PFS event occurs. If at any time the chemotherapy regimen is switched from the protocol-specified treatment, the patient will be discontinued from the study.

Dosage Modification

No modification of the onartuzumab/placebo dose will be allowed during this study.

If onartuzumab/placebo is discontinued because of tolerability concerns, a patient may continue on mFOLFOX6 treatment (if onartuzumab/placebo is stopped during the first 12 cycles of study treatment) or 5-FU/folinic acid if agreed upon by the investigator and patient.

5.1.1.1.2 mFOLFOX6

Dose adjustments at the start of each 14-day cycle will be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy. Dose level adjustments for oxaliplatin, 5-FU bolus, and 5-FU infusion will be reduced according to Table 3 after determining the appropriate hematologic criteria in Table 4 or non-hematologic criteria in Table 5. Once a dose reduction is made, the dose will not be re-escalated during subsequent cycles. *For each agent,* no more than two dose reductions will be allowed for any patient *(see Table 3). Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. If a dose reduction beyond −2 dose levels for any agent is required, that agent should be discontinued.*

During mFOLFOX6 treatment, dose modification due to oxaliplatin-related neurotoxicity will be made according to Table 6.

If there is toxicity requiring a delay in chemotherapy, patients may continue on onartuzumab (or placebo) as clinically appropriate. Patients should be evaluated weekly (at a minimum) if chemotherapy is on hold until the toxicity has resolved to Grade ≤ 1 or is deemed to be at a new stable baseline. The maximum treatment delay allowed is 28 days. Upon recovery, patients should be retreated as specified in Table 4, Table 5,

or Table 6. If toxicity remains unresolved for ≥ 28 days, the patient will discontinue chemotherapy treatment.

Folinic acid *(*400 mg/m^2 *or as deemed appropriate by the investigator)* will be given prior to each 5-FU dose. If 5-FU is delayed, folinic acid will be delayed. If folinic acid is not available, levofolinic acid (200 mg/m^2 *or as deemed appropriate by the investigator*) may be administered. Folinic acid or levofolinic acid may be omitted from study treatment in the event that they are both unavailable.

Table 3 Dose Adjustment Levels for *Oxaliplatin and 5-FU*

	Oxaliplatin (mg/m^2)	5-FU (mg/m^2)	
		Bolus	Infusion
Starting Dose	85	400	2400
– 1 Dose Level	65	320	1900
– 2 Dose Levels	50	260	1500

If the patient requires further dose reductions than specified above, the patient will be removed from treatment with that agent. If the patient is removed from treatment with 5-FU or 5-FU treatment is held, oxaliplatin should be discontinued or held until 5-FU is resumed. Onartuzumab (or placebo) dosing may continue if clinically appropriate, if 5-FU and/or oxaliplatin are discontinued.

Dose adjustments will be made based on the following criteria.

mFOLFOX6: Dose Modification for Hematologic Toxicity

Table 4 shows the dose modifications for hematological toxicity, which apply for 5-FU, folinic acid, and oxaliplatin. Treatment *should* be dose-modified or delayed until recovery of hematological parameters as stated in Table 4. If recovery has not occurred after a delay of 28 days, the patient should stop chemotherapy permanently.

Table 4 mFOLFOX6 Dose Modification Due to Hematologic Toxicity

Toxicity	Action	Dose Modification (vs. Previous Course; see Table 3)
Neutropenia		
Grade 1 (ANC > 1.5×10^9/L) or Grade 2 (ANC 1.0–1.5×10^9/L)	Continue treatment.	Maintain dose level.
Grade 3 (ANC 0.5–1.0×10^9/L)	Hold treatment. Recheck blood counts weekly until ANC > 1.5×10^9/L, then restart treatment. If ANC <1.5×10^9/L after treatment is delayed by 28 days, discontinue FOLFOX.	Decrease oxaliplatin one dose level [a]. If the patient is not receiving oxaliplatin, omit bolus of 5-FU.
Grade 4 (ANC < 0.5×10^9/L)	Same as above for Grade 3.	First Occurrence: Omit bolus of 5-FU and reduce oxaliplatin one dose level [a]. Second Occurrence: Decrease 5-FU infusion and oxaliplatin one dose level [a]
Neutropenic Fever [a,b]		
Grade 3 (ANC < 1.0×10^9/L and fever ≥ 38.5°C)	Treat neutropenic fever according to standard guidelines.	First Occurrence: Omit bolus of 5-FU and reduce oxaliplatin one dose level [a]. Second Occurrence: Decrease 5-FU infusion and oxaliplatin one dose level [a].
Grade 4 (life-threatening consequences including septic shock, hypotension, acidosis)	Proceed with next cycle when fever is resolved and ANC > 1.5×10^9/L.	Same as above for Grade 3.
Thrombocytopenia		
Grade 1 (PLT > 75×10^9/L) or Grade 2 (PLT 50–75×10^9/L)	Continue treatment.	Maintain dose level.
Grade 3 (PLT 25–50×10^9/L)	Hold treatment. Recheck blood counts weekly until PLT > 75×10^9/L, then restart treatment. If PLT < 75×10^9/L after treatment is delayed by 28 days, discontinue FOLFOX.	Decrease oxaliplatin one dose level. If the patient is not receiving oxaliplatin, omit bolus 5-FU.
Grade 4 (PLT < 25×10^9/L)	Same as above for Grade 3.	First Occurrence: Omit bolus of 5-FU and reduce oxaliplatin one dose level [a]. Second Occurrence: Decrease 5-FU and oxaliplatin one dose level [a].

ANC = absolute neutrophil count; PTL = platelet count.

[a] At the investigator's discretion growth factors may be used according to standard practice guidelines.

mFOLFOX6: Dose Modification for Non-Hematologic Toxicity

Based on the most severe toxicity experienced since the last treatment, the following dose modifications should be used for non-hematologic toxicities. Retreatment should be delayed until all non-hematologic toxicities have subsided to Grade ≤ 1 or less, except for increased bilirubin and ALT, which must recover to Grade 1 or baseline grade, whichever is higher. Treatment may be delayed up to 28 days to allow for this recovery. If the patient cannot meet the retreatment criteria in this timeframe, mFOLFOX6 should be discontinued (see Table 5).

If Grade 2–4 non-hematologic toxicity occurs, follow instructions below for further actions (see Table 5).

Once the dose has been reduced, it should not be increased at a later time.

Table 5 mFOLFOX6 Dose Modification Due to Non-Hematologic Toxicity

Toxicity	Action	Dose Modification (vs. Previous Course; see Table 3)
Diarrhea		
Grade 1	Continue treatment.	Maintain dose level.
Grade 2	Start medical management for diarrhea. Continue treatment.	Maintain dose level. If Grade 2 diarrhea persists despite medical management, reduce 5-FU bolus and infusion one dose level.
Grade 3	Start medical management for diarrhea. Hold all treatment. Restart treatment after diarrhea Grade ≤ 1.	Decrease 5-FU bolus and 5-FU infusion one dose level.
Grade 4	Start medical management for diarrhea. Hold all treatment. Restart treatment after diarrhea Grade ≤1.	Decrease 5-FU bolus, 5-FU infusion, and oxaliplatin one dose level.
Other Non-Hematologic Toxicities Attributable to mFOLFOX6 [a, b]		
Grade 3–4	Hold all treatment until toxicity improves to Grade ≤ 1.	Reduce dose of agent or agents responsible for toxicity by one dose level. At the investigator's discretion, the 5-FU bolus may also be dropped in lieu of or in combination with dose reduction(s) of the continuous infusion 5-FU and/or oxaliplatin.

[a] For mucositis/stomatitis, decrease only 5-FU, not oxaliplatin.

[b] Exceptions: alopecia, fatigue, anorexia, nausea/vomiting (if can be controlled by antiemetics), and constipation (if can be controlled with laxatives, stool softeners, etc).

5.1.1.1.3 Oxaliplatin-Induced Neurotoxicity

Oxaliplatin is consistently associated with two types of peripheral neuropathy, which includes paresthesia and dysesthesia of the hands, feet, and peri-oral region. Patients treated with oxaliplatin in this study will be counseled to avoid cold drinks and exposure to cold water or air, especially for 3–5 days following oxaliplatin administration.

In the event of neurotoxicity, the recommended dose adjustment for oxaliplatin is shown in Table 6. Patients should discontinue oxaliplatin if Grade 3 or 4 neurotoxicity is observed.

Table 6 Oxaliplatin Dose Modification for Associated Neurotoxicity

Toxicity	Grade	Duration of Toxicity		
		1–7 Days	> 7 Days	Persistent between cycles [a]
Paresthesia or dysesthesia [b] that does not interfere with function	1	No dose reduction.	No dose reduction.	No dose reduction.
Paresthesia or dysesthesia [b], interfering with function, but not ADL	2	No dose reduction.	No dose reduction	Decrease oxaliplatin by one dose level.
Paresthesia or dysesthesia [b] with pain or with functional impairment that also interferes with ADL	3	First Occurrence: Decrease oxaliplatin by one dose level. Second Occurrence: Decrease oxaliplatin by a second dose level.	Discontinue oxaliplatin.	Discontinue oxaliplatin.
Persistent paresthesia or dysesthesia that is disabling or life-threatening	4	Discontinue oxaliplatin.	Discontinue oxaliplatin.	Discontinue oxaliplatin.
Acute (during or after the 2-hour infusion) laryngopharyngeal dysesthesia [b]		Increase duration of next infusion to 6 hours [c]	NA	NA

ADL = activities of daily living; NA = not applicable.

[a] Not resolved by the beginning of the next cycle.

[b] May be cold-induced.

[c] May also be pre-treated with benzodiazapines.

Oxaliplatin-Induced Laryngopharyngeal Dysesthesia

Laryngopharyngeal dysesthesia, an unusual loss of sensation of breathing (acute respiratory distress) without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm), also has been observed. This neurotoxicity may be induced or exacerbated upon exposure to cold.

If a patient develops laryngopharyngeal dysesthesia, the patient's oxygen saturation should be evaluated via a pulse oximeter; if normal, reassurance should be provided, a benzodiazepine or other anxiolytic agent should be considered, and the patient should be observed in the clinic until the episode has resolved. The oxaliplatin infusion may then be continued at one-third the rate.

Because this syndrome may be associated with the rapidity of oxaliplatin infusion, subsequent doses of oxaliplatin should be administered as 6-hour infusions (instead of the normal 2-hour infusion).

Patients on oxaliplatin should not receive cold drinks or ice chips on Day 1 of each cycle as this may exacerbate oral or throat dysesthesia, as well as laryngopharyngeal dysesthesia. Administration of prophylactic medication such as Mg^{2+}/Ca^{2+} infusions or others is at the discretion of the investigator.

Table 7 compares the symptoms and treatments of laryngopharyngeal dysesthesia and platinum hypersensitivity reactions.

Table 7 Comparison of the Symptoms and Treatment of Laryngopharyngeal and Platinum Hypersensitivity Reactions

Clinical Symptoms	Laryngopharyngeal Dysesthesia	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Reassurance, anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Allergic Reaction to Oxaliplatin

If a patient experiences Grade 1 or 2 allergic reaction to oxaliplatin, pre-medication *should be given according to institutional practice* prior to *further* study drug administration. If Grade 1–2 allergic reaction persists into the next cycle, *appropriate premedication should be given according to institutional practice* prior to administration of oxaliplatin.

For the patients experiencing Grade 3–4 allergic reactions, treatment with oxaliplatin should be discontinued.

In the case of respiratory symptoms indicative of pulmonary fibrosis such as nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates, oxaliplatin should be interrupted pending further investigations.

If interstitial pulmonary fibrosis is confirmed, permanently discontinue oxaliplatin.

Extravasation of Oxaliplatin

Extravasation of oxaliplatin has been associated with necrosis. If extravasation is suspected, the infusion should be stopped and the drug administered at another site. Extravasation may be treated according to institutional guidelines.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor within 24 hours following knowledge of the event (see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period,

investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The NCI CTCAE (v4.0) grading scale will be used for assessing adverse event severity. For assessing severity of adverse events that are not specifically listed in the NCI CTCAE, the grading scale in Table 8 will be used.

Table 8 Severity Grading Scale for Adverse Events Not Specifically Listed in the NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug

- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

Other Adverse Events

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. *Initial adverse event intensity should be recorded at the time the event is reported. If a persistent adverse event becomes more severe, the most extreme intensity should also be recorded in the Adverse Event eCRF. Example: Headache, Grade 1 headache increases to Grade 2 headache. At the time of the intensity change, the Grade 2 intensity should be recorded in the Adverse Event eCRF in the most extreme intensity data field.*

A recurrent adverse event is one that *occurs and* resolves between patient evaluation timepoints and subsequently recurs. *All recurrent adverse events* should be recorded separately on *an* Adverse Event eCRF.

If a change in intensity of an adverse event qualifies it as an SAE per the seriousness criteria (refer to Section 0), the event should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor following the SAE reporting procedure outlined in Section 5.4.2.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which 35% is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours following knowledge of the event as a serious adverse event (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths occurring during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of GEC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During post-study-drug survival follow-up, deaths attributed to progression of GEC should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Lack of Efficacy or Worsening of Gastroesophageal Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria as outlined in RECIST v1.1. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not suffered an adverse event.

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor within 24 hours following knowledge of the event (see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data. However, if any patient responses suggestive of a possible adverse event are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours following knowledge of the event, regardless of relationship to study drug:

- Serious adverse events
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours following knowledge of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event’s outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information (for medical inquiries or patient-specific discussions)

Medical Monitor: Steve Hack, M.D., Ph.D. *(based in South San Francisco, CA, U.S.A.)*

Telephone No.: +1 650 467 2063

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events

For reports of serious adverse events, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours following knowledge of the event, using the fax numbers provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the last dose of onartuzumab/placebo or within 6 months after the last dose of oxaliplatin. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the last dose of onartuzumab/placebo or within 6 months after the last dose of oxaliplatin. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours following knowledge of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours following knowledge of the event (see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. For serious adverse events, if, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the additional case details section of the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST–STUDY PARTICIPATION ADVERSE EVENTS

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, serious adverse event, or other adverse event of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

During post-study-drug survival follow-up, deaths attributed to progression of GEC should be recorded only on the Study Completion/Early Discontinuation eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Onartuzumab Investigator's Brochure
- Local prescribing information for 5-FU, folinic acid (or levofolinic acid), and oxaliplatin

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An IDMC will review the incidence of all adverse events at pre-defined timepoints during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

This Phase III trial is designed to further assess the efficacy and safety of onartuzumab in combination with mFOLFOX6 chemotherapy in patients with previously untreated metastatic GEC in HER2 negative and Met-positive populations (Met 1+, 2+, or 3+, or Met 2+/3+ only).

The study will enroll approximately 800 patients, with recruitment of Met 1+ patients capped at 600. Estimates of the number of events required to demonstrate efficacy with regard to OS are based on the following assumptions:

- One-sided significance level of 0.025 (accounting for the correlation between the two populations, the nominal alpha is 0.00577 for the Met 2+/3+ subgroup and 0.02 for the ITT population; see Appendix 8 for details)
- Ninety-one percent power to detect an HR of onartuzumab + mFOLFOX6 versus placebo + mFOLFOX6 of 0.49, corresponding to an improvement in median OS from 9 months to 18 months, in the Met 2+/3+ subgroup
- Ninety percent power to detect an HR of onartuzumab + mFOLFOX6 versus placebo + mFOLFOX6 of 0.73, corresponding to an improvement in median OS from 9 months to 12.3 months, in the ITT population
- Dropout rate of 5% per year
- One interim efficacy and futility analysis planned for the Met 2+/3+ subgroup occurring at the time of the ITT final analysis, which is triggered by obtaining 67% of total OS information (79 events) from the Met 2+/3+ subgroup and 449 events from the ITT population
- Final efficacy analysis for the 2+/3+ subgroup triggered by 118 OS events (this will likely occur after the final analysis of the ITT population)

With these assumptions, the interim analysis of the Met 2+/3+ subgroup and the final analysis of the ITT population will occur approximately 29 months after the first patient has been enrolled. The final analysis of the Met 2+/3+ subgroup will occur approximately 38 months after the first patient is enrolled.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuations from the study will be summarized by treatment arm for the ITT population and by Met diagnostic status. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated by treatment arm. Major protocol violations, including violations of inclusion/exclusion criteria, will be summarized by treatment arm for the ITT population and by Met diagnostic status.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, and baseline disease characteristics such as Met expression level, histologic subtype, primary location of disease, weight loss history, and ECOG performance status will be summarized by treatment arm for the ITT population and by Met diagnostic status. Descriptive baseline summaries of continuous data will present mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all randomized patients (ITT population) and the Met IHC 2+/3+ subgroup, with patients grouped according to the treatment assigned at randomization. The same analysis methods for primary and secondary analyses will be applied to both the ITT and Met 2+/3+ populations.

6.4.1 Co-Primary Efficacy Endpoints

Overall Survival. OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive.

The two treatment comparisons of OS will be based on a stratified log-rank test at: 1) a one-sided significance level of 0.00577 for the Met 2+/3+ subgroup (see Section 6.1), and 2) a one-sided significance level of 0.02 for the ITT population. The stratification factors are Met expression (*level I, II, III, IV, or V*), world region (Asia-Pacific vs. other), and prior gastrectomy (yes vs. no).

Results from an unstratified log-rank test will also be presented. Kaplan–Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan–Meier curve will be constructed to provide a visual description of the difference between the treatment arms. Estimates of the treatment effect will be expressed as HRs using a stratified Cox model, including 95% confidence intervals (CIs).

6.4.2 Secondary Efficacy Endpoints

If the primary endpoint of OS is statistically significant in either or both of the co-primary comparisons at the individually specified significance level (0.00577 for the Met 2+/3+ subgroup and 0.02 for the ITT population), the secondary endpoints of PFS and ORR for each population will be tested in order (i.e., PFS followed by ORR), each at the same significance level of the primary endpoint in the same population.

Progression-Free Survival. PFS is defined as the time between date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment using RECIST v1.1. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the randomization date.

PFS will be analyzed in the same method as OS.

Objective Response Rate. Objective response is defined as a CR or PR assessed by the investigator based on RECIST v1.1. Patients without a post-baseline tumor assessment will be considered as non-responders. The analysis population for ORR will be all randomized patients. An estimate of ORR and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. CIs for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution. The ORR will be compared between the two treatment arms using the stratified Mantel-Haenszel test.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who are included in the randomization and receive at least one dose of study treatment (the safety population), with patients allocated to the treatment arm associated with the regimen actually received.

Drug exposure will be summarized to include treatment duration, dosage, and dose intensity.

Verbatim description of adverse events will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade 3 and above), and adverse events leading to

study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside of the normal ranges will be identified. In addition, select laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm and grade.

Deaths reported during the study treatment period and those reported during follow-up after treatment completion/discontinuation will be summarized by treatment arm.

Serum levels and incidence of ATAs to onartuzumab will be summarized to assess any potential relationship of immunogenicity response with pharmacokinetics, safety, and efficacy.

6.6 PHARMACOKINETIC ANALYSES

In this study, onartuzumab concentrations will be determined in serum samples. Samples will be analyzed by one or more contract laboratories selected by the Sponsor. Onartuzumab will be quantified by enzyme-linked immunosorbent assay (ELISA).

For onartuzumab, serum concentrations (C_{min} and C_{max}) will be tabulated and summarized and compared with single-agent data from other clinical studies.

Summary statistics will include mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum. Additional PK/pharmacodynamic and exposure-response analyses will be conducted as appropriate.

6.7 PATIENT-REPORTED OUTCOME ANALYSIS

The analysis of PRO (assessed using the EORTC QLQ-C30 and QLQ-STO22 questionnaires) will be performed according to the EORTC Scoring and Reference Values Manual.

The details of the analyses will be specified in the Statistical Analysis Plan.
The respective subscales from the EORTC QLQ-C30 and QLQ-STO22 will be used to evaluate and compare the time to deterioration in abdominal pain, reflux, eating restrictions (premature safety), weight loss, appetite loss, and fatigue between treatment arms. All scores and subscales will be assessed through descriptive summary statistics.

EQ-5D health status data will be used only for obtaining utility measures for economic modeling and will not be analyzed as part of clinical efficacy (and thus will not be included in the Clinical Study Report).

6.8 EXPLORATORY ANALYSES

Duration of Objective Response. DOR is defined as the time from initial response to disease progression or death among patients who have experienced a CR or PR during the study. Patients who have not progressed or died at the time of analysis will be censored at the time of last tumor assessment date. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms through use of the unstratified log-rank test will be made for descriptive purposes only.

Disease Control Rate (DCR). DCR is defined as the rate of patients with CR, PR or stable disease maintained for ≥ 6 weeks. The analysis methods for DCR will be the same as those for the analysis of ORR.

Exploratory Biomarker Analysis. Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or adverse events. Results will be presented in a separate report.

6.9 HANDLING OF MISSING DATA

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date when they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization.

For objective response, patients without a post-baseline assessment will be considered nonresponders.

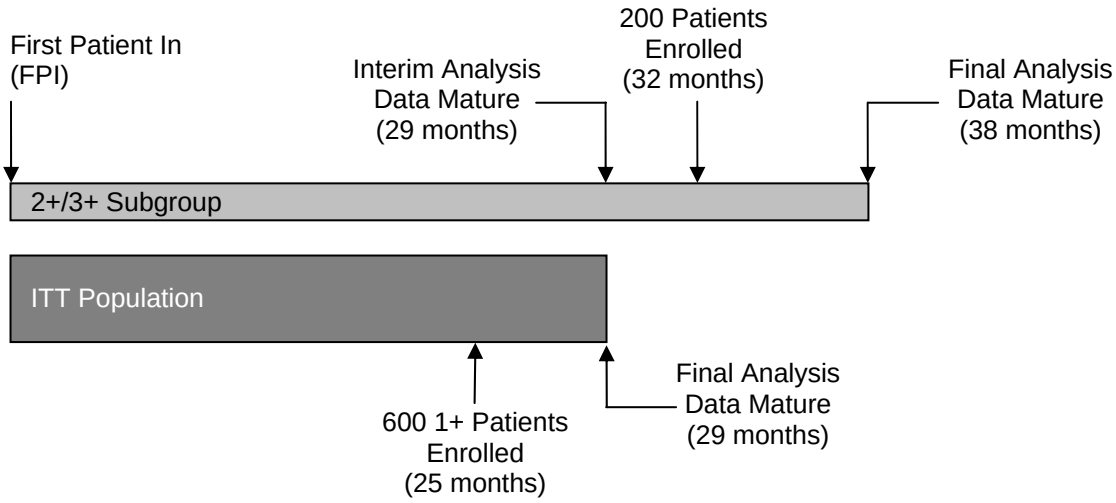
6.10 INTERIM ANALYSES

One formal interim analysis for efficacy and futility is planned for the Met 2+/3+ subgroup in this study. The interim analysis will be conducted after approximately 67% of the information (i.e., 79 deaths in the Met 2+/3+ subgroup) has been observed. This is expected to occur approximately 29 months after the first patient is enrolled. The timing of this interim analysis will depend on the accrual rate and will be driven by the occurrence of 79 deaths. Approximately 780 patients (180 in the Met 2+/3+ subgroup and 600 Met 1+ patients) will have been randomized by the time of the interim analysis, and 449 deaths in the ITT population will have been observed. Hence, the final analysis for the ITT population and the interim analysis for the Met 2+/3 subgroup will occur when both 79 deaths are observed in the Met 2+/3+ subgroup and 449 deaths are observed in the ITT population. As 449 deaths provide enough power for hypothesis testing for the ITT analysis, no further analysis for the ITT population is planned. The final analysis of the Met 2+/3+ subgroup will occur after 118 events are observed in this subgroup (see Figure 3).

The stopping boundaries for efficacy are to be computed using the Lan-DeMets approximation to the O'Brien-Fleming boundary:

- For the Met 2+/3+ subgroup, the rejection boundary for superior efficacy will be an HR ≤ 0.496 (p = 0.00093) at the interim analysis and an HR ≤ 0.626 (p = 0.00544) at the final analysis. The stopping boundary for futility is to be computed using a Rho-family spending function (Rho = 6) for the Met 2+/3+ subgroup. The rejection boundary for futility will be an HR ≥ 0.83 (p = 0.21).
- For the ITT population, the rejection boundary for superior efficacy will be HR ≤ 0.824 (p = 0.02) at the final analysis. The estimated timing of the interim and final analyses is illustrated in Figure 3 below.

Figure 3 Estimated Timing of Data Analyses



7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Roche will develop electronic eCRF specifications for this study. Roche will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, Roche will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

Central laboratory data will be sent directly to Roche using standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data and records retention for the study data will be consistent with Roche's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Roche and should be handled in accordance with instructions from Roche.

All eCRFs should be completed by designated trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO questionnaires, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of Roche. Written notification should be provided to Roche prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Roche's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Roche or its designee must review and approve any proposed deviations from Roche's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples (tissue, serum, plasma, and DNA) for optional future research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the 15-year storage period. Separate, specific signatures will be required to document a patient's agreement to allow any remaining specimens to be stored for future research in the Roche Clinical Repository (RCR). Patients who decline to participate will check a "no" box in the appropriate section and will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to Roche for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a

separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from Roche. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Roche maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Roche location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Roche monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 SITE INSPECTIONS

Site visits will be conducted by Roche or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Roche monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. Approximately 120 study centers will participate in this study globally, enrolling a total of approximately 800 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring. An IxRS will be used to manage site drug supply and to randomize patients to study drug.

Tumor tissue will be sent to a central laboratory for analysis of Met status and HER2 status. Tumor tissue, plasma, and serum will be sent to a central laboratory for analysis and sample storage. Sample analysis will be performed by an external vendor or the Sponsor.

A pharmacist who is separated from the study staff will be unblinded to onartuzumab/placebo and will prepare onartuzumab and placebo for administration. An IDMC will review unblinded safety data at pre-defined time points during the study and determine whether the study should be stopped or amended if needed.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

Roche will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB/EC of any amendments to the protocol. Approval must be obtained from the IRB/EC before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

Cycle	Screening	Baseline	Treatment Phase (q14d) [a]		Unplanned Visit [b]	SDDV [a,c]	Survival Follow-Up [a, d]
			1–12	≥ 13	Until PD	≤30 days after end of study tx	
Day	≤ 28 days	≤ 7 days	1	1	1		
Assessment Window [a] (days)	—	—	± 7	± 7	—	± 7	± 7
Informed consent	x						
Demographic data, height, medical history, BL conditions	x						
General medical history and baseline conditions	x						
Complete physical exam, including vital signs [e]	x					x	
Symptom-directed physical exam, including vital signs [f]			x	x	x		
Brain CT scan or MRI	x [g]						
ECG		*x*	*As clinically indicated*				
Weight		x	x	x		x	
ECOG performance status		x	x	x	x	x	
Chest X-ray	x [h]		As clinically indicated				
Tumor assessments [i, j]	x		x [j]	x [j]	x [k]	x [l]	*x j*
Tumor tissue for Met and HER2 status	x [m]						
Hematology [n]		x	x	x	x	x	
Chemistry [o]		x	x	x	x	x	
INR and PT		x	As clinically indicated [p]				
Pregnancy test [q]		x	As clinically indicated				
Dipstick urinalysis		x	x	x	x	x	

Appendix 1
Schedule of Assessments (cont'd)

Cycle	Screening	Baseline	Treatment Phase (q14d) [a]		Unplanned Visit [b]	SDDV [a,c]	Survival Follow-Up [a, d]
			1–12	≥ 13	Until PD	≤30 days after end of study tx	
Day	≤ 28 days	≤ 7 days	1	1	1		
Assessment Window [a] (days)	—	—	± 7	± 7	—	± 7	± 7
Onartuzumab/placebo			x	x			
Oxaliplatin and folinic acid (or levofolinic acid) infusions			x				
5-FU bolus and infusion			x				
EORTC QLQ-C30, STO22, and EQ-5D [r]			x	x		x	
Serum sample (ATA) *(at selected centers)*		See Appendix 2					
Serum samples (onartuzumab PK) *(at selected centers)*		See Appendix 2					
Plasma (somatic tumor mutations)		See Appendix 2					
Plasma and serum (exploratory biomarkers)		See Appendix 2					
Optional blood for DNA extraction (RCR)		See Appendix 2					
Concomitant medications	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x [s]	x [s]
SAEs	x	x	x	x	x	x	x
Patient survival and anti-cancer therapies							x

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; PD = progressive disease; q14d = every 14 days; SDDV = study drug discontinuation visit.

[a] Except for Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

[b] Visit not specified by the protocol.

[c] When a patient discontinues all study treatment, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days after the last dose of study drug for a study drug discontinuation visit (SDDV).

Appendix 1
Schedule of Assessments (cont'd)

[d] Survival follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[e] Complete physical examination includes height, HEENT, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Vital signs include temperature, respiratory rate, heart rate, systolic and diastolic blood pressure while the patient is in a seated position. Exam should also include presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly for tumor assessment. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF.

[f] Changes from baseline recorded; record new or worsened abnormalities as AEs if appropriate. Include evaluation of enlarged lymph nodes, hepatomegaly, and splenomegaly for tumor assessment. Vital signs include temperature, respiratory rate, heart rate, systolic and diastolic blood pressure while the patient is in a seated position.

[g] A CT scan or MRI of the brain should be conducted at screening only when there is a clinical suspicion of CNS metastases. Scans obtained within 6 weeks prior to randomization are acceptable for baseline assessment, unless the patient demonstrates clinical signs and symptoms of CNS disease progression.

[h] Screening chest X-ray is optional for the assessment of infectious process.

[i] *Tumor assessments with computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis are to be performed every 6 weeks ± 7 business days (during the last week of every third cycle) for the first 12 months and then every 12 weeks ±14 days (during the last week of every sixth cycle) until disease progression, independently of the schedule of treatment administration or early treatment discontinuation. CT scans of the neck should be included if clinically indicated. Tumor assessments should include an evaluation of all known and/or suspected sites of disease, whenever possible. Response assessments will be assessed by the investigator based on physical examinations, CT or MRI scans, and bone scans using RECIST v. 1.1. Tumor measurements should be made by the same investigator or radiologist for each patient during the study to the extent that this is feasible. Bone scans and plain X-rays may also be obtained at baseline as clinically indicated to follow clinically important lesions if they are not well visualized on the CT or MRI scans. If a bone scan is performed at baseline and indicates bone metastases, it should be repeated at the time of a confirmation of response to rule out any progression of bone metastases. At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if progressive disease is suspected.*

[j] *If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present. In cases where there is suspicion of clinical progression before the next scheduled assessment, an unscheduled assessment should be performed. For patients with no progressive disease after terminating study treatment, tumor assessments will be evaluated per local standard of care until disease progression is noted.*

[k] If clinically indicated with signs and symptoms suggestive of disease progression.

[l] Tumor assessments not required after disease progression has been documented.

[m] Archival tissue block (preferred) or 15 serial, freshly cut unstained slides accompanied by an associated pathology report is required for participation in this study. Tissue quality and adequate viable tumor cell content are specified in the accompanying lab manual. Cytological samples are not acceptable.

[n] Includes hemoglobin, hematocrit, platelet count, WBC count, differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells). If screening hematology and chemistries are performed within 3 days before Cycle 1 Day 1, these tests do not need to be repeated. Reporting the differential as absolute counts is required.

[o] Includes sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus, and magnesium.

[p] For patients on anticoagulation therapy.

[q] All women of childbearing potential (including those who have had a tubal ligation) will have a pregnancy test at baseline and if clinically indicated. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[r] Complete before all other assessments during the study visit.

[s] Ongoing or new toxicity that is thought to be in any way related to protocol-specified treatment.

Appendix 2
Schedule for Collection of Blood Samples for Pharmacokinetics, Anti-Therapeutic Antibodies, and Exploratory Biomarkers

Study Visit	Time Point	Sample Type
Baseline	≤ 7 days before first dose	Serum (exploratory biomarkers) Plasma (exploratory biomarkers) Plasma (somatic tumor mutations) Optional RCR Blood (for DNA extraction) [a]
Cycle 1 Day 1	Prior to onartuzumab/placebo infusion (within 1 hr)	Serum onartuzumab ATA [b] Serum onartuzumab PK [b]
	30 minutes (± 10 minutes) after end of onartuzumab/placebo infusion	Serum onartuzumab PK [b]
Cycle 2 Day 1	Prior to onartuzumab/placebo infusion	Serum onartuzumab PK [b] Serum (exploratory biomarkers) Plasma (exploratory biomarkers)
Cycle 4 Day 1	Prior to onartuzumab/placebo infusion	Serum onartuzumab ATA [b] Serum onartuzumab PK [b]
Cycle 8 Day 1	Prior to onartuzumab/placebo infusion	Serum (exploratory biomarkers) Plasma (exploratory biomarkers)
Cycle 12 Day 1	Prior to onartuzumab/placebo infusion	Serum (exploratory biomarkers) Plasma (exploratory biomarkers)
Study Drug Discontinuation Visit	At visit	Serum onartuzumab ATA [b] Serum onartuzumab PK [b] Serum (exploratory biomarkers) Plasma (exploratory biomarkers) Plasma (somatic tumor mutations)

ATA = anti-therapeutic antibody; PK = pharmacokinetic; RCR = Roche Clinical Repository.

[a] The optional RCR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study.

[b] *Onartuzumab PK and ATA sampling will be assessed in patients at selected centers. Centers will be selected based their ability and willingness to execute PK/ATA sampling.*

Note: Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ± 7 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

Serum exploratory biomarker samples may be used for measuring onartuzumab drug concentrations and ATA.

Appendix 3
Ventana Anti-Total c-MET (SP44) Rabbit Monoclonal Antibody IHC Assay

The Anti-Total c-MET (SP44) Rabbit Monoclonal Antibody IHC assay will be used as the assay to determine Met IHC status and to select Met-positive patients for enrollment in Study YO28322. The Anti-Total c-MET (SP44) Rabbit Monoclonal Antibody IHC assay is currently being developed by Ventana Medical Systems and will be labeled For Investigational Use Only (IUO) for the study.

The Anti-Total c-MET (SP44) Rabbit Monoclonal Antibody IHC assay is an immunohistochemical assay for the detection of Met expressing cells via light microscopy in formalin-fixed paraffin-embedded GEC tissues following staining on a Ventana automated slide stainer. Anti-Total c-MET (SP44) is a recombinant rabbit monoclonal antibody produced against a synthetic peptide of the human c-Met protein.

The scoring system includes evaluation of both staining intensity (negative, weak, moderate, or strong) and the proportion of tumor cells that stain at each intensity level. Met-positive is defined as ≥50% tumor cells with weak, moderate, or strong membrane and/or cytoplasmic staining (see table below).

Met Status	Clinical Score	Scoring Criteria
Positive	3+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with strong intensity
	2+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with moderate or higher intensity but < 50% tumor cells with strong intensity
	1+	≥ 50% tumor cells with membrane and/or cytoplasmic staining with weak or higher intensity but < 50% tumor cells with moderate or higher intensity
Negative	0	Samples with no staining, or with < 50% tumor cells with membrane and/or cytoplasmic staining (could be combination of any staining intensities)

Device Description

The Anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody IHC assay is an automated immunohistochemical staining assay system comprising a pre-dilute, ready-to-use Anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody, the BenchMark ULTRA automated slide staining platform, *ultra*View Universal DAB detection kit, and Anti-Total c-Met (SP44) 4-in-1 cell line control slides. The reagents and the staining procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing VSS software (Ventana System Software).

Appendix 4
Examples of Patient Assignment to Met IHC Stratification Levels (I–V)

The following table provides examples of how eligible patient assignments to the five Met IHC stratification levels (I–V; see Table 1 in Section 3.3.4.1) will be conducted during the trial. These five patient examples demonstrate the assignment of each patient to a single stratification level based on the Met IHC status cutoff parameters defined in Table 1. As shown in the following table, each patient is first assigned to a category based on a 50% cutoff and then to a category based on a 90% cutoff, and these jointly determine the patient's Met IHC stratification level.

	Percentages (%) of Met IHC Staining Intensity [a]				*Met Score Based on*	*Met Score Based on*	*Met IHC Stratification*
Patient	*Weak*	*Moderate*	*Strong*	*No Staining*	*50% cutoff*	*90% cutoff*	*Level*
A	*0*	*0*	*100*	—	*3+*	*3+*	*I*
B	*20*	*70*	*10*	—	*2+*	*1+*	*II*
C	*20*	*30*	*30*	*20*	*2+*	*0*	*III*
D	*60*	*30*	*10*	—	*1+*	*1+*	*IV*
E	*60*	*0*	*0*	*40*	*1+*	*0*	*V*

Appendix 5
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a. Measurable Tumor Lesions

Tumor Lesions. Tumor 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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that 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 the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) 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, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring 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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Lesions with Prior Local Treatment:

- Tumor 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.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should

also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

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 that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$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 tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 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 $\geq$ 10 mm but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$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 of 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 of diameters will be used as a reference to further characterize any objective tumor 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."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters

- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. 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 <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 complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Target Lesions That Become Too Small to Measure. During the 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 that 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 CRF, as follows:

- 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 and BML (below measurable limit) should be ticked. (BML is equivalent to a "less than" sign.) (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 and BML should also be ticked).

<u>To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.</u>

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 maximum longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor 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 timepoints specified in the protocol.

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor 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 lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

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 in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor 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 qualify 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 III 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,

that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized 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.

e. 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, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting 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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

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:

- A negative FDG-PET scan at baseline with a positive[3] FDG-PET scan during the study is a sign of PD based on a new lesion.
- In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

  If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.

  If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether 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 scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will <u>not</u> be considered PD.

[3] A "positive" FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation-corrected image.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Evaluation of Response

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint 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 during the study 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Appendix 5 (cont'd)
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

c. 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 CRF.

Patients 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 objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 and 2.

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.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 6
EORTC QLQ-C30 and QLQ-STO22

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:

Today's date (Day, Month, Year):

		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

Appendix 6 (cont'd)
EORTC QLQ-C30 and QLQ-STO22

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

Appendix 6 (cont'd)
EORTC QLQ-C30 and QLQ-STO22

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

Appendix 7
EuroQol EQ-5D

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

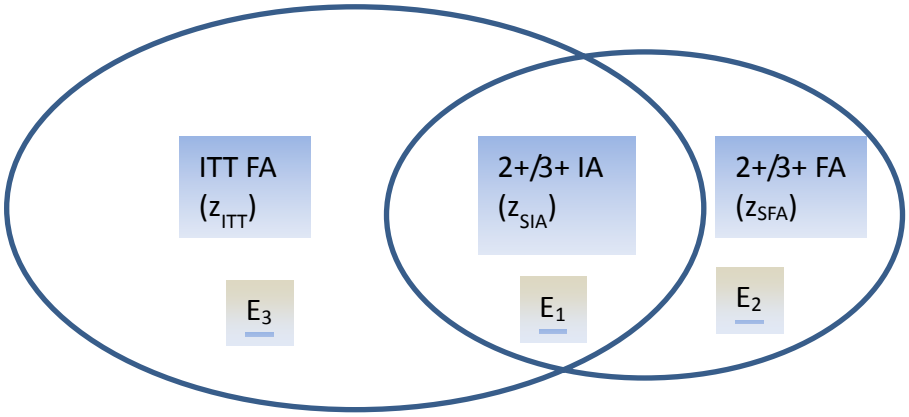
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

Appendix 8
Adjusted Significance Levels for Analysis of the ITT Population and Met 2+/3+ Subgroup

The co-primary endpoints of this study are overall survival in the ITT population and in the Met 2+/3+ subgroup (see Section 6.4.1). Correlation will exist between the log-rank statistic calculated for the Met 2+/3+ subgroup and the log-rank statistic calculated for the ITT population because patients that are part of the subgroup analysis also contribute to the ITT analysis. Hence, the nominal type I error levels of each hypothesis using a testing procedure that incorporates this correlation will be higher than the significance levels derived from testing procedures that do not (e.g., the Bonferroni procedure). Although the nominal significance levels of the testing procedures that account for the correlation will be higher for each individual group, the familywise error rate (FWER) will still be controlled at the prespecified one-sided 0.025 level. A method that accounts for this correlation in a manner similar to that used in group-sequential analysis is described below, and further details can be found in the references.

Let Z_{SIA} be the standardized log-rank statistic for the interim analysis of the Met 2+/3+ subgroup, Z_{SFA} be the standardized log-rank statistic for the final analysis of the Met 2+/3+ subgroup, and Z_{ITT} be the standardized log-rank statistic for the single ITT analysis; a diagram of the non-nested hypotheses is shown below.



Appendix 8 (cont'd)
Adjusted Significance Levels for Analysis of the ITT Population and Met 2+/3+ Subgroup

Note that the information (i.e., the number of events) can be partitioned into three independent parts: E_1, E_2, and E_3, as shown above. Let Z_1, Z_2, and Z_3 represent the corresponding standardized log-rank statistics; the following relationships hold:

$$Z_{SIA} = Z_1$$
$$Z_{SFA} = Z_1\sqrt{E_1/(E_1+E_2)} + Z_2\sqrt{E_2/(E_1+E_2)}$$
$$Z_{ITT} = Z_1\sqrt{E_1/(E_1+E_3)} + Z_3\sqrt{E_3/(E_1+E_3)}$$

The correlation terms can be calculated as follows:

$$Corr\,(Z_{SIA}, Z_{SFA}) = \sqrt{E_1/(E_1+E_2)}$$
$$Corr\,(Z_{SIA}, Z_{ITT}) = \sqrt{E_1/(E_1+E_3)}$$
$$Corr\,(Z_{SFA}, Z_{ITT}) = \sqrt{E_1/(E_1+E_2)} * \sqrt{E_1/(E_1+E_3)}$$

Thus, under H_0, Z_{SIA}, Z_{SFA}, and Z_{ITT} follow a multivariate normal distribution:

$$\begin{pmatrix} z_{SIA} \\ z_{SFA} \\ z_{ITT} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sqrt{E_1/(E_1+E_2)} & \sqrt{E_1/(E_1+E_3)} \\ \sqrt{E_1/(E_1+E_2)} & 1 & \sqrt{E_1/(E_1+E_2)}*\sqrt{E_1/(E_1+E_3)} \\ \sqrt{E_1/(E_1+E_3)} & \sqrt{E_1/(E_1+E_2)}*\sqrt{E_1/(E_1+E_3)} & 1 \end{pmatrix} \right)$$

Under protocol assumptions, 79 (E_1), 118 ($E_1 + E_2$), and 449 ($E_1 + E_3$) events will have been observed at the time of the interim analysis of the Met 2+/3+ subgroup, the final analysis of the Met 2+/3+ subgroup, and the single ITT analysis, respectively. The multivariate normal distribution thus reduces as follows:

$$\begin{pmatrix} z_{SIA} \\ z_{SFA} \\ z_{ITT} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & 0.818 & 0.419 \\ 0.818 & 1 & 0.343 \\ 0.419 & 0.343 & 1 \end{pmatrix} \right)$$

Appendix 8 (cont'd)
Adjusted Significance Levels for Analysis of the ITT Population and Met 2+/3+ Subgroup

The FWER, i.e. $p(\textit{reject ITT analysis, or reject } 2+/3+ \textit{ at IA or FA})$, needs to be conserved at 0.025 level; thus, the critical values for $Z_{SIA,}$ $Z_{SFA,}$ and Z_{ITT} need to be determined so that under H_0,

$$
\begin{aligned}
& p(\textit{reject ITT analysis, or reject } 2+/3+ \textit{ at IA or FA}) \\
&= p(z_{ITT} > z_{\alpha_{ITT}}, \textit{or } z_{SIA} > z_{\alpha_{SIA}}, \textit{or } (z_{SIA} \le z_{\alpha_{SIA}} \,\&\, z_{SFA} > z_{\alpha_{SFA}})) \\
&= p(z_{ITT} > z_{\alpha_{ITT}}) + p(z_{SIA} > z_{\alpha_{SIA}}) + \\
&\quad p\,(z_{SIA} \le z_{\alpha_{SIA}} \,\&\, z_{SFA} > z_{\alpha_{SFA}})) - \qquad (1) \\
&\quad p(z_{ITT} > z_{\alpha_{ITT}} \,\&\, z_{SIA} > z_{\alpha_{SIA}}) - \qquad (2) \\
&\quad p(z_{ITT} > z_{\alpha_{ITT}} \,\&\, z_{SIA} \le z_{\alpha_{SIA}} \,\&\, z_{SFA} > z_{\alpha_{SFA}}) \qquad (3) \\
&= 0.025
\end{aligned}
$$

where (1) and (2) can be obtained from the SAS function *probbnrm*, and (3) can be obtained from numerical integration. The nominal power of the ITT analysis is $p(z_{ITT} > z_{\alpha_{ITT}} \mid H_1)$.

The overall nominal power of the subgroup analysis is
$p(z_{SIA} > z_{\alpha_{SIA}}, or\ (z_{SIA} \le z_{\alpha_{SIA}} \,\&\, z_{SFA} > z_{\alpha_{SFA}}) \mid H_1)$

which can be calculated using the SPLUS function *pmvnorm*.

The nominal significance level for the ITT analysis will be prespecified to be 0.02. The overall nominal significance level for the subgroup analysis will be determined such that the overall type I error remains at 0.025. The nominal significance level for Z_{SIA} and Z_{SFA} will be calculated according to an O'Brien-Fleming boundary, with the information fraction at the interim analysis being E1/(E1 + E2), where E1 + E2 are specified in the protocol to be 118 events. The characteristics of the protocol specified design are summarized below.

Appendix 8 (cont'd)
Adjusted Significance Levels for Analysis of the ITT Population and Met 2+/3+ Subgroup

Analysis	Critical Values (z_α)	Nominal Alpha	Type I Error [a]	HR Boundary	Power
Met 2+/3+ interim analysis	3.112	0.00093	0.00093	0.496	0.523
Met 2+/3+ final analysis	2.547	0.00544	0.00577	0.626	0.909
ITT final analysis	2.054	0.02000	0.02000	0.824	0.900

[a] The overall type I error is 0.025.

As stated in the protocol, the single analysis of the ITT population and the interim analysis of the Met 2+/3+ subgroup will be performed when 449 events in the ITT population or 79 events in the Met 2+/3+ subgroup occur, whichever occurs later. The nominal alpha for the ITT analysis will remain at 0.02, and the significance levels for the interim analysis and final analysis of the Met 2+/3+ subgroup will be recalculated based on the actual information fractions, just as in group sequential methods. The rejection boundaries will need to be recalculated for all three analyses based on the actual number of events.

References:

Spiessens B, Debois M. Adjusted significance levels for subgroup analyses in clinical trials. Contemp Clin Trials 2010;31:647–56.

Bristol DR. p-value adjustments for subgroup analyses. J Biopharm Stat 1997;7:313–21; discussion 323–31.