Official Title:	**AN OPEN-LABEL, MULTICENTER EXTENSION STUDY OF ONARTUZUMAB IN PATIENTS WITH SOLID TUMORS ON STUDY TREATMENT PREVIOUSLY ENROLLED IN AN F. HOFFMANN-LA ROCHE- AND/OR GENENTECH-SPONSORED STUDY**
NCT Number:	**NCT02488330**
Document Date:	**Protocol Version 5: 17-August-2017**

PROTOCOL

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PROTOCOL NUMBER:	GO29646
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-005438-69
IND NUMBER:	100537
TEST PRODUCT:	Onartuzumab (RO5490258)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 16 January 2015
DATES AMENDED:	Version 2: 1 September 2015 Version 3: 30 June 2016 Version 4: 22 July 2016 Version 5: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	17-Aug-2017 14:38:04

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PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- The protocol has been amended to update that all serious adverse events, whether related or unrelated to onartuzumab, erlotinib, or bevacizumab that occurred while enrolled on study and also within the protocol-specified reporting period after the last dose of study drug, need to be reported to the Sponsor (Sections 3.3, 3.4.2, 4.4.1, 5.2, 5.3, 5.4, 5.5, 5.7, and 6.5).
- Clarification has been added that bevacizumab and/or erlotinib are considered control treatment for this study (Sections 3.1 and 5.1.7).
- The reporting of the term “sudden death” has been updated to also require the presumed cause of death (Section 5.3.5.3).
- Event reporting for hospitalization has been clarified (Section 5.3.5.4).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).

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 5:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol.

SECTION 1.5: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

- The Sponsor will collect safety data ~~related to~~ *for* the investigational agent, onartuzumab, as well as any drugs manufactured by the Sponsor and given as the control treatment in accordance with all local regulations.

SECTION 3.1: DESCRIPTION OF STUDY

All patients will continue on the same dose and schedule of control treatment *(bevacizumab and/or erlotinib)* as specified in their respective P-trial.

SECTION 3.3: RATIONALE FOR STUDY DESIGN

~~Only~~ *All* serious adverse events ~~assessed as related to onartuzumab, erlotinib, or bevacizumab~~ will be reported.

SECTION 3.4.2: Safety Outcome Measure

The safety outcome measure for this study is as follows:

- Serious adverse events considered related *or unrelated* to onartuzumab

SECTION 4.4.1: Informed Consent Forms and Screening Log

After informed consent signature but prior to the first dose of study therapy in the E-trial (onartuzumab and/or, if applicable, other P-trial IMP), serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, should be reported.

SECTION 5.1.7: Adverse Events Related to Control Treatment

Any adverse events known to be related to the control treatment *(bevacizumab and/or erlotinib),* whether given alone or in conjunction with onartuzumab, should be managed as per local standard of care.

SECTION 5.2: SAFETY PARAMETERS AND DEFINITIONS

Only adverse events that fall into the category below should be reported to the Sponsor.

- Serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to onartuzumab, Avastin (bevacizumab), or Tarceva (erlotinib)

SECTION 5.2.2: Serious Adverse Events (Immediately Reportable to the Sponsor)

Serious adverse events*, whether related or unrelated,* are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

SECTION 5.3: METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all serious adverse events (see Section 5.2.1 for definition) ~~assessed as related to onartuzumab, bevacizumab, or erlotinib~~ 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.

SECTION 5.3.1: Adverse Event Reporting Period

Investigators will seek information on serious adverse events ~~related to onartuzumab, bevacizumab, or erlotinib~~ at each patient contact.

After informed consent has been obtained, all serious adverse events ~~considered related to onartuzumab, erlotinib, or bevacizumab should be reported (see Section for instructions for reporting serious adverse events). After~~ *will be recorded during the study and for up to 30 days after* the last dose of ~~onartuzumab~~ *study treatment. After this period*, the investigator should ~~only~~ report any serious adverse events that are ~~assessed~~ *believed* to be related to prior ~~onartuzumab treatment. For patients receiving only control~~ *study drug* treatment~~, only serious adverse events related to treatment will be reported for bevacizumab and/or erlotinib if applicable to that patient~~ (see Section 5.6).

SECTION 5.3.5: Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording *all* serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

SECTION 5.3.5.3: Deaths

~~The term **"sudden death"** should be used only 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 after 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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.4: Hospitalization or Prolonged Hospitalization

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event ~~The following hospitalization scenarios are not considered to be adverse events~~:

[…]

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead ~~The following hospitalization scenarios are not considered to be serious adverse events, but should be considered as adverse events instead~~:

[…]

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event:

- Serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to onartuzumab
- Serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to Avastin (bevacizumab)
- Serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to Tarceva (erlotinib)
- Pregnancies

SECTION 5.4.2.1: Events That Are Ongoing from the Previous Protocol

Events that are ongoing from the P-trial should not be reported again under this protocol, unless the severity increases, ~~and~~ *whether* the event is ~~assessed as~~ related *or unrelated* to onartuzumab*, erlotinib, or bevacizumab*.

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events, ~~assessed as~~ *whether* related *or unrelated* to onartuzumab, bevacizumab, or erlotinib, will be reported until 30 days after the last dose of study drug.

SECTION 5.5.1: Investigator Follow-Up

Every effort should be made to follow all serious adverse events, ~~considered to be~~ *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, until a final outcome can be reported.

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

The Sponsor will promptly evaluate all serious adverse events ~~that are assessed as related to onartuzumab~~ against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

SECTION 6.5: SAFETY ANALYSES

A summary of administration of study treatment (onartuzumab) and serious adverse events, ~~considered~~ *whether* related *or unrelated* to onartuzumab, will be generated for these patients.

SECTION 9.2: PROTOCOL DEVIATIONS

The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

ww.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf
~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], M.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 retain the signed original of this form for your study files. Please return a copy to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER EXTENSION STUDY OF ONARTUZUMAB IN PATIENTS WITH SOLID TUMORS ON STUDY TREATMENT PREVIOUSLY ENROLLED IN AN F. HOFFMANN-LA ROCHE- AND/OR GENENTECH-SPONSORED STUDY**
PROTOCOL NUMBER:	GO29646
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-005438-69
IND NUMBER:	100537
TEST PRODUCT:	Onartuzumab (RO5490258)
PHASE:	Phase IIIb/IV
INDICATION:	Solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

The objectives for this study are as follows:

- To provide continued onartuzumab and/or parent trial (P-trial)–designated control treatments to patients with cancer who were previously enrolled in a Roche/Genentech-sponsored onartuzumab P-trial and who derived benefit, as assessed by the responsible investigator, from the therapy administered in the P-trial.
- To collect safety data with regard to administration of continued onartuzumab therapy.

Study Design

Description of Study

This is a multicenter, open-label Phase IIIb/IV study. Patients on treatment at the completion of the P-trial, defined as when relevant efficacy and safety analyses for the trial are completed by the Sponsor, should be enrolled into this extension trial (E-trial). Patients will receive treatment with either the control treatment *(bevacizumab and/or erlotinib)* and/or onartuzumab-based study treatment (as during their P-trial) until progression of disease, unacceptable treatment related toxicity, withdrawal of consent, or death (whichever occurs first).

Only patients previously enrolled and currently receiving treatment in the P-trials are eligible for this trial. Patients may be enrolled into the E-trial upon notification from the Sponsor to the investigator that the P-trial is completed.

All patients will continue on the same dose and schedule of control treatment as specified in their respective P-trial. The dose of onartuzumab will be calculated based on the patient's weight at the screening visit for the E-trial. Data will be collected for administration of onartuzumab and any serious adverse event deemed related to onartuzumab, erlotinib, and/or bevacizumab treatment.

This trial will remain open for enrollment until all patients from eligible P-trials have completed their protocol-specified therapies. The trial will close upon discontinuation of treatment of the last enrolled patient.

Number of Patients

Up to 14 study centers will participate in this study in Europe, Africa, and Asia, enrolling a total of up to 17 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed E-trial Informed Consent Form
- Enrolled and receiving either control treatment and/or onartuzumab-based study treatment in an eligible P-trial
- Has not met the treatment discontinuation criteria specified in their P-trial protocol at the time of enrollment into the E-trial
- Ability to begin treatment in the extension (rollover) protocol within 42 days following the last day of the study in the antecedent protocol
- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study drug

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.
- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study drug and agreement to refrain from donating sperm during this same period

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Pregnancy or lactation or intention to become pregnant during the study (serum pregnancy test required before enrollment)
- Any non-protocol anti-cancer therapy started between discontinuation from treatment in P-trial and start of enrollment in E-trial.

All patients will continue the therapy that they last received on their respective P-trials. Dose or schedule modifications made during a patient's treatment in the P-trial should be carried over into the E-trial (i.e., if a component of a combination chemotherapy had been discontinued for toxicity, that component should not be resumed).

Length of Study

It is estimated that this study will last approximately 2 years.

End of Study

The end of this study is defined as the date of the last patient, last visit (LPLV). This corresponds to 30 days after the last patient discontinues all treatment (either onartuzumab, control treatment, or both) for any reason. Once patients have discontinued either control treatment and/or onartuzumab-based study treatment and completed a 30-day follow-up visit, their participation in the trial is considered complete.

Outcome Measures

Efficacy Outcome Measures

This study includes no efficacy outcome measures.

Safety Outcome Measures

The safety outcome measure for this study is as follows:

- Serious adverse events, *whether* related *or unrelated* to onartuzumab

Investigational Medicinal Products

Onartuzumab (RO5490258)

Onartuzumab will be supplied as a sterile liquid in a single-use 15-cc vial. Each 15-cc vial contains 600 mg of onartuzumab in 10 mL at a concentration of 60 mg/mL in [redacted] mM histidine acetate, [redacted] mM sucrose, [redacted]% 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.

Onartuzumab will be administered intravenously at either a dose of 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks.

Erlotinib

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Erlotinib immediate-release tablets are available in 25-, 100-, and 150-mg strengths.

Bevacizumab

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for IV infusion. Bevacizumab will be supplied in 20-mL (400-mg) glass vials containing 16 mL bevacizumab (25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are suitable for single use only.

Non-Investigational Medicinal Products

Comparator

Non-investigational medicinal products for each subject in the E-trial will be the same as that in their P-trial.

Statistical Methods

Primary Analysis

The safety analyses will include only patients who received at least one dose of onartuzumab. A summary of administration of study treatment (onartuzumab) and serious adverse events considered related to onartuzumab will be generated for these patients.

Determination of Sample Size

The sample size of this E-trial will depend upon the number of patients eligible from P-trials who elect to transfer to this trial for continued treatment of their underlying cancer.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ASCO	American Society of Clinical Oncology
CRO	contract research organization
CSF	colony-stimulating factors
CT	computed tomography (scan)
CVAD	central venous access devices
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
E-trial	extension trial
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	interactive web/voice response system
IV	intravenous
LPLV	last patient, last visit
MET	mesenchymal–epithelial transition factor
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
P-trial	parent trial
PE/PP	polyethylene/polypropylene
PRO	patient-reported outcome
PVC	polyvinyl chloride
SPC	Summary of Product Characteristics
VTE	venous thromboembolic events
WOCP	women of childbearing potential

1. BACKGROUND

1.1 BACKGROUND ON MET SIGNALING PATHWAY

Hepatocyte growth factor (HGF; also known as scatter factor) and its receptor mesenchymal–epithelial transition factor (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). The HGF/MET pathway is frequently dysregulated in many human malignancies via multiple mechanisms, including receptor mutation, aberrant autocrine production of HGF and MET in the same tumor cell, and MET overexpression.

Evidence of activating mutations in the MET kinase domain was characterized in cases of spontaneous and hereditary papillary renal cell carcinoma (Schmidt et al. 1997; Olivero et al. 1999). These activating mutations are transforming in NIH-3T3 cells and normal epithelial cells, in which the mutant receptors make cells hyperresponsive to HGF (Jeffers et al. 1997, 1998; Schmidt et al.1997, 1998; Michieli et al. 1999; Olivero et al. 1999; Lorenzato et al. 2002; Graveel et al. 2004). Similarly, mutations in or loss of the juxtamembrane region of MET have been found in 2% of non–small cell lung cancer (NSCLC) (Kong-Beltran et al. 2006). Loss of function of the juxtamembrane domain, which encodes for a binding site for the Cbl E3 ubiquitin ligase, results in prolonged MET signaling following ligand stimulation, making tumor cells hyperresponsive to HGF. Other mutations and polymorphisms have been characterized in the MET extracellular domain; however, their role in driving tumorigenesis is not clear (Ma et al. 2005). Most commonly, the level of MET expression is increased.

Aberrant expression of HGF in epithelial-based tumor cells or MET in mesenchymally derived tumor cells results in the co-expression of both MET and HGF in an autocrine manner. Because both MET and HGF need proteolytic activation outside of the cells, localized HGF production likely acts in both an autocrine and paracrine fashion with neighboring cells. Co-expression of MET and HGF in tumors is fairly infrequent, occurring in $<1\%$ in most tumor indications. However, some indications have demonstrated higher rates of autocrine co-expression, including glioblastoma (GBM) and some sarcomas such as osteosarcoma (Koochekpour et al. 1997; Fukuda et al. 1998; Moriyama et al. 1999). Nonclinical HGF/MET autocrine tumor models have demonstrated exquisite sensitivity to MET inhibitors in vitro and in vivo (Martens et al 2006; Jin et al. 2008).

By far, the most common mechanism of dysregulation of the MET pathway is overexpression. Levels of MET can be increased via MET gene amplification or through amplification-independent means (Kuniyasu et al. 1992; Seruca et al. 1995). Although rates of MET amplification are typically low in most tumor indications (~1%), rates can be

as high as 2%–4% in NSCLC (Toschi and Cappuzzo 2010). MET amplification and MET overexpression have also been reported to occur as a mechanism of acquired resistance to other therapeutics such as epidermal growth factor receptor (EGFR) inhibitors (Bean et al. 2007; Engelman et al. 2007; Cappuzzo et al. 2009). HGF is also increased in patients with cancer, although it is not commonly found to be dysregulated at the gene copy level, nor is it as dynamically changed as the receptor. High levels of HGF and/or MET have been correlated with poor prognosis in several tumor types, including NSCLC (Ichimura et al 1996; Masuya et al. 2004).

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

1.2 BACKGROUND ON ONARTUZUMAB

Onartuzumab (MetMAb) 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 of only 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). Onartuzumab is currently the only monovalent antibody in the clinic that targets the MET receptor.

See the Onartuzumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Safety of Onartuzumab

To date, more than 1300 patients have been exposed to onartuzumab as part of the clinical development program. Adverse events assessed as causally related to onartuzumab are peripheral edema (including anasarca), gastrointestinal (GI) perforation, venous thromboembolic events (VTEs), arterial thromboembolic events, and neutropenia. Refer to the Onartuzumab Investigator's Brochure for further information.

1.3 BACKGROUND ON ERLOTINIB

Erlotinib (Tarceva®, OSI-774) is an orally active antitumor agent developed for the treatment of NSCLC, pancreatic cancer, and other solid tumors. Astellas Pharma US, Inc. (on behalf of OSI Pharmaceuticals, LLC), Genentech, Inc., and F. Hoffmann-La

Roche Ltd are co-developing erlotinib globally. Tarceva is currently approved for marketing in approximately 110 countries worldwide.

Erlotinib acts through direct and reversible inhibition of the human epidermal growth factor receptor 1/epidermal growth factor receptor (HER1/EGFR, hereafter referred to as EGFR) tyrosine kinase. Erlotinib inhibits human EGFR tyrosine kinase with a 50% inhibitory concentration (IC50) of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC50 of 20 nM (7.9 ng/mL). EGFR is overexpressed in a significant proportion of epithelium-derived carcinomas. Erlotinib inhibits the epidermal growth factor (EGF)-dependent proliferation of cells at nanomolar concentrations and blocks cell cycle progression at the G1 phase. Erlotinib binding affinity for EGFR exon 19 deletion or exon 21 L858R mutations is higher than its affinity for the wild type receptor.

See the Erlotinib Summary of Product Characteristics (SPC) for details on nonclinical and clinical studies.

1.4 BACKGROUND ON BEVACIZUMAB

Bevacizumab (Avastin®) is a recombinant humanized anti-vascular endothelial growth factor monoclonal IgG1 antibody that has undergone clinical development in numerous oncology indications. The development program includes studies sponsored and conducted by Genentech, Inc., F. Hoffmann-La Roche Ltd, and the National Cancer Institute in the U.S. On the basis of these studies, bevacizumab received marketing authorization approval in over 100 countries (including the U.S. and E.U.) for the treatment of patients with metastatic carcinoma of the colon or rectum. Marketing authorization has also been received in some of these countries for the treatment of patients with either unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC; metastatic breast cancer; advanced and/or metastatic renal cell cancer; or malignant glioma (WHO Grade IV) glioblastoma. For specific details of approved indications, please refer to the approved local prescribing information.

See the Bevacizumab SPC for details on nonclinical and clinical studies.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Onartuzumab has been investigated in several tumor types for which MET signaling has been implicated, generally through randomized Phase II and Phase III clinical trials. In most of these investigative trials, henceforth referred to as “P-trials” (or parent trials), the addition of onartuzumab to a standard therapy (with which MET inhibition may be additive or synergistic) was evaluated. Patients were randomized in blinded fashion to either the control arm consisting of standard therapy or to the study arm consisting of standard therapy combined with onartuzumab.

Per protocol, patients received control or study treatment until the earliest event of disease progression, an adverse event leading to discontinuation, or discontinuation per physician or patient decision. After the completion of the final analysis or discontinuation of these trials, study patients could remain on their protocol-specified treatment if none of these events have occurred. Roche/Genentech have committed to provide continued protocol-defined treatment for patients enrolled on a P-trial if medically appropriate and desired by the treating physician and the patient until one of the listed events has occurred.

This trial, henceforth referred to as the "E-trial" (or extension trial), allows continued treatment of patients on their P-trial protocol specified treatment after termination of their P-trial. This E-trial is designed to ensure an optimal benefit-risk ratio. The study protocol includes the following measures to manage the risk:

- The Sponsor will assess each trial carefully before declaring it a "qualifying" P-trial and enrolling its eligible patients into this E-trial. For example, a trial that is prematurely stopped for safety issues related to onartuzumab would not become a P-trial.
- The dose of onartuzumab for each patient will be calculated based on the weight of the patient obtained during the screening visit for the E-trial.
- The control treatment for each patient will remain as specified in the P-trial, including protocol-mandated dose modifications, from which the patient had been enrolled. Doses for all drugs in the control treatment regimen will remain the same as the last dose received on the P-trial.
- Clear guidance is provided on interruption and discontinuation for onartuzumab in case a patient develops severe side effects; this also takes into account side effects experienced during treatment in the P-trial.
- The Sponsor will collect safety data *for* the investigational agent, onartuzumab, as well as any drugs manufactured by the Sponsor and given as the control treatment in accordance with all local regulations.
- Doses of study therapy have been chosen in accordance with Summary of Product Characteristics (SPC) and taking into account the available data on clinical studies as well as usual practices.
- Because this is an E-trial, all centers already have experience with the study treatment and have qualified and experienced specialists involved who are motivated to continue caring for the patients.

2. OBJECTIVES

The objectives for this study are as follows:

- To provide continued onartuzumab and/or P-trial–designated control treatments to patients with cancer who were previously enrolled in a Roche/Genentech-sponsored onartuzumab P-trial and who derived benefit, as assessed by the responsible investigator, from the therapy administered in the P-trial.
- To collect safety data with regard to administration of continued onartuzumab therapy.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a multicenter, open-label Phase IIIb/IV study. Patients on treatment at the completion of the P-trial, defined as when relevant efficacy and safety analyses for the trial are completed by the Sponsor, should be enrolled into this E-trial. Patients will receive treatment with either the control treatment and/or onartuzumab-based study treatment (as during their P-trial) until progression of disease, unacceptable treatment related toxicity, withdrawal of consent, or death (whichever occurs first).

Only patients previously enrolled and currently receiving treatment in the P-trials are eligible for this trial. Patients may be enrolled into the E-trial upon notification from the Sponsor to the investigator that the P-trial is completed.

All patients will continue on the same dose and schedule of control treatment *(bevacizumab and/or erlotinib)* as specified in their respective P-trial. The dose of onartuzumab will be calculated based on the patient's weight at the screening visit for the E-trial. Data will be collected for administration of onartuzumab and any serious adverse event deemed related to onartuzumab, erlotinib, and/or bevacizumab treatment.

This trial will remain open for enrollment until all patients from eligible P-trials have completed their protocol-specified therapies. The trial will close upon discontinuation of treatment of the last enrolled patient.

3.2 END OF STUDY

The end of this study is defined as the date of the last patient, last visit (LPLV). This corresponds to 30 days after the last patient discontinues all treatment (either onartuzumab, control treatment, or both) for any reason. Once patients have discontinued either control treatment and/or onartuzumab-based study treatment and completed a 30-day follow-up visit, their participation in the trial is considered complete.

3.3 RATIONALE FOR STUDY DESIGN

The primary aim is to provide continued protocol-specified control therapy and/or onartuzumab-based study therapy to patients with cancer who are benefiting from the therapy administered in the P-trial at time of termination of the P-trial. Therefore, this is an open-label, non-comparative study. No efficacy analyses are planned. *All* serious adverse events will be reported.

3.3.1 Rationale for Onartuzumab Dose and Schedule

The dosing schedule of administration in the E-trial will follow the corresponding P-trial dosing administration schedule. Upon enrollment, patients in this E-trial will continue at the same dose of control treatment that they were receiving in the P-trial. The dose of onartuzumab will be calculated based on the patient's weight obtained at the screening visit for the E-trial. Any dose modifications will mirror dose modification criteria described in the corresponding P-trial.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

This study includes no efficacy outcome measures.

3.4.2 Safety Outcome Measure

The safety outcome measure for this study is as follows:

- Serious adverse events considered related *or unrelated* to onartuzumab

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients enrolled in an eligible onartuzumab P-trial that is being terminated and who remain on either protocol-mandated control treatment or onartuzumab-based study treatment are eligible for enrollment.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed E-trial Informed Consent Form
- Enrolled and receiving either control treatment and/or onartuzumab-based study treatment in an eligible P-trial
- Has not met the treatment discontinuation criteria specified in their P-trial protocol at the time of enrollment into the E-trial
- Ability to begin treatment in the extension (rollover) protocol within 42 days following the last day of the study in the antecedent protocol
- For women who are not postmenopausal (≥ 12 months of non–therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to

remain abstinent or use single or combined non-hormonal contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study drug

Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study drug and agreement to refrain from donating sperm during this same period

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

  Abstinence is acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

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

- Pregnancy or lactation or intention to become pregnant during the study (serum pregnancy test required before enrollment)
- Any non-protocol anti-cancer therapy started between discontinuation from treatment in P-trial and start of enrollment in E-trial.

All patients will continue the therapy that they last received on their respective P-trials. Dose or schedule modifications made during a patient's treatment in the P-trial should be carried over into the E-trial (i.e., if a component of a combination chemotherapy had been discontinued for toxicity, that component should not be resumed).

4.2 STUDY TREATMENT

If not specified by this E-trial protocol, the default is to follow the guidance from the respective P-trial protocol per clinical judgment or discretion of the investigator.

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Onartuzumab

Onartuzumab will be supplied as a sterile liquid in a single-use 15-cc vial. Each 15-cc vial contains 600 mg of onartuzumab in 10 mL at a concentration of 60 mg/mL in [redacted] mM histidine acetate, [redacted] mM sucrose, [redacted] % 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.

For further details, see the Onartuzumab Investigator's Brochure.

4.2.1.2 Erlotinib

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient (erlotinib), tablets contain lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and magnesium stearate.

Erlotinib immediate-release tablets are available in 25-, 100-, and 150-mg strengths.

For further details, see the manufacturer's prescribing information for Tarceva® (erlotinib).

4.2.1.3 Bevacizumab

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for IV infusion. Bevacizumab will be supplied in 20-mL (400-mg) glass vials containing 16 mL bevacizumab (25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are suitable for single use only.

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be kept in the outer carton due to light sensitivity.

For further details, see the manufacturer's prescribing information for Avastin (bevacizumab).

4.2.1.4 Non-Investigational Medicinal Product

Anti-cancer therapy, not manufactured by the Sponsor, given with or without onartuzumab in the P-trial will be administered as per instructions in the P-trial and classified as Non-IMP in this E-trial. The Sponsor will continue to provide those anti-cancer therapies until treatment is permanently discontinued.

If onartuzumab is permanently stopped for reasons other than disease progression, other P-trial IMP treatment may be continued under the E-trial until progression if the patient has no other form of access to treatment with those anti-cancer therapies.

Management (i.e., handling, storage, administration, accountability, and disposal) of those anti-cancer drugs will be in accordance with instructions defined in the P-trial.

Investigators can prescribe non-IMP in accordance with their local label and standard of care. Their use will be in accordance with the relevant local guidelines and SPC. Management (i.e., handling, storage, administration and disposal) will be in accordance with Good Clinical Practice (GCP) and local guidelines.

Please use commercial stock in keeping with the usual practice of the institution.

There are no special accountability arrangements.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Onartuzumab

Onartuzumab will be dosed in the clinic on Day 1 of each 14- or 21-day cycle as specified in the P-trial and as per clinical judgment and discretion of the investigator. The individual dose of onartuzumab for each patient will be 10 mg/kg for 14-day cycles or 15 mg/kg for 21-day cycles. The patient's weight at enrollment of the E-trial will be used to determine the actual dose of study drug. This dose will be administered throughout the study and will not change according to weight.

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.

Onartuzumab is administered as an IV infusion. Doses of onartuzumab may be administered over 30 $\pm$ 10 minutes, with at least a 60-minute observation period after the infusion.

Vials are for single use only; vials used for one patient may not be used for any other patient.

The infusion solution must be administered using an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 0.2 micrometer or less).

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.

Guidelines for dose modification and treatment interruption or discontinuation of study treatment are provided in the respective P-trial protocol.

Serious adverse events related to an overdose or incorrect administration of onartuzumab, erlotinib, or bevacizumab should be recorded on the Adverse Event electronic Case Report Form (eCRF).

4.2.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (onartuzumab, erlotinib, and bevacizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the interactive web/voice response system (IWRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to 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 IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3 CONCOMITANT THERAPY

4.3.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from the end of his or her participation in the P-trial to start of his or her participation in the E-trial.

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

Bisphosphonates or denosumab are acceptable for bone metastases if clinically indicated.

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

4.3.1.1 Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy and colony-stimulating factors (CSFs) if clinically indicated. Use of CSFs for subsequent cycles or dose reduction should be considered.

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

4.3.2 Prohibited Therapy

Therapies prohibited in a P-trial remain prohibited when patients continue with their study treatment in the E-trial.

No other experimental or systemic anti-cancer therapy is permitted during study treatment except for localized radiotherapy for pain control.

4.4 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of assessments performed during the study.

4.4.1 Informed Consent Forms and Screening Log

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.

A screening examination ("baseline") should be performed between 42 days and 1 day before the first dose of treatment in this E-trial (for specific timelines, see Appendix 1), which will include the following procedures (unless the procedures have already been conducted during this time period as part of the patient's routine clinical care):

- Eligibility (inclusion and exclusion criteria, as listed in Section 4.1.1 and Section 4.1.2, respectively)
- Minimal patient characteristics will be collected (i.e., date of birth, sex, P-trial protocol, and patient number).
- Blood sampling for serum pregnancy test for women of childbearing potential (WOCP) should be obtained within 7 days of the E-trial treatment.

The following procedures **are recommended** and will usually be part of the patient's routine care:

- Complete physical examination and measurement of vital signs (including blood pressure)
- Assessment of laboratory parameters
- Tumor assessment (see Section 4.4.5)

Serious adverse events: After informed consent signature but prior to the first dose of study therapy in the E-trial (onartuzumab and/or, if applicable, other P-trial IMP), serious adverse events, *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, should be reported.

Patients who meet all of the inclusion and exclusion criteria will be enrolled in the E-trial.

The investigator's assessment of each screened patient with regard to the E-trial's inclusion and exclusion criteria is to be documented in the patient's medical record.

4.4.2 Medical History and Demographic Data

Medical history and demographic data will be taken from a patient's respective P-trial.

4.4.3 Physical Examinations

Physical examinations will be performed as per the institutions standard of care.

4.4.4 Vital Signs

Vital signs will be measured as per the institutions standard of care.

4.4.5 Tumor and Response Evaluations

The baseline for the tumor evaluation (i.e., determination of progressive disease) is as per the P-trial.

Tumor assessments in this E-trial will be performed according to local standards. It is **recommended** to continue using the same imaging technique (computed tomography (CT) scans, X-rays, or magnetic resonance imaging [MRIs]) and the same tumor evaluation criteria (e.g., RECIST v1.0 or V1.1) as in the P-trial throughout this E-trial. Whenever possible, the same investigator or radiologist should make measurements for all assessments for each patient as per the P-trial.

- Patients known to have bone metastases at baseline or with signs or symptoms suggestive of bone metastasis should undergo an isotope bone scan (this procedure is not mandatory if an 18-FDG PET scan has already been performed).
- CT/MRI scan of the brain is not mandatory but should be performed as soon as possible if there is a clinical suspicion of CNS metastasis (also see Section 4.4.6).
- If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next prescribed assessment, unless signs of clinical progression are present. If there is suspicion of disease progression based on clinical or laboratory findings before the next prescribed assessment, an earlier assessment should be performed.
- Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Additionally, the pharmacodynamics may be so evident in

some cases that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression will be based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy with appropriate imaging.

4.4.6 Laboratory Samples

Laboratory tests, including those done for safety assessments, should be performed as per local standard of care and as indicated in Appendix 1. In order to determine a patient's eligibility for the E-trial, a serum pregnancy test for WOCP must be performed within 7 days of the E-trial treatment and recorded in the Screening section of the eCRF.

Local laboratories will be used for all laboratory testing.

4.5 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for 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 determines it is in the best interest of the patient

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. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they become pregnant.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.5.3 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 serious adverse events in this study indicates a potential health hazard to patients.
- Inadequate supply of onartuzumab for patient administration.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

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

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Onartuzumab is not planned to be developed towards registration. Thus, the entire safety profile is not known at this time. There is no antidote for the adverse events related to onartuzumab administration. Patients should discontinue onartuzumab if any adverse event, thought to be related or not, compromises the physical condition of the patient. Onartuzumab should not be restarted without agreement from the E-trial's medical monitor.

5.1.1 Peripheral Edema and Generalized Edema (Anasarca)

The most frequently reported adverse events include peripheral edema and anasarca. In Study OAM4558g (2L/3L non–small cell lung cancer [NSCLC]), the incidence of edema (group term) irrespective of severity was 30.4% in the onartuzumab + erlotinib arm compared with 10.5% in the placebo + erlotinib arm. In Study OAM4861g (TNBC), the incidence of edema (group term) was 62.9% in the onartuzumab + bevacizumab + paclitaxel arm, 63.8% in the onartuzumab + placebo + paclitaxel arm, and 21.0% in the placebo + bevacizumab + paclitaxel arm.

The incidence of generalized edema (anasarca) in Study OAM4861g was 3.2% in the onartuzumab + bevacizumab + paclitaxel arm, 5.2% in the onartuzumab + placebo + paclitaxel arm, and 0% in placebo + bevacizumab + paclitaxel arm.

There is no specific treatment guidance for edema. Investigators have administered antidiuretics, albumin and/or mechanical pressure with bandaging of the affected limb with limited success.

5.1.2 Gastrointestinal Perforation

A program-wide review of all ongoing and completed trials revealed a disproportionate incidence of GI perforation (by SMQ) in patients who received onartuzumab compared

with those who received the respective control treatment. Seventeen events were reported in 1013 patients (1.6%) receiving onartuzumab-containing regimens, with 5 events reported in 891 patients (0.5%) receiving control regimens. The imbalance was also observed when the analysis was limited only to reports of actual GI perforation events: 12 events (1.1%) in patients receiving onartuzumab-containing regimens and 2 events (0.2%) in patients receiving control regimens.

Patients may be at increased risk for the development of GI perforation when treated with onartuzumab. In patients who develop GI perforation, treatment with onartuzumab must be permanently discontinued.

5.1.3 Venous Thromboembolic Events

An analysis of all Phase II clinical trials revealed a disproportionate incidence of VTEs in patients who received onartuzumab compared with those who received the control treatment. A total of 79 VTEs of any grade were reported in 529 patients (14.9%) receiving onartuzumab-containing regimens, whereas 38 VTEs of any grade were observed in 454 patients (8.4%) receiving control regimens.

The analysis of serious events took into consideration a variety of potential interacting factors (central venous access devices [CVADs], edema, history of VTE, risk factors for VTE, and anatomical site of thrombus). No imbalance of numbers was noted between onartuzumab and control arms that may suggest any one factor contributing to the increased risk observed with onartuzumab. However, limitations of this analysis were the inclusion of only serious events, no weighting of risk factors for thrombosis, no inclusion of CVAD presence on case report forms, and the lack of risk factor data on patients without VTE.

It is the Sponsor's view, based on the currently available data from all trials, that patients may be at increased risk for the development of VTE when treated with onartuzumab. Patients and physicians are advised to be observant for the signs and symptoms of VTE and to instruct patients to seek medical care if they develop symptoms, such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis should be considered based on a careful assessment of an individual patient's underlying risk factors. Any thromboprophylaxis should follow current local institutional guidelines and best practice.

5.1.4 Hypoalbuminemia

In Study OAM4861g (TNBC), the incidence of low albumin laboratory value was 75.8% in the onartuzumab + bevacizumab + paclitaxel arm, 87.9% in the onartuzumab + placebo + paclitaxel arm, and 26.2% in the placebo + bevacizumab + paclitaxel arm.

There was no increase in proteinuria reported in Study OAM4861g; the incidence was 3.2% in the onartuzumab + bevacizumab + paclitaxel arm, 3.4% in the onartuzumab + placebo + paclitaxel arm, and 11.3% in the placebo + bevacizumab + paclitaxel arm.

There are no specific management guidelines for the event of hypoalbuminemia that the Sponsor can recommend. Any treatment should follow current local institutional guidelines and best practice.

5.1.5 Arterial Thromboembolic Events

An imbalance in the incidence of ATEs was noted with 11 of 877 patients (1.3%) in onartuzumab-containing arms and 2 of 794 patients (0.3%) in control arms experiencing such an event (as of 13 June 2014). All the events were reported as serious. One fatal event each was reported in the onartuzumab-containing and control arms. The most frequent event was acute myocardial infarction/myocardial infarction (8 patients [0.9%]) in the onartuzumab-containing arms and 1 patient [0.1%] in the control arms).

It is the Sponsor's view, based on the currently available data from all trials, that patients may be at increased risk for the development of ATE when treated with onartuzumab. Patients and physicians are advised to be observant for the signs and symptoms of ATE and to instruct patients to seek medical care if they develop symptoms, such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis should be considered based on a careful assessment of an individual patient's underlying risk factors. Any thromboprophylaxis should follow current local institutional guidelines and best practice.

5.1.6 Neutropenia

Neutropenia was reported as an adverse event in studies where onartuzumab was evaluated in combination with infusional chemotherapy or infusional chemotherapy in combination with bevacizumab. In several of these studies, adverse event rates of neutropenia were higher in the onartuzumab-containing arms than the placebo-containing control arms. In studies with an infusional chemotherapy backbone, neutropenia adverse events (of any grade) in onartuzumab-containing arms were reported at a rate up to 63.3% (Study YO28252; onartuzumab + mFOLFOX6 [n = 60] vs. 50% for placebo + mFOLFOX6 [n = 60]) and as low as 17.2% (Study OAM4861g; onartuzumab + placebo + paclitaxel [n = 58] vs. 16.1% for placebo + bevacizumab + paclitaxel [n = 62]). Grade $\geq$ 3 neutropenia adverse events in onartuzumab-containing arms were reported at a rate up to 58.3% (Study YO28252; onartuzumab + mFOLFOX6 [n = 60] vs. 45% for placebo + mFOLFOX6 [n = 60]) and as low as 12.1% (Study GO27821; onartuzumab + pemetrexed + platinum [n = 58] vs. 17.5% for placebo + pemetrexed + platinum [n = 57]).

There has been no observed imbalance in severe infection events between control and onartuzumab arms. Patients receiving onartuzumab in combination with infusional chemotherapy (with or without concomitant bevacizumab) may be at risk of developing neutropenia. Patients should be monitored closely for this, and dosing of concomitant infusional chemotherapies should be modified or interrupted according to study protocol.

Any treatment for neutropenia should follow current local institutional guidelines and best practice.

5.1.7 Adverse Events Related to Control Treatment

Any adverse events known to be related to the control treatment *(bevacizumab and/or erlotinib),* whether given alone or in conjunction with onartuzumab, should be managed as per local standard of care.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring serious adverse events, performing protocol-specified safety laboratory assessments, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the patient on study.

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

Only adverse events that fall into the category below should be reported to the Sponsor.

- Serious adverse events, *whether* related *or unrelated* to onartuzumab, Avastin (bevacizumab), or Tarceva (erlotinib)

5.2.1 Adverse Events

According to the ICH guideline for GCP, 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) other than the cancer for which the patient is receiving treatment on the P-trial and E-trial
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) 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:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is 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 5.3.5.4)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a 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 (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [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, *whether related or unrelated,* are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning 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 serious 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 serious 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 serious adverse events at each patient contact.

After informed consent has been obtained, all serious adverse events *will be recorded during the study and for up to 30 days after* the last dose of *study treatment. After this period*, the investigator should report any serious adverse events that are *believed* to be related to prior *study drug* treatment (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 adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in 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,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[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 oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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 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 (see also Table 2):

- 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 (as 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

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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 *all* serious adverse events, *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, 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 Adverse Events That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be considered as an independent event. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be considered the adverse event.
- If vomiting results in severe dehydration, both events should be considered separately.
- If a severe GI hemorrhage leads to renal failure, both events should be considered separately.
- If dizziness leads to a fall and consequent fracture, all three events should be considered separately.

- If neutropenia is accompanied by an infection, both events should be considered separately.

Only serious adverse events related to onartuzumab, bevacizumab, or erlotinib will be reported for this E-trial.

5.3.5.2 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions).

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs.

5.3.5.3 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of solid tumors 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. 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. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

5.3.5.4 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) 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.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- 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 experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event:

- Serious adverse events, *whether* related *or unrelated* to onartuzumab
- Serious adverse events, *whether* related *or unrelated* to Avastin (bevacizumab)
- Serious adverse events, *whether* related *or unrelated* to Tarceva (erlotinib)
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware 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 Institutional Review Board (IRB)/ethics committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D.
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D., Ph.D.
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

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, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events

5.4.2.1 Events That Are Ongoing from the Previous Protocol

Events that are ongoing from the P-trial should not be reported again under this protocol, unless the severity increases, *whether* the event is related *or unrelated* to onartuzumab, *erlotinib, or bevacizumab*.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events, *whether* related *or unrelated* to onartuzumab, bevacizumab, or erlotinib, will be reported until 30 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) 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, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

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 6 months after the last dose of onartuzumab. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 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. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 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 180 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 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 abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning 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 exposed to study drug or the 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 immediately (i.e., no more than 24 hours after learning 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, *whether* related *or unrelated* to onartuzumab, erlotinib, or bevacizumab, 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.

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 ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the Onartuzumab, Erlotinib, and Bevacizumab Investigator's Brochures.

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.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include but are not limited to the following:

- Events related to infusional chemotherapy, such as alopecia and myelosuppression

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

No formal statistical hypothesis testing is planned for this study.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size of this E-trial will depend upon the number of patients eligible from P-trials who elect to transfer to this trial for continued treatment of their underlying cancer.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment of patients and discontinuation from the study will be summarized.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

No formal comparisons of treatment groups are planned.

6.4 EFFICACY ANALYSES

No formal efficacy analyses are planned.

6.5 SAFETY ANALYSES

The safety analyses will include only patients who received at least one dose of onartuzumab. A summary of administration of study treatment (onartuzumab) and serious adverse events, *whether* related *or unrelated* to onartuzumab, will be generated for these patients.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) 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, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used 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 stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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 (PROs), 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 study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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, electric PRO data (if applicable), 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 the Sponsor. Written notification should be provided to the Sponsor 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 GCP 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. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor'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 the Sponsor for health authority submission purposes according to local requirements.

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 the Sponsor 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.

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 9.6).

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 the Sponsor. 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

The Sponsor 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 Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only 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 FDA and other national and local health authorities, Sponsor 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., LPLV).

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, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor or designee and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits may be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will

permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffmann-La Roche Ltd. Up to 14 study centers will participate in this study in Europe, Africa, and Asia, enrolling a total of up to 17 patients. The Sponsor will provide clinical operations oversight, data management support, and medical monitoring. An IWRS will be used to manage site drug supply. The analysis of any laboratory samples (taken for safety assessments as per Appendix 1) will be performed by the local laboratories.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

ww.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within six months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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.

In accordance with standard editorial and ethical practice, the Sponsor 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 Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor 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 the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) 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).

10. REFERENCES

Bean J, Brennan C, Shih JY, et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci U S A 2007;104:20932–7.

Bottaro DP, Rubin JS, Faletto DL, et al. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. Science 1991;251:802−4

Cappuzzo F, Jänne PA, Skokan M, et al. MET increased gene copy number and primary resistance to gefitinib therapy in non-small-cell lung cancer patients. Ann Oncol 2009;20:298–304

Colson JH, Armour WJ. Sports injuries and their treatment. 2nd rev. ed. London: Penguin, 1986.

Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43

Fukuda T, Ichimura E, Shinozaki T, et al. Coexpression of HGF and c-Met/HGF receptor in human bone and soft tissue tumors. Pathol Int 1998;48:757–62

Gherardi E, Stoker M. Hepatocytes and scatter factor. Nature 1990;346:228

Graveel C, Su Y, Koeman J, et al. Activating Met mutations produce unique tumor profiles in mice with selective duplication of the mutant allele. Proc Natl Acad Sci U S A 2004;101:17198–203

Ichimura E, Maeshima A, Nakajima T, et al. Expression of c-met/HGF receptor in human non-small cell lung carcinomas in vitro and in vivo and its prognostic significance. Jpn J Cancer Res 1996;87:1063−9

Jeffers M, Schmidt L, Nakaigawa N, et al. Activating mutations for the met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci U S A 1997;94:11445–50

Jeffers M, Fiscella M, Webb CP, et al. The mutationally activated Met receptor mediates motility and metastasis. Proc Natl Acad Sci U S A 1998;95:14417-22

Jin H, Yang R, Zheng Z, et al. MetMAb, the one-armed 5D5 anti-c-Met antibody, inhibits orthotopic pancreatic tumor growth and improves survival. Cancer Res 2008;68:4360–8

Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res 2006;66:283–9

Koochekpour S, Jeffers M, Rulong S, et al. Met and hepatocyte growth factor/scatter factor expression in human gliomas. Cancer Res 1997;57:5391–8

Kuniyasu H, Yasui W, Kitadai Y, et al. Frequent amplification of the c-met gene in scirrhous type stomach cancer. Biochem Biophys Res Commun 1992;189:227–32

Lorenzato A, Olivero M, Patanè S, et al. Novel somatic mutations of the MET oncogene in human carcinoma metastases activating cell motility and invasion. Cancer Res 2002;62:7025–30

Ma PC, Maulik G, Christensen J, et al. c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev 2003;22:309–25

Ma PC, Jagadeeswaran R, Jagadeesh S, et al. Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in non-small cell lung cancer. Cancer Res 2005;65:1479–88

Masuya D, Huang C, Liu D, et al. The tumour-stromal interaction between intratumoral c-Met and stromal hepatocyte growth factor associated with tumour growth and prognosis in non-small-cell lung cancer patients. Br J Cancer 2004;90:1555–62

Martens T, Schmidt NO, Eckerich C, et al. A novel one-armed anti-c-Met antibody inhibits glioblastoma growth in vivo. Clin Cancer Res 2006;12:6144–52

Michieli P, Basilico C, Pennacchietti S. Mutant Met-mediated transformation is ligand-dependent and can be inhibited by HGF antagonists. Oncogene 1999;18:5221–31

Miyazawa K, Tsubouchi H, Naka D, et al. Molecular cloning and sequence analysis of cDNA for human hepatocyte growth factor. Biochem Biophys Res Commun 1989;163:967–73

Moriyama T, Kataoka H, Koono M, et al. Expression of hepatocyte growth factor/scatter factor and its receptor c-Met in brain tumors: evidence for a role in progression of astrocytic tumors (review). Int J Mol Med 1999;3 531–6

Nakamura T, Nishizawa T, Hagiya M, et al. Molecular cloning and expression of human hepatocyte growth factor. Nature 1989;342:440–3

Olivero M, Valente G, Bardelli A, et al. Novel mutation in the ATP-binding site of the MET oncogene tyrosine kinase in a HPRCC family. Int J Cancer 1999;82:640-3

Prat M, Crepaldi T, Pennacchietti S. Agonistic monoclonal antibodies against the Met receptor dissect the biological responses to HGF. Cell 1998;111(Pt 2):237–47

Seruca R, Suijkerbuijk RF, Gärtner F, et al. Increasing levels of MYC and MET co-amplification during tumor progression of a case of gastric cancer. Cancer Genet Cytogenet 1995;82:140–5

Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet 1997;16:68–73

Schmidt L, Junker K, Weirich G, et al. Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET protooncogene. Cancer Res 1998;58:1719–22

Shak S, Capon DJ, Hellmiss R, et al. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 1990;87:9188–92.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187–205

Stoker M, Gherardi E, Perryman M, et al. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature 1987;327:239−42

Toschi L, Cappuzzo F. Clinical implications of MET gene copy number in lung cancer. Future Oncol 2010;6:239–47

Weidner KM, Arakaki N, Hartmann G, et al. Evidence for the identity of human scatter factor and human hepatocyte growth factor. Proc Natl Acad Sci U S A 1991;88:7001−5

Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, editors. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–79.

Zarnegar R, Michalopoulos G. Purification and biological characterization of human hepatopoietin A, a polypeptide growth factor for hepatocytes. Cancer Res 1989;49:3314−20

Zhao D, Wang SH, Feng Y, et al. Intratumoral c-Met expression is associated with vascular endothelial growth factor C expression, lymphangiogenesis, and lymph node metastasis in oral squamous cell carcinoma: implicationsfor use as a prognostic marker. Hum Pathol 2011 Apr 28. [Epub ahead of print; doi:10.1016/j.humpath.2010.03.012]

Appendix 1
Schedule of Assessments

	Screening (Rollover from P-trial into E-Trial; Day –42 to Day 1)	Treatment Period Per Patient Visit	Treatment Period Per 6 Patient Visits or 90–120 days (± 10 days)	Safety FU 30 (± 3 days) after Last Dose of Study Therapy
Informed Consent	x			
Confirmation of eligibility	x			
Patient characteristics (Sex, date of birth, tumor type)	x			
Serum pregnancy test for WOCP[a]	x			
Urine pregnancy test for WOCP		x[f]		
Weight	x			
Onartuzumab Other P-trial anti-cancer IMP(s) if applicable[b]		x		
Hematology and chemistry laboratory testing[e]	x		x[c]	
Progression assessment		Per local standard[d]		
SAE	x (see Section 5.1)	x		x

Note: Additional assessments (as per local standard and clinical judgment of the investigator) will only be documented in the patients' source documents.

FU = follow-up; IMP = investigational medicinal product; SAE = serious adverse event; WOCP = women of childbearing potential.

[a] Pregnancy test: WOCP will have a serum pregnancy test no more than 7 days prior to the first trial treatment.

[b] Classified as non-IMP in the E-trial; see also Section 4.2.1.

[c] Hematology and chemistry laboratory testing at screening visit and then every six visits or 90–120 days (± 10 days) of treatment to include:

- Hematology: including hemoglobin, hematocrit, platelets count, WBC count, WBC differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells). WBC differential count in absolute value is preferred, however percentages are also acceptable.
- Chemistry: including sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus, and magnesium.

[d] The same methods as per P-trial are recommended.

[e] The chemistry and hematology laboratory tests are not collected on the eCRF.

f Urine pregnancy test to be performed before each patient visit. If the urine pregnancy test is positive, study drug will not be administered and a serum pregnancy test must be performed.