CLINICAL STUDY PROTOCOL

NCT No.:	NCT02979977
Protocol No.:	1608018260
Investigational Product:	Afatinib

Title: Single-Arm Phase II trial of Dual Inhibition of EGFR with Afatinib and Cetuximab with Correlative Studies in the Treatment of Advanced Squamous Cell Cancers of the Head and Neck.

Clinical Phase: II

Principal Investigator: Aarti Bhatia, MD, MPH

Sponsor: Yale Cancer Center

Funding Source: Funding provided by the National Comprehensive Cancer Network (NCCN) through a grant provided by Boehringer Ingelheim Pharmaceuticals, Inc.

Version and Date of Protocol: Version 7.0 dated 13 December 2022

APPROVED BY THE YALE UNIVERSITY IRB 2/24/2023

INVESTIGATOR SIGNATURE PAGE

Study Title: Single-Arm Phase II trial of Dual Inhibition of EGFR with Afatinib and Cetuximab with Correlative Studies in the Treatment of Advanced Squamous Cell Cancers of the Head and Neck

Protocol No.: 1608018260

I herewith certify that I agree to adhere to the study protocol

and to all documents referenced in the study protocol.

_____ _____

Signature **Date**

APPROVED BY THE YALE UNIVERSITY IRB 2/24/2023

SPONSOR SIGNATURE PAGE

Study Title: Single-Arm Phase II trial of Dual Inhibition of EGFR with Afatinib and Cetuximab with Correlative Studies in the Treatment of Advanced Squamous Cell Cancers of the Head and Neck

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Protocol date:	**Protocol number:**
13 December 2022	1608018260

Title of study: Single-Arm Phase II trial of Dual Inhibition of EGFR with Afatinib and Cetuximab with Correlative Studies in the Treatment of Advanced Squamous Cell Cancers of the Head and Neck

Principal Investigator: Aarti Bhatia, MD, MPH

Sponsor: Yale Cancer Center

Clinical Phase: II

Objectives:

1. To determine the response of recurrent or metastatic squamous cell carcinoma of the head and neck region to treatment with a combination of afatinib and cetuximab.
2. To determine impact on long-term outcome, safety and tolerability of the combination and laboratory correlates for more effective inhibition of Epidermal Growth Factor Receptor (EGFR) signaling with the combination of Cetuximab and Afatinib.

Methodology:

This study will be a single center, single-arm, open-label Phase II trial. Patients with advanced squamous cell carcinoma of the head and neck, who are previously treated with a platinum based regimen or with immune checkpoint inhibitor therapy or both, will be eligible for participation on the study. After a baseline evaluation and biopsy (where feasible), they will be treated with weekly/bi-weekly IV cetuximab and daily oral afatinib. Biopsy will be repeated where feasible after 4 weeks (window of +1 week) on therapy and again at disease progression or end of treatment. Treatment will continue until disease progression or development of grade 3 or higher drug related toxicities that fail to resolve to Grade 2 despite appropriate supportive care.

No. of Patients:

Total entered: 50

Each Treatment: 50

Indication:

Advanced squamous cell carcinoma of the head and neck region, having previously been treated with a platinum-based regimen or with immune checkpoint inhibitor therapy or both.

Main Criteria for Inclusion:

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1. Histologically confirmed squamous cell carcinoma of the head and neck that is metastatic, recurrent or locally advanced and not treatable with curative intent.
2. Previous treatment with platinum-based regimen or immune checkpoint inhibitor therapy or both in the R/M (Recurrent/Metastatic) setting. 2-week washout period prior to treatment start will be required.
3. Patients who have experienced progression of disease within 6 months following completion of a platinum-based chemoradiation in the definitive or adjuvant setting will be permitted.
4. Prior cetuximab permitted if it was given as part of multi-modality therapy for initial treatment of locally advanced disease but not for recurrent/metastatic disease.
5. Measurable disease based on RECIST v 1.1.
6. Age ≥18 years
7. ECOG performance status ≤2
8. Adequate organ function, defined as all of the following:
   - Hemoglobin ≥ 8 g/dl.
   - Absolute neutrophil count (ANC) ≥1000 / mm^3.
   - Platelet count ≥75,000 / mm^3.
   - Estimated creatinine clearance > 45ml / min.
   - Total Bilirubin ≤ 1.5 times upper limit of (institutional/central) normal *(Patients with Gilbert's syndrome total bilirubin must be ≤4 times institutional upper limit of normal).*
   - Aspartate amino transferase (AST) or alanine amino transferase (ALT) ≤ three times the upper limit of (institutional/central) normal (ULN) (if related to liver metastases ≤ five times ULN).
9. Ability to understand and the willingness to sign a written informed consent that is consistent with ICH-GCP guidelines.
10. Negative urine or serum pregnancy test for women of childbearing potential.
11. A second eligibility review will always be provided by a Head and Neck Research Team associated for the New Haven Campus and a third review will be provided by the PI.

Main Criteria for Exclusion:

1. Prior erlotinib, gefitinib or lapatinib therapy or prior exposure to any investigational EGFR or panErbB reversible or irreversible inhibitor or any prior panitumumab or investigational EGFR-directed monoclonal antibody. Cetuximab is permitted if used for locally advanced disease, as long as no disease progression within 6 months. Cetuximab use is not permitted for recurrent/metastatic disease.
2. Radiotherapy within 2 weeks prior to enrolment. Palliative radiation to target organs may be allowed up to 2 weeks prior to enrolment, as long as there are other target lesions that can be monitored for response to study treatment.
3. Known hypersensitivity to afatinib or its excipients.

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4. Women of child-bearing potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use highly effective methods of birth control prior to study entry, for the duration of study participation and for at least 4 weeks after treatment has ended.
5. Pregnant or nursing women.
6. Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safetyof the test drug.
7. Concomitant malignancies at other sites that are being actively treated with systemic therapy.
8. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2.1 that cannot be stopped for the duration of trial participation.
9. Clinically significant interstitial lung disease.
10. Known history of untreated viral hepatitis or HIV.
11. Patients with parenchymal brain metastases are not eligible, unless they have completed local therapy.
12. Leptomeningeal carcinomatosis.

Test Product(s):

Dose: Afatinib dose 30 mg per day

Mode of admin: oral

Duration of Treatment: Until disease progression, development of ≥ grade 3 drug related toxicities that fail to resolve to Grade 2 despite appropriate supportive care, clinically significant deterioration of the patient's condition, patient noncompliance, investigator determination that it is no longer in the patient's best interest to continue, pregnancy, or withdrawal of consent.

Criteria for Efficacy: Clinical efficacy of the combination treatment will be determined through assessment of response to treatment (tumor shrinkage) based on RECIST v 1.1., duration of response, progression-free survival and overall survival.

Criteria for Safety: Safety of the combination will be assessed through collection of adverse event (AE) and serious adverse event (SAE) data and monitoring of laboratory tests. To ensure patient safety, we have pre-specified stopping rules based on grade of toxicities in the protocol.

Statistical Methods: All statistical analyses will be performed using the SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

We plan to enroll 50 patients which provide us 80% power to detect an alternative hypothetical ORR of 24% by rejecting a null hypothesis of 10%. This sample size will achieve 80% power to detect an absolute difference of 18% if the historical control of ORR is 15% (i.e. 33% vs. 15%).

The primary analysis will use a 2-sided binomial test to compare the ORR with historical control of 10%. 95% confidence interval of ORR will be reported as well. As an exploratory analysis, Logistic

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regression will be used to identify potential risk factors that are associated with ORR.

The secondary endpoint is progression-free survival and overall survival with 1 year follow-up. We will use Kaplan-Meier survival analysis to estimate the median PFS and OS in the cohort. Additional Cox regression analyses will be carried out to examine the association between demographical or clinical variables and survival outcome.

Study Duration: 2 years

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FLOW CHART

	Screening[a]	Treatment Period			Every 8 weeks after cycle 2[d]	Discontinuation		Post-Treatment		
		Cycle 1 (Weekly/Bi-weekly)	Cycle 2 (Weekly/Bi-weekly)	Cycle 3 and beyond (Weekly/Bi-weekly)		End of Treatment (EOT)	End of Residual Effect Period (EOR)[g]	Additional Follow-Up[h]	End of Follow-Up[i]	Overall Survival Follow-Up[j]
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics and Medical History	X									
Prior and Concomitant Medication Review	X	X	X	X		X	X	X	X	
Physical Exam	X	X	X	X		X	X	X	X	
Height/Weight/Vitals[l]	X	X	X	X		X	X	X	X	
ECOG Performance Status	X	X	X	X		X	X	X	X	
CBC with differential[n]	X	X	X	X		X	X			
CMP, Magnesium[n]	X	X	X	X		X	X			
AE assessment		X	X	X		X	X	X	X	
EKG	X									
CT/MRI of involved disease sites	X		X[d]		X					

P16 Status (IHC staining)	X									
PT/PTT/INR[c]	X	X	X	X		X	X			
Pregnancy test (Urine or Serum β-HCG)[m]	X	X	X	X		X	X			
Afatinib Administration[k]		X	X	X						
IV Cetuximab Administration[k]		X	X	X						
Tumor Measurements	X		X		X					
Medically Feasible : Correlative Tumor Biopsies	X[b]	X[b]				X[e]				
Survival Status										X

a: Screening history, concomitant medications, physical exam, height, weight, vitals, performance status and laboratory evaluations (including pregnancy test) should be obtained within 2 weeks prior to treatment initiation. Screening EKG and CT scans or MRI should be obtained within 28 days prior to treatment initiation.
b: Tumor sample for correlative analyses can be archival or fresh, should be since the last systemic treatment administered and should be obtained where feasible. Repeat tumor biopsy to be obtained at end of cycle 1 (4 weeks after treatment initiation, with a window of +1 week), where medically feasible
c: Coagulation studies recommended every 4 weeks (+/- 3 days) only for patients on anticoagulation therapy (excluding a daily baby aspirin).
d: Restaging scans for tumor assessment as appropriate for site of disease to be obtained at end of cycle 2 (8 weeks +/- 3 days), and then every 8 weeks thereafter (+/- 3 days) through the EOR visit, or EoFU visit for patients who discontinued treatment for reasons other than disease progression
e: Repeat tumor biopsy for correlative analyses to be obtained where medically feasible at disease progression or EOT.
f: EOT visit within 7 days of discontinuation from study treatment period.
g: EOR visit at 30 days (window of + 2 weeks) after discontinuation from study treatment period.
h: Additional f/u visits for disease progression to continue every 4 weeks (with a window of +7 days) for a maximum of 24 weeks for patients who discontinued study treatment for reasons other than disease progression.
i: Last visit for disease progression assessment. Follow-up period will continue until progression, start of new anti-cancer therapy, or a max of 24 weeks, whichever comes first. The EoFU visit will be performed within 2 weeks of known progression, start of new anti-cancer therapy, or completion of predefined follow-up progression period.
j: Monthly (+/- 1 week) telephone f/u for survival (to continue until death).

k: Cetuximab will be administered beginning on cycle 1 day 1, and then subsequently weekly (+/- 1 day) or bi-weekly (+/- 2 days) at the discretion of the treating physician. Alternating Cetuximab dosing schedules from a weekly to bi-weekly dosing schedule, and vice versa, between and within cycles of treatment is permitted per protocol following Sponsor PI discussion and approval. Daily oral afatinib dosing will start the same day as the initial cetuximab administration. For patients who are on afatinib alone due to cetuximab being discontinued for a serious infusion reaction or for any other reason, they will be scheduled for follow-up on days 1 and 15 (+/- 3 days) of the first two 28-day cycles. The following assessments will be performed during these visits: adverse event assessment, concomitant medications, physical exam, weight, vital signs and ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium). Pregnancy test for reproductive age women and coagulation studies if on anticoagulant therapy will be performed every 4 weeks throughout the treatment period. After the first 2 cycles, visits can be scheduled on day 1 of every 28-day cycle (+/- 3 days) per physician discretion.
l: Height to be collected at screening only
m: Pregnancy test for women of child bearing potential to be conducted every 4 weeks (+/- 3 days) while on treatment.
n: CBC with differential, CMP and magnesium performed weekly (+/- 1 day) or bi-weekly (+/- 2 days) while on treatment, prior to cetuximab dosing. Clinic visits weekly (+/- 1 day) or bi-weekly (+/- 2 days) depending on cetuximab dosing.

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ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
CMP	Comprehensive Metabolic Panel
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DP	Disease Progression
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EoFU	End of Follow-Up
EOR	End of Residual Effect Period
EOT	End of Treatment
GCP	Good Clinical Practice
HER	Human Epidermal Growth Factor Receptor
HR	Hazard Ratio
IB	Investigator's Brochure
ILD	Intersitital Lung Disease
MRI	Magnetic Resonance imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PC	Patient Completion
PCNA	Proliferating Cell Nuclear Antigen
pEGFR	Phosphorylated Epidermal Growth Factor Receptor
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-Kinase
PK	Pharmacokinetics
PTEN	Phosphatase and Tensin homolog
REP	Residual Effect Period
SAE	Serious Adverse Event
SCCHN	Squamous Cell Cancers of the Head and Neck region
SUSAR	Suspected Unexpected Serious Adverse Reactions
TKI	Tyrosine-Kinase Inhibitor
WOCBP	Women of child-bearing potential
YCC	Yale Cancer Center
YCCI	Yale Center for Clinical Investigation

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Approximately 62,000 patients will be newly diagnosed with squamous cell cancers of the head and neck region (SCCHN) in the United States in 2016 [1]. Majority of the patients present with advanced disease and despite recent advances, the cure rate is only about 50%. Due to the effects of field cancerization, development of recurrences and second primary tumors is a frequent occurrence [2]. Retreatment with locally directed therapies is fraught with difficulties and limitations. Many patients therefore, eventually need systemic therapy for symptom palliation and disease control to increase longevity [3].

Until recently, chemotherapy regimens using platinum were a standard systemic therapy option for these patients. Now we know that the majority of SCCHN tumors overexpress the epidermal growth factor receptor (EGFR/ErbB1) and this correlates with poorer clinical outcomes [4]. The addition of the monoclonal antibody Cetuximab to standard chemotherapy has improved response rates, progression-free survival and overall survival in patients with advanced SCCHN [3]. The combination with chemotherapy however, has significant toxicities. Single agent Cetuximab is well tolerated but is only seen to have modest responses (10-15%), which aren't durable [5]. Predictive biomarkers for efficacy are also not elicited.

Recently, comprehensive genomic analysis of SCCHN tumor specimens has found the human epidermal growth factor receptor 2 (HER2/ErbB2) also to be amplified in a subset of patients [6]. Afatinib is an irreversible, oral pan-ErbB family tyrosine kinase inhibitor, seen to have potent preclinical activity against both wild-type and mutant EGFR and HER2 and clinical trials using Afatinib in the recurrent or metastatic setting have also shown encouraging results within the past year [7].

A multicenter randomized Phase III study assessed the efficacy of afatinib compared with methotrexate as second-line treatment in 483 patients with recurrent or metastatic SCCHN progressing on or after platinum-based therapy [8]. After a median follow-up of 6·7 months, progression-free survival was longer in the afatinib group than in the methotrexate group (median 2·6 months for the afatinib group vs 1·7 months for the methotrexate group; hazard ratio [HR] 0·80 [95% CI 0·65-0·98], p=0·030) and the drug had a manageable toxicity profile.

A multicenter randomized Phase II trial compared Afatinib to Cetuximab in the recurrent or metastatic setting [9]. Crossover was permitted on disease progression to the other treatment arm. Afatinib showed antitumor activity comparable to cetuximab in this exploratory phase II trial. Sequential EGFR/ErbB treatment with afatinib and cetuximab provided sustained clinical benefit in patients after crossover, suggesting a lack of cross-resistance.

Our own group presented data at the American Society of Clinical Oncology's 2016 Annual Meeting from a single-arm Phase II study that combined Erlotinib, another EGFR tyrosine kinase inhibitor and Cetuximab with a chemotherapy backbone for patients with recurrent/metastatic head and neck cancer [10]. We saw very encouraging responses (50% had partial responses and an additional 29% had stable disease with a median progression-free survival of 5.8 months in the intent-to-treat population). Median overall survival was 8.1 months in the intent to treat population and 10.6 months in the per-protocol population. One patient had a pathological complete response (Image 1 attached) and two were consolidated with definitive radiation with no recurrence at 9 and 41 months follow-up.

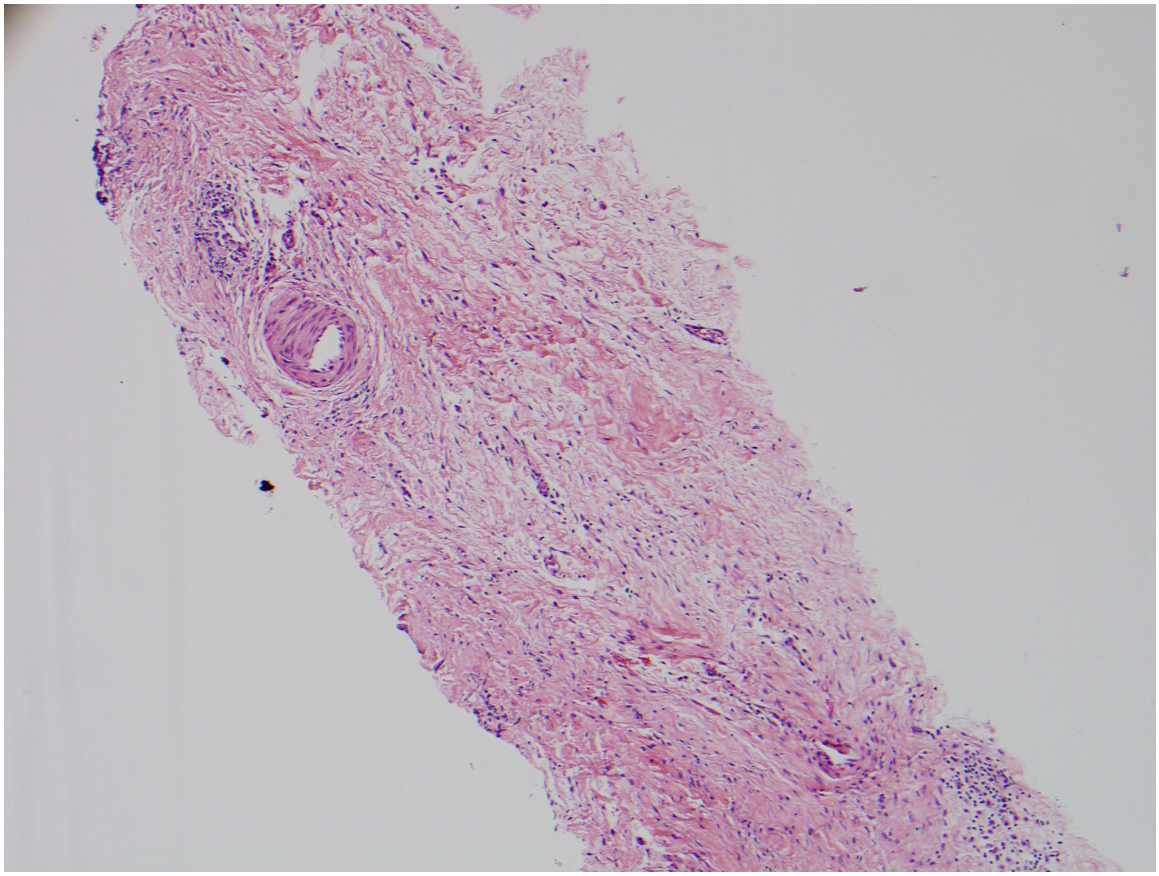

Image 1: Pathological complete response in a node in a patient with metastatic SCCHN treated with combination chemotherapy/cetuximab/erlotinib on trial.

Based on its promising role in squamous cell cancers of the head and neck, several trials have been initiated and are evaluating the use of Afatinib as part of a chemotherapy combination induction regimen, in the adjuvant setting following chemoradiation and also as a radio sensitizing agent for locally advanced disease [11, 12].

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1.2 DRUG PROFILE

1.2.1 Afatinib

For the latest information on the drug profile of afatinib, please refer to the current Investigator's Brochure (IB) and/or local product label information. All references in this protocol concerning afatinib refer to the free base compound, which is used as the oral formulation.

Afatinib is a small molecule, selective and irreversible ErbB family blocker. In preclinical models it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

Afatinib is moderately fast absorbed after oral administration. Maximum plasma concentrations of afatinib were achieved mainly at 2 to 5 hours after oral drug administration. Afatinib maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Afatinib is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Afatinib is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Afatinib is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg afatinib when taken simultaneously with or 6 h after afatinib but increased the bioavailability of afatinib (single dose of 20 mg) by 48% and 39% for $AUC_{0-\infty}$ and C_{max} when given 1 h before afatinib, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg afatinib by 34 % afatinib ($AUC_{0-\infty}$) and 22 % (C_{max}), respectively. Caution should be exercised when combining afatinib with potent P-gp modulators.

In pre-clinical studies afatinib is not irritant to intact skin but an ocular irritant. Afatinib is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested

up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two Phase I open-label dose-escalation studies determined the MTD with continuous dosing of afatinib in patients with advanced solid tumors at 40mg and 50mg daily, respectively [13, 14]. Both daily doses (40mg and 50mg) have been used in Phase II and Phase III trials depending on the patient population evaluated. Adverse events (AE) observed with afatinib are consistent with those reported for EGFR and dual EGFR/HER2 inhibitors. The most common AEs in Afatinib monotherapy trials were associated with gastrointestinal disorders (including diarrhea, and stomatitis), skin and subcutaneous tissue disorders (rash/acne, dry skin, pruritus), nail effects, fatigue and decreased appetite. Early and proactive management of diarrhea, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies [15-19].

Afatinib was approved as monotherapy to treat patients with advanced or metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.

1.2.2 Cetuximab

Cetuximab (Erbitux®) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. Cetuximab is produced in mammalian (murine myeloma) cell culture.

Cetuximab is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Cetuximab is supplied at a concentration of 2 mg/mL in either 100 mg (50 mL) or 200 mg (100 mL), single-use vials. Cetuximab is formulated in a solution with no preservatives, which contains 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.41 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

The epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR, HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Expression of EGFR is also detected in many human cancers including those of the head and neck, colon, and rectum.

Cetuximab binds specifically to the EGFR on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. *In vitro* assays and *in vivo* animal studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Signal transduction through the EGFR results in activation of wild-type *Ras* proteins, but in cells with activating *Ras* somatic mutations, the resulting mutant *Ras* proteins are continuously active regardless of EGFR regulation.

In vitro, cetuximab can mediate antibody-dependent cellular cytotoxicity (ADCC) against certain human tumor types. *In vitro* assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to radiation therapy or irinotecan in human tumor xenograft models in mice resulted in an increase in anti-tumor effects compared to radiation therapy or chemotherapy alone.

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiation therapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner while clearance of cetuximab decreased from 0.08 to 0.02 L/h/m2 as the dose increased from 20 to 200 mg/m2, and at doses >200 mg/m2, it appeared to plateau. The volume of the distribution for cetuximab appeared to be independent of dose and approximated the vascular space of 2–3 L/m2.

Following the recommended dose regimen (400 mg/m2 initial dose; 250 mg/m2 weekly dose), concentrations of cetuximab reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life of cetuximab was approximately 112 hours (range 63–230 hours). The pharmacokinetics of cetuximab were similar in patients with SCCHN and those with colorectal cancer.

Cetuximab had an approximately 22%(90% confidence interval; 6%, 38%) higher systemic exposure relative to the EU-approved cetuximab used based on a population pharmacokinetic analysis.

Cetuximab is approved in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck, in combination with platinum-based therapy with 5-FU for the first-line treatment of patients with recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck or the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The addition of the monoclonal antibody Cetuximab, which targets the epidermal growth factor receptor (EGFR), to chemotherapy, has improved the response rate, progression-free survival and overall survival for patients with recurrent or metastatic squamous cell cancers of the head and neck (SCCHN) [3]. Cetuximab acts by binding to the extracellular portion of the EGFR molecule and competitively inhibiting the binding of its ligand. However, it does not interfere with ligand-independent EGFR signaling [20].

Although clinically active in a subset of patients, most responders eventually acquire resistance to treatment [21]. Several researchers have published data on molecular mechanisms of acquired resistance to Cetuximab, including dysregulation of EGFR internalization/degradation, alternatively localized EGFR from the cell membrane into the cell's nucleus and strong activation of HER2, HER3 and cMET. Nuclear localized EGFR is highly associated with disease progression, worse overall survival, and enhanced resistance to radiation, chemotherapy, and to anti-EGFR therapies. EGFR up-regulation promotes increased dimerization with HER2 and HER3 leading to their transactivation. Blockade of EGFR and HER2 is shown to lead to loss of HER3 and PI(3)K/Akt dependent signaling.

Afatinib is an oral, irreversible pan-ErbB family tyrosine kinase inhibitor with intracellular activity, which makes it an attractive combinatorial partner to Cetuximab to overcome some of the putative resistance mechanisms described above. A recently published randomized Phase II study has shown that it does not demonstrate cross-resistance with Cetuximab [9].

We hypothesize that the combination of Cetuximab and Afatinib will demonstrate superior clinical efficacy than when used singly or sequentially in the management of advanced SCCHN and propose this single-arm Phase II trial. Tissue arrays will be constructed from where medically feasible tumor biopsies obtained pre-treatment, after 4 weeks on treatment with the combination and again at progression or end of treatment in an attempt to develop predictive biomarkers of response and study mechanisms of inherent or acquired resistance. Multiple high quality immunohistochemical assays will be performed and analyzed with automated image analysis (AQUA, Genoptix®) for EGFR, phospho-EGFR, HER-2, phospho-HER-2, HER-3, HER-4, phospho-Akt, PTEN, cyclin D1, p53 and nuclear proliferating cell nuclear antigen (PCNA).

Results from this exploratory trial will inform future studies with this combination or with other novel targeted therapies in the metastatic setting.

2.2 TRIAL OBJECTIVES

PRIMARY OBJECTIVE

To determine the response of advanced squamous cell carcinoma of the head and neck region to treatment with a combination of afatinib and cetuximab. Clinical efficacy of the combination treatment will be determined through assessment of response to treatment (tumor shrinkage) based on RECIST v 1.1., duration of response, progression-free survival and overall survival.

SECONDARY OBJECTIVES

To determine impact on long-term efficacy outcomes, safety and tolerability of the combination and laboratory correlates for more effective inhibition of Epidermal Growth Factor Receptor (EGFR) signaling with the combination of Cetuximab and Afatinib. Efficacy outcomes will be assessed by tumor response based on RECIST v 1.1., duration of response, progression-free survival and overall survival. Safety of the combination will be assessed through collection of adverse event (AE) and serious adverse event (SAE) data and monitoring of laboratory tests.

2.3 BENEFIT – RISK ASSESSMENT

For patients with advanced head and neck cancer who have disease progression on a chemotherapy regimen using a platinum compound, there are few salvage therapies that are currently standard of care. We know that the majority of SCCHN tumors overexpress EGFR. Targeting the receptor helps gain disease control in a subset of these patients. Recently, it has been shown that resistance to the EGFR monoclonal antibody (Cetuximab) does not automatically confer cross-resistance to the small molecule inhibitor (Erlotinib) [9]. It therefore seems logical to test a combination of cetuximab and a potent EGFR small molecule inhibitor like afatinib to see if we can improve on response rates and durability of response seen with either agent alone.

Cetuximab and Afatinib combination regimen at the proposed doses has been previously tested in patients with lung cancer who harbor the EGFR mutation and was shown to be safe and effective [22]. We have also built in adequate monitoring measures (periodic physical examinations and laboratory monitoring, AE and SAE reporting) into our trial design to ensure patient safety.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

Baseline medical history and demographics, prior and concomitant medications, physical exam, weight, height, vital signs, ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium levels, pregnancy test for women of reproductive age and coagulation studies (if on anticoagulant therapy), an EKG, CT or MRI of involved disease sites, human papillomavirus (HPV) status (immunohistochemical staining for p16) and a tumor biopsy (where feasible, after progression on previous line of treatment), will be obtained for all patients after they sign the consent form.

Patients will initiate treatment on the afatinib and cetuximab combination regimen. Pre-medication with decadron 10mg, H1 and H2 blockade (at the discretion of the treating facility and physician) may precede the first dose of Cetuximab in week 1 of cycle 1. Premedication with H1 blockade alone may be used beyond the initial dose for patients who do not experience an infusion reaction with the first dose. Oral Afatinib at 30mg daily will start the same day as the Cetuximab. Subsequently, Cetuximab will be dosed at 250mg/m2 body surface area, given intravenously weekly (+/- 1 day) or at 500 mg/m2 body surface area, given intravenously bi-weekly (+/- 2 days), at the discretion of the treating physician. Each treatment cycle will be 28 days (+/- 3 days) in length.

Alternating Cetuximab dosing schedules from a weekly to bi-weekly dosing schedule, and vice versa, between and within cycles of treatment is permitted per protocol following Sponsor PI discussion and approval.

While on study treatment, patients will be seen weekly (+/- 1 day) or bi-weekly (+/- 2 days) depending on the frequency of cetuximab dosing. During these visits, the following evaluations will be done: adverse event assessment, concomitant medications, physical exam, weight, vital signs and ECOG performance status. Laboratory assessments (CBC with differential, CMP, Magnesium) will be performed prior to cetuximab infusion throughout treatment. Pregnancy test for reproductive age women and coagulation studies if on anticoagulant therapy will be performed every 4 weeks throughout treatment. CT or MRI (at physician discretion) will be performed at the end of cycle 2 (+/- 3 days) and every 2 cycles thereafter (+/- 3 days).

Treatment will be discontinued in the event of ≥ grade 3 drug related toxicities that fail to resolve to Grade 2 despite appropriate supportive care or unequivocally progressive disease on clinical exam or surveillance scans. Treatment may also be discontinued for reasons noted in Section 3.3.4, including clinically significant deterioration of the patient's condition, patient noncompliance, investigator determination that it is no longer in the patient's best interest to continue, pregnancy, or withdrawal of consent. Tissue biopsies will be repeated, where

medically feasible, at the end of cycle 1, and at disease progression or end of treatment if discontinued for reasons other than disease progression.

In the situation where patients withdraw consent for treatment on study, we will permit progression and survival data collection unless they specifically withdraw consent for data collection for the trial.

3.2 DISCUSSION OF TRIAL DESIGN

This study will be a single center, single-arm, open-label Phase II trial. The study is expected to enroll 50 patients with advanced squamous cell cancers of the head and neck, who have previously been treated with a platinum-based regimen or with immune checkpoint inhibitor therapy or both. After obtaining consent, patients will undergo a baseline evaluation including tumor assessment (scans performed within 4 weeks of treatment start will be accepted), biopsy (where feasible) and verification of HPV status and then initiate treatment with cetuximab weekly/bi-weekly and oral afatinib daily. Up to a 2-day interval between two 4-week cycles will be permitted. Following the first cycle of treatment, a tumor biopsy will be repeated where medically feasible (for correlative studies), and therapy will be continued. Tumor assessment will be repeated after cycle 2 and every 2 cycles thereafter. Tumor biopsy (for correlative studies) will be repeated again where medically feasible, at disease progression or end of treatment if discontinued for reasons other than disease progression. Results will be compared with historical controls.

3.3 SELECTION OF TRIAL POPULATION

3.3.1 Main diagnosis for study entry

Advanced Squamous Cell Cancers of the Head and Neck Region.

3.3.2 Inclusion criteria

1. Histologically or cytologically confirmed squamous cell carcinoma of the head and neck that is metastatic, recurrent or locally advanced and not treatable with curative intent.

2. Previous treatment with a platinum-based regimen or immune checkpoint inhibitor therapy or both in the R/M (Recurrent/Metastatic) setting. 2-week washout period prior to treatment start will be required.

3. Patients who have experienced progression of disease within 6 months following completion of a platinum-based chemoradiation in the definitive or adjuvant setting will be permitted.

4. Prior cetuximab permitted if it was given as part of multi-modality therapy for initial treatment of locally advanced disease but not for recurrent/metastatic disease.

5. Measurable disease based on RECIST v 1.1. Baseline measurements and evaluations must be obtained within 4 weeks of enrollment. Disease in previously irradiated sites is considered measurable if there has been unequivocal disease progression or biopsy-proven residual carcinoma following radiation therapy.

6. Age ≥18 years

7. ECOG performance status ≤2

8. Adequate organ function, defined as all of the following:
   - Hemoglobin ≥ 8 g/dl.
   - Absolute neutrophil count (ANC) ≥1000 / mm^3.
   - Platelet count ≥75,000 / mm^3.
   - Estimated creatinine clearance > 45ml / min.
   - Total Bilirubin ≤ 1.5 times upper limit of (institutional/central) normal *(Patients with Gilbert's syndrome total bilirubin must be ≤4 times institutional upper limit of normal).*
   - Aspartate amino transferase (AST) or alanine amino transferase (ALT) ≤ three times the upper limit of (institutional/central) normal (ULN) (if related to liver metastases ≤ five times ULN).

9. Ability to understand and the willingness to sign a written informed consent that is consistent with ICH-GCP guidelines.

10. Negative urine or serum pregnancy test for women of childbearing potential

11. A second eligibility review will always be provided by a Head and Neck Research Team associated for the New Haven Campus and a third review will be provided by the PI.

3.3.3 Exclusion criteria

1. Prior erlotinib, gefitinib or lapatinib therapy or prior exposure to any investigational EGFR or panErbB reversible or irreversible inhibitor or any prior panitumumab or investigational EGFR-directed monoclonal antibody. Cetuximab is permitted if used for locally advanced disease, as long as no disease progression within 6 months. Cetuximab use is not permitted for recurrent/metastatic disease.

2. Radiotherapy within 2 weeks prior to enrollment. Palliative radiation to target organs may be allowed up to 2 weeks prior to enrolment, as long as there are other target lesions that can be monitored for response to study treatment.

3. Known hypersensitivity to afatinib or its excipients

4. Women of child-bearing potential (WOCBP) and men who are able to father a child, unwilling to be abstinent or use highly effective methods of birth control prior to study entry, for the duration of study participation and for at least 4 weeks after treatment has ended.

5. Pregnant or nursing women.

6. Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug.

7. Concomitant malignancies at other sites that are being actively treated with systemic therapy

8. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.2.1 that cannot be stopped for the duration of trial participation.

9. Clinically significant interstitial lung disease.

10. Known history of untreated viral hepatitis or HIV.

11. Patients with parenchymal brain metastases are not eligible, unless they have completed local therapy.

12. Leptomeningeal carcinomatosis.

3.3.4 Removal of patients from therapy or assessments

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be encouraged to return to the study center to undergo treatment discontinuation assessments and to receive supportive care as indicated. We will permit progression and survival data collection unless the patient specifically withdraws consent for data collection for

the trial. The primary reason for discontinuation should be recorded. Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

- Documented disease progression
- Intolerable side effects, defined as grade 3 or higher drug related toxicity that fails to resolve to Grade 2 despite appropriate supportive care
- Clinically significant deterioration of the patient's condition causing a change in performance status prior to treatment discontinuation
- Patient noncompliance
- Investigator determination that it is not in the patient's best interest to continue participation
- Pregnancy
- Patient withdrawal of consent

APPROVED BY THE YALE UNIVERSITY IRB 2/24/2023

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of Investigational Product

Substance (INN)	**Afatinib**
(Brand name):	GIOTRIF®/GILOTRIF®
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20 and 30 mg film-coated tablets (the dose of afatinib in the film-coated tablets is related to the free base equivalent to afatinib)
Route of administration:	Oral
Posology	Once daily

4.1.2 Standard therapy: Cetuximab

Brand Name:	Erbitux
Pharmaceutical form:	Injection for intravenous infusion
Source:	to be covered by patient's insurance carrier
Unit strength:	400mg/m^2 body surface area loading dose, followed by 250 mg/m^2 body surface area weekly thereafter OR 500mg/m^2 body surface area initial dose and bi-weekly thereafter
Route of administration:	Intravenous injection
Posology:	Weekly/Bi-weekly

Premedications:

May premedicate with an H1 antagonist (eg, 50 mg of diphenhydramine) intravenously and steroid (dexamethasone 10 mg oral/intravenous) 30–60 minutes prior to the first dose. It is also

recommended to give a dose of dexamethasone 8 mg PO approximately 12 hours before the first and second scheduled cetuximab infusions. Premedication should be administered for subsequent cetuximab doses based upon clinical judgment and presence/severity of prior infusion reactions.

4.1.2 Method of assigning patients to treatment groups

Since this is an open-label, single-arm study, all enrolled patients will receive the combination of Cetuximab (standard therapy covered by patient's insurance carrier) and Afatinib (provided by Boehringer Ingelheim).

4.1.3 Selection of doses in the trial

Cetuximab at the proposed doses is FDA approved for the treatment of metastatic SCCHN. In the Phase I open-label dose-escalation study, the MTD of Afatinib was determined to be 40mg [14]. This dose has been tested in several Phase II and III trials as outlined in Section 1 above and found to be safe and effective. Afatinib 40 mg was also tested in combination with Cetuximab in patients with lung cancer who harbor the EGFR mutation and was shown to have a manageable side effect profile with not disproportionate treatment related mortality [22]. This was the dose initially used for patients accrued to the study, however, most patients needed a dose reduction to 30 mg daily. We will start all subsequent patients on this trial at a 30 mg daily dose.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Administration of afatinib

Patients will take a single oral dose of afatinib each day starting at a dose of 30 mg, continuously, until the development of progressive disease or unacceptable adverse events. Dose reductions of afatinib can occur. See Sections 4.1.4.1.1 and 4.1.4.1.2.

The medication should be taken at approximately the same time each day without food (at least one hour before or at least three hours after a meal).

Missed doses of afatinib can be made up during the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped. Patients with emesis must not take a replacement dose.

If dosing of whole tablets is not possible, afatinib tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 min until the tablet is broken up into very small particles. The dispersion should be drunk immediately. The glass should be rinsed with approximately 100 ml of water which should also be drunk. The dispersion can also be administered through a naso-gastric tube or enteral feeding tube.

Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment cycle. For administrative purposes, a treatment cycle is defined as 28 (+/- 3) days. Treatment will start after baseline evaluations and stop when the patient is diagnosed with disease progression or for any reason detailed in Section 3.3.4. Study drug will be prescribed by the investigator and will be dispensed by the affiliated investigational pharmacy on day 1 of each cycle.

4.1.4.1.1 Dose escalation for afatinib

Afatinib dose will not be escalated beyond the 30 mg daily oral dose on this trial.

4.1.4.1.2 Dose reduction for afatinib

Treatment related AEs will be managed by treatment interruptions and subsequent dose reductions of afatinib according to the schedule described in Table 4.1.4.1.2: 1. Given overlapping toxicities, afatinib dose reductions should precede cetuximab dose reductions. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhea or rash should be managed early and proactively as described in Section 4.2.3.

Table 4.1.4.1.2: 1 Dose reduction scheme for afatinib

AE type and CTCAE Grade	Action	Dose reduction scheme
Events <u>related to study drug:</u> • Diarrhea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrheal medication/hydration • Reduced renal function to ≥ Grade 2 as measured by serum creatinine, *proteinuria* or decrease in glomerular filtration rate of more than 50% from baseline • Any other drug related AE Grade ≥3	Pause treatment until patient has recovered to Grade ≤2 (Grade ≤1 for diarrhea or impaired renal function only) or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to Grade ≤2 (Grade ≤1 for diarrhea or impaired renal function) or baseline[1] within 14 days, study treatment	If patient was receiving Afatinib 30 mg daily, resume treatment at a dose of 20 mg daily. If patient was receiving Afatinib 20 mg daily, resume treatment at 20 mg intermittent dosing, 5 days on, 2 days off. If patient was receiving Afatinib 20 mg intermittent dosing, discontinue treatment.

AE type and CTCAE Grade	Action	Dose reduction scheme
	must be permanently discontinued[2].	
Acute onset and/or unexplained worsening of pulmonary systems (dyspnoea, cough, fever)	Pause afatinib while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume afatinib at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue afatinib

[1] Baseline is defined as the CTCAE Grade at the start of treatment
[2] In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with afatinib will be made by the sponsor in agreement with the investigator.

4.1.4.2 Administration of Cetuximab

Pre-medication with dexamethasone 8 mg po or by feeding tube approximately 12 hours prior to cetuximab dosing for the first and second doses. This may be omitted if there is a relative contraindication (eg. poorly controlled diabetes or hypertension), and may be stopped after the second dose of cetuximab if no hypersensitivity is observed. Use of IV dexamethasone premedication on the treatment day is recommended.

30-60 minutes after the recommended pre-medications per treating physician discretion, cetuximab will be administered intravenously at a dose of 400mg/m^2 on cycle 1, day 1 of treatment (loading dose) and at a dose of 250mg/m^2 every 7 days (+/- 1 day) thereafter. Alternatively, patients can be treated at a dose of 500mg/m^2 every 14 days (+/- 2 days). Alternating Cetuximab dosing schedules from a weekly to bi-weekly dosing schedule, and vice versa, between and within cycles of treatment is permitted per protocol following Sponsor PI discussion and approval.

Do not administer cetuximab as an intravenous push or bolus.

Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min.

Administer through a low protein binding 0.22-micrometer in-line filter.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. **Do not shake or dilute.**

4.1.4.2.1 Dose escalation for cetuximab

Cetuximab dose beyond the recommended and approved dosing will not be escalated on this trial.

4.1.4.2.2 Dose reduction for cetuximab

Infusion Reactions

Reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reaction.

Immediately and permanently discontinue Erbitux for serious infusion reactions. Afatinib may be continued by itself at the discretion of the treating physician, in patients who have experienced a serious infusion reaction with cetuximab.

Dermatologic Toxicity

Recommended dose modifications for severe (NCI CTC Grade 3 or 4) acneiform rash are specified in Table 4.1.4.2.2: 1 below. Afatininb should be dose reduced first per the guidelines in Table 4.1.4.1.2 above, before dose reducing cetuximab.

Table 4.1.4.2.2: 1 Cetuximab Dose Modification Guidelines for Rash

Grade 3/4 Acneiform Rash	Erbitux	Outcome	Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Continue at 250 mg/m^2 (500mg/m^2 for bi-weekly dosing)

			Discontinue Erbitux
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 200mg/m^2 (400mg/m^2 for bi-weekly dosing) Discontinue Erbitux
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement No Improvement	Reduce dose to 150mg/m^2 (300mg/m^2 for bi-weekly dosing) Discontinue Erbitux
4th occurrence	Discontinue Erbitux		

In the event of any adverse event, the treating physician may choose to interrupt cetuximab for up to 14 days. Treatment can then be resumed at the same or lower dose level. If the medication is interrupted for more than 14 days, the decision to continue with cetuximab will be made by the sponsor in agreement with the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is a single-arm, open-label study and will not employ randomization to assign treatment. All enrolled patients will receive the planned study treatment.

4.1.5.2 Procedures for emergency unblinding

This is a single-arm, open-label study and will not employ randomization to assign treatment. All enrolled patients with receive the planned study treatment.

4.1.6 Packaging, labelling, and re-supply

Afatinib will be supplied as film-coated tablets. Available dosage strengths will be 20 and 30 mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles.

Bottles/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number
- Product name (Afatinib)
- Contents of the bottle (30 tablets)
- Tablet strength (mg)
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical study use only
- A caution statement

Erbitux (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, injectable liquid containing no preservatives.

NDC 66733-948-23 100 mg/50 mL, single-use vial, individually packaged in a carton

NDC 66733-958-23 200 mg/100 mL, single-use vial, individually packaged in a carton

4.1.7 Storage conditions

Afatinib will be kept in their original packaging and a secure, limited access storage area according to the recommended storage conditions on the medication label.

Cetuximab vials will be stored under refrigeration at 2° C to 8° C (36° F to 46° F). **Do not freeze.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° C to 8° C. Discard any unused portion of the vial.

4.1.8 Drug accountability

All study drug (Afatinib) will be provided by Boehringer Ingelheim (manufacturer). Cetuximab is commercially available.

The recipient will acknowledge receipt of the drug (afatinib) by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced. Study drug accountability records should be maintained by the site in accordance with the local SOPs and regulations.

At the time of study closure, any unused or expired study drug will be destroyed at the site per Institutional SOPs. Any partially used study drug will be destroyed at the site, either during the course of the study or at the time of study closure, per Institutional SOPs.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medication

Rescue medications to reverse the actions of afatinib are not available. There is no specific antidote for overdosage with afatinib. In cases of suspected overdose, afatinib should be withheld and supportive care initiated. If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage. Potential adverse events should be treated symptomatically.

Common adverse events of treatment with afatinib with specified management recommendations and/or requirements include diarrhea, stomatitis/mucositis, and rash/acne. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

Concomitant treatments

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After study enrollment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for tumor response assessment. During palliative radiotherapy, study treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by the sponsor in

agreement with the investigator. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, must be recorded in the (e)CRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.
In case of major surgery (as judged by the investigator), it is recommended to stop treatment with afatinib around one week prior to the surgery, and to restart treatment after complete wound healing. If afatinib is interrupted for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.

Palliative radiotherapy may be given as described in Section 4.2.1.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment (with the exception of megestrol acetate and use of anti-androgens and/or gonadorelin analogues for treatment of prostate cancer), or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.1.

4.2.2.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhea.

To prevent skin related adverse events, it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.2.3.2.

4.2.2.3 Restrictions regarding women of child-bearing potential

Patients who are not of childbearing potential due to being postmenopausal (i.e. 12 months with no menses without alternative medical cause, predefined hormonal level according to local regulation or etc.) or being permanently sterilized (bilateral oophorectomy, bilateral

salphingectomy, hysterectomy and/or tubal ligation) do not need to use contraception to be eligible for the trial.

All other patients are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until end of trial participation or 4 weeks after last dose of trial medication, whichever is later).

Highly effective methods of birth control should be applied to women of childbearing potential as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year – placement of intrauterine device or intrauterine system, "double barrier" methods of contraception, male sterilisation or etc.) when used consistently and correctly, and must be in accordance with local regulations where applicable. The list of contraception methods meeting these criteria is provided in the patient information.

Women who become pregnant while participating in the study must discontinue study medication immediately. The pregnancy must be reported following procedures detailed in section 5.3.7.4

4.2.3 Management of expected adverse events

Dermatologic adverse events and diarrhea are the most common side-effects associated with treatment with afatinib. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

4.2.3.1 Management of diarrhea and hydration status following treatment with afatinib

Diarrhea occurs at a high frequency and generally begins within 2 weeks of exposure to afatinib. Although usually mild to moderate, diarrhea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.3.1: 1). At the time of initiation of treatment with afatinib patients should be given a supply of loperamide to keep with them at all times or access to afatinib should be confirmed; and patients should be counselled on the appropriate use.

Patients must be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhea.

Table 4.2.3.1: 1 Grade specific treatment recommendations for afatinib related diarrhea

Severity (CTCAE Grading)	**Description**	**Intervention concerning afatinib treatment**	**Specific intervention**

Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose **unless Grade 2 diarrhea continues for ≥ 2 days (48 hours)** in which case treatment must be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement
Severe (Grade 3)	Increase of ≥ 7 stools per day over baseline; incontinence; IV fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 2; plus: an infectious process should be ruled out with stool cultures; aggressive iv fluid replacement ≥ 24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic;
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhea does not resolve to CTC AE Grade ≤ 1 within 14 days, treatment with afatinib must be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgment, further treatment with afatinib will be decided in agreement between the sponsor and the investigator.

4.2.3.2 Management recommendations for dermatological AEs following treatment with afatinib

Dermatologic AEs of afatinib include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 4.2.3.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.3.2: 2. For dose adjustment of afatinib refer to Table 4.1.4.1.2.

Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered. (4)

Table 4.2.3.2: 1 General recommendations for prophylaxis while receiving afatinib

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PABA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended Patients should be encouraged to consequently stay out of the sun. Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	It is important to moisturize the skin as soon as anti-EGFR therapy is started.

	Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications
Prevention of paronychia	Patients should keep their hands dry and out of water if ever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.3.2: 2 Grade specific treatment recommendations of skin reactions to afatinib

Severity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical treatment as for Grade 1 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist Consider systemic steroids

Life threatening (Grade 4)	Generalized exfoliative, ulcerative, or bullous dermatitis	See Grade 3 Systemic steroids are recommended
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine)
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics
FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths)

		Topical application of aqueous silver nitrate solutions to fissures
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics.
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
1 If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of afatinib according to the dose reduction scheme in Table 4.1.4.1.2: 1		

4.2.3.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.3.3:1. For dose adjustment refer to Section 4.1.4.1.2 and for restrictions on concomitant therapies refer to Sections 4.2.2 and 10.1.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.3.3:1 include: topical analgesics –viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from 8)

Table 4.2.3.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations	Intervention concerning afatinib treatment/ dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution.	No change.

Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤2 or baseline, then restart at the reduced dose according to Section 4.1.4.
Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated.	Hold dose until recovery to grade ≤2 or baseline, then restart at the reduced dose according to Section 4.1.4

4.2.3.4 Management of interstitial lung disease (ILD) and keratitis

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug must be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with afatinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with afatinib should be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

4.3 TREATMENT COMPLIANCE

Patients will be dispensed Afatinib on a monthly basis in pill bottles with 30 tablets each. At every follow-up visit, they will be asked to bring in their pill bottles and pill count will be

performed. Pill diary will also be provided to document every dose taken. Missed doses and compliance to treatment will be documented.

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5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoint(s)

Objective Response Rate (Complete Response + Partial Response), defined by tumor shrinkage (mm), per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

5.1.2 Secondary endpoint(s)

Duration of response (measured in weeks), Progression-free survival (PFS) in weeks, overall survival (OS) in months, toxicity assessments using CTCAE v4.0, analysis of tumor-tissue microarrays by high-quality immunohistochemical assays and automated image analysis (AQUA, Genoptix®) from biopsies obtained at baseline, after four weeks of treatment with the combination, and again at disease progression or end of treatment.

5.2 ASSESSMENT OF EFFICACY

Response and progression will be evaluated in this study using Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (9). Tumor response will be assessed by investigator.

See APPENDIX 10.4, RECIST 1.1 Criteria for details on lesion measurements and response assessment.

5.3 ASSESSMENT OF SAFETY

The safety of afatinib will be assessed through collection and analyses of adverse events (AEs) and laboratory tests. AE's and their management will be recorded at every treatment and follow-up visit while subjects are on study. SAE's will be appropriately reported as per Section 5.3.7.

5.3.1 Physical examination and ECOG performance status

A physical examination will be performed as part of the screening visit prior to initiation of study treatment. Subsequently, patients will be seen for every cetuximab dose. A physical examination and ECOG performance status will be recorded at every evaluation.

5.3.2 Vital signs

Vital signs will be recorded at every visit as outlined in Section 5.3.1 above.

5.3.3 Safety laboratory parameters

Baseline Complete Blood Count (CBC) with differential, Comprehensive Metabolic Panel (CMP) and Magnesium levels will be obtained at the Screening visit to ensure eligibility criteria are

met. These laboratory evaluations will be repeated prior to every cetuximab dose throughout treatment. In addition, for women of childbearing potential, urine/serum Human Chorionic Gonadotropin (HCG) test will also be obtained at least every 4 weeks. Coagulation studies are recommended every 4 weeks for patients on anticoagulation therapy (excluding a daily baby aspirin).

5.3.4 Electrocardiogram

Baseline EKG will be obtained at the screening visit to rule out active cardiac issues. Subsequent EKG's will be obtained as clinically indicated.

5.3.5 Other safety parameters

Studies such as Echocardiogram and Pulmonary Function Tests, etc. will be obtained as clinically indicated for individual patients.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable 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.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

or

- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

If cancer is the indication for treatment, only cancers of new histology and cases where there is clear evidence of exacerbation of an existing cancer qualify as a serious event.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Severity of adverse event

The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. in the (e)CRF.

For events not listed in the CTCAE, severity will be designated as mild, moderate, severe or life threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild:** An event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate:** An event not resulting in disability or incapacity but which requires intervention;
- **Severe:** An event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening:** An event in which the patient was at risk of death at the time of the event;
- **Fatal:** An event that results in the death of the patient.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Causality will be reported as either "Yes" or "No".

Yes: There is a reasonable causal relationship between the investigational product administered and the AE (i.e., the AE is possibly, probably, or definitely related to the investigational product).
No: There is no reasonable causal relationship between the investigational product administered and the AE.

5.3.7 Adverse event collection and reporting

5.3.7.1 AE collection

The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual patient's end of trial (through the EOR or end of follow-up visit):
  -all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial (after the EOR or end of follow-up visit, but including the overall survival follow-up period): the investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

For Afatinib the residual effect period (REP) is defined as 30 days after last intake of it.

5.3.7.2 Exemptions to SAE reporting

None

5.3.7.3 Information required

For each adverse event, the investigator should provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator should determine the causal relationship and expectedness with the investigational drug to all AEs as defined in the listed adverse event section of Boehringer Ingelheim's (BI's) Investigator Brochure.

The following should also be recorded as an (S)AE in the (e)CRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, EKG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

5.3.7.4 Pregnancy

The sponsor-investigator shall be responsible to follow up on all information regarding a reported Drug Exposure during Pregnancy. The investigator shall ensure that any SAEs during and after pregnancy obtained by the Investigator will be reported to the Boehringer Ingelheim Unique Entry Point in the same format and timeline as any other SAE.

5.3.7.5 S(AE) reporting to Boehringer Ingelheim and NCCN

The sponsor-investigator must report all SAEs and non-serious AEs which are relevant for the reported SAE to BI by fax using BI IIS SAE form to BI Unique Entry Point as detailed below in accordance with the timelines specified in the safety exchange agreement

The SAE contact (fax number) is :

Boehringer Ingleheim Pharmaceuticals, Inc

900 Ridgebury Road

Ridgefield, CT 06877

Fax: 1-203-837-4329

In addition, SAEs must also be sent to NCCN via email to ORPReports@nccn.org or fax at 215-358-7699.

5.4 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Pre-treatment biopsies or archived tumor tissue (if no other systemic treatment was administered since that biopsy/excision) will be used to establish a baseline presence and quantification of EGFR, phosphorylated EGFR, and HER2 using immune-fluorescent staining and automated image analysis (AQUA, Genoptix®). These levels will then be compared with levels measured on tumor tissue obtained after 4 weeks of treatment with both Afatinib and Cetuximab to determine effects of treatment and again from tumor tissue obtained at the time of disease progression on treatment. Through sequential measurement of these biomarkers we hope to determine the prevalence of over expression in our patient population, whether EGFR,

phosphor-EGFR and HER2 levels change with treatment with dual EGFR inhibitors and correlate with clinical response and whether they can be used in the future as predictive of response to treatment.

Taking a core needle biopsy (CNB)is anticipated to be the most likely methodology employed in acquiring tissue for analysis in this patient group with advanced cancer of the head and neck region. This can usually be performed in a head and neck surgeon's office under local anesthesia. Tissue samples obtained from all participating sites will be transported to Yale Pathology to Veronique Neumeister's lab for processing and analysis. Instructions for tissue acquisition and handling, and shipping of samples can be found in the study Laboratory Manual.

5.4.1 Biobanking

A tissue repository will be created from the tumor samples derived from patients enrolled on this study. All samples will be submitted to Pete Doukas MD (cell 475-267-9188), Yale Head and Neck Biosample Repository (Dr. Benjamin Judson, Director) at Brady Memorial Laboratory BML212,, 310 Cedar St, New Haven Connecticut. Material may be archived for future use including but not limited to immunohistochemistry. Selected specimens will processed for immediate patient-derived xenograft development in the Burtness Lab. Collection of these samples will be coordinated with Sundong Kim (813-420-1746), Nathan Smith 286, 333 Cedar Street, New Haven, Connecticut. Development of patient-derived xenografts is conducted with funding from the Department of Defense [CA201045P1; PI: Barbara Burtness, MD].

5.4.2 Sequencing

Pre- and post-treatment tumor specimens from up to 50 enrolled patients will be submitted for whole exome sequencing to the Yale Center for Genome Analysis. Outcome will be analyzed by the presence or absence of *TP53* mutation, as well as *TP53* mutation class (disruptive, gain of function, non-disruptive). This work is conducted with funding from the Department of Defense [CA201045P1; PI: Barbara Burtness, MD].

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The Trial Flow Chart summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Baseline medical history and demographics, prior and concomitant medications, physical exam, weight, height, vital signs, ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium levels, pregnancy test for women of reproductive age and coagulation studies if on anticoagulant therapy), EKG, CT or MRI of involved disease sites, HPV status (determined by p16 IHC staining) and a tumor biopsy (where feasible, obtained after progression on previous line of treatment), will be obtained for all patients at the initial screening visit after they sign the consent form.

Medical history and demographics, prior and concomitant medications, physical exam, weight, height, vital signs, ECOG performance status, and laboratory assessments should be obtained within 48 hours of initiation of treatment, EKG and imaging should be obtained within 28 days of treatment initiation.

6.2.2 Treatment period(s)

During the treatment period, patients will take afatinib once daily at a dose of 30mg. Subjects will visit clinic on day 1 (+/- 3 days) of each 28 day cycle and prior to every cetuximab dose thereafter. Pre-medication with decadron 10mg, H1 and H2 blockade may precede theinitial dose of Cetuximab in week 1 of cycle 1, per the discretion of the treating physician. Premedication with H1 blockade may be used beyond the initial dose for patients who do not experience an infusion reaction with the loading dose. 30-60 minutes after the recommended pre-medications, cetuximab will be administered intravenously at a dose of 400mg/m2 in the first week of treatment (loading dose) and at a dose of 250mg/m2 every week thereafter. Alternatively, cetuximab can also be administered at a dose of 500 mg/m2 every 2 weeks. While on study treatment, patients will be seen prior to every cetuximab dose. During these visits, the following evaluations will be done: adverse event assessment, concomitant medications, physical exam, weight, vital signs and ECOG performance status. Laboratory assessments (CBC with differential, CMP, Magnesium) will also be performed prior to the cetuximab dose, throughout the treatment period. Pregnancy test for reproductive age women and coagulation studies if on anticoagulant therapy will be performed every 4 weeks throughout the treatment period.

For patients who are on afatinib alone due to cetuximab being discontinued for a serious infusion reaction or for any other reason, they will be scheduled for follow-up on days 1 and 15 (+/- 3 days) of the first two 28-day cycles. The following assessments will be performed during these visits: adverse event assessment, concomitant medications, physical exam, weight, vital signs and ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium). Pregnancy test for reproductive age women and coagulation studies if on

anticoagulant therapy will be performed every 4 weeks throughout the treatment period. After the first 2 cycles, visits can be scheduled on day 1 of every 28-day cycle (+/- 3 days) per physician discretion.

Tissue biopsies will be repeated, where medically feasible, at the end of cycle 1, and at disease progression or end of treatment if discontinued for reasons other than disease progression.

CT or MRI (at physician discretion) will be performed at the end of cycle 2 (+/- 3 days) and every 2 cycles thereafter (+/- 3 days). Treatment will be discontinued in the event of intolerable side effects or unequivocally progressive disease on clinical exam or surveillance scans.

6.2.3 Follow-up period and Trial Completion

6.2.3.1 End of treatment visit (EOT)

The EOT visit will be performed at the time of permanent discontinuation of trial medication for any reason (within 7 days of treatment discontinuation as defined as the removal of the subject from the study treatment period).

At this visit, patients will undergo the following evaluations: adverse event assessment, concomitant medications, physical exam, weight, vital signs, ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium). Tumor assessment and imaging will be performed if applicable.

Tissue biopsies will be repeated at this visit, where medically feasible.

6.2.3.2 Residual effect period (REP)

The REP is defined in Section 5.3.7. The End of REP (EoR) visit should be performed at 30 days (+ 14 days) after permanent discontinuation of the trial medication.

The information collected at this visit should include all new AEs that occurred after EOT and a follow-up of adverse events ongoing at EOT.

Additionally, patients will undergo the following evaluations at this visit: concomitant medications, physical exam, weight, vitals, ECOG performance status, laboratory assessments (CBC with differential, CMP, Magnesium). Tumor assessment and imaging will be performed if applicable.

6.2.3.3 Extended follow-up period

6.2.3.3.1 Follow-up for progression

Additional follow-up visits after the EoR visit will be performed for patients who did not progress on treatment. Visits should occur every 4 weeks (+7 days) for up to 24 weeks.

The follow-up for progression period will end at the earliest if one of the following events is met:

- Completion of the predefined follow-up for progression period
- Lost to follow-up
- Disease progression (either clinical or per RECIST)
- Start of a new anti–cancer therapy
- Death
- End of whole trial as specified in Section 8.6

At the end of the follow-up period, the EoFU (End of Follow-Up) visit will be performed. The EoFU visit will be performed within 14 days of known progression, start of new anti-cancer therapy, or completion of predefined follow-up progression period.

The following will be obtained and / or performed during the follow-up visits and the EoFU visit: adverse event assessment and follow-up of adverse events ongoing since EoR to EoFU, concomitant medications, physical exam, weight, vitals, and ECOG performance status,. Tumor assessment and imaging will be performed if applicable.

Treatment with any other anti-cancer drug including the name and type of the anti-cancer drug and/or best supportive care and the date initiated should be recorded, if applicable. Additionally, the patient's outcome should be recorded, including the date of and reason for death [if applicable], or the date of progressive disease.

6.2.3.3.2 Follow-up for Overall Survival

Patients who discontinued study treatment due to disease progression will have at least a monthly telephone call (+/- 1 week) to ascertain survival status. This will continue until patient death.

6.2.3.4 Trial completion for an individual patient

A patient is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period (or follow-up for overall survival if applicable)
- Lost to follow-up

- Withdrawal to be followed-up
- Death

At the earliest of the above criteria, the Patient Completion (PC) information should be entered in the (e)CRF.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This is a single-arm prospective Phase II trial.

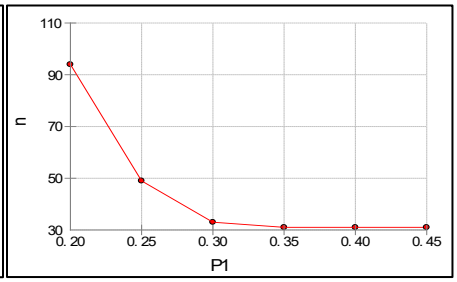
7.2 DETERMINATION OF SAMPLE SIZE

The sample size calculation was based on the primary endpoint, the objective response rate. Historical data with single agent Cetuximab have yielded response rates of 10-15%, as discussed in Section 1.1. We used Software PASS 2012 (Kayesville, UT) ***Inequality Tests for One Proportion*** module for sample size calculation. The results were shown in the tables and figures below for different historical control rate. A sample size of 33 will allow us to detect an absolute difference of 20% (alternative hypothesis 30% - null hypothesis 10%) in ORR using a two-sided binomial test with 80% power and significance level of 0.05. Should the historical ORR be 15% (null hypothesis), a sample size of 34 will achieve 80% power to detect an absolute difference of 20% in ORR too.

Null hypothesis: ORR=10%

Numeric Results for testing H0: P = P0 versus H1: P <> P0
Test Statistic: Exact Test

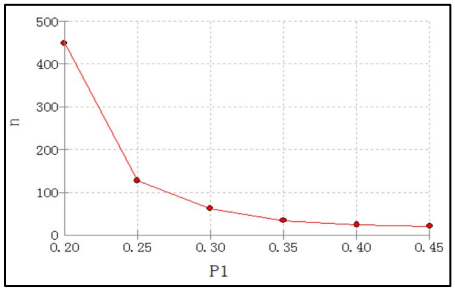
Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If <=R|>=R
0.8006	94	0.1000	0.2000	0.0500	0.0364	0.1994	3|16
0.8166	49	0.1000	0.2500	0.0500	0.0272	0.1834	0|10
0.8179	33	0.1000	0.3000	0.0500	0.0450	0.1821	0|8
0.8991	31	0.1000	0.3500	0.0500	0.0477	0.1009	0|8
0.9670	31	0.1000	0.4000	0.0500	0.0477	0.0330	0|8
0.9915	31	0.1000	0.4500	0.0500	0.0477	0.0085	0|8



Null hypothesis: ORR=15%

Numeric Results for testing H0: P = P0 versus H1: P <> P0
Test Statistic: Exact Test

Power	N	Proportion Given H0 (P0)	Proportion Given H1 (P1)	Target Alpha	Actual Alpha	Beta	Reject H0 If <=R|>=R
0.8046	449	0.1500	0.2000	0.0500	0.0470	0.1954	52|83
0.8070	127	0.1500	0.2500	0.0500	0.0462	0.1930	11|28
0.8035	62	0.1500	0.3000	0.0500	0.0303	0.1965	3|16
0.8045	34	0.1500	0.3500	0.0500	0.0280	0.1955	0|10
0.8081	24	0.1500	0.4000	0.0500	0.0401	0.1919	0|8
0.8029	21	0.1500	0.4500	0.0500	0.0413	0.1971	0|8



Based on the calculation as above, we plan to enroll 50 patients which provide us 80% power to detect an alternative hypothetical ORR of 24% by rejecting a null hypothesis of 10%. This

sample size will achieve 80% power to detect an absolute difference of 18% if the historical control of ORR is 15% (i.e. 33% vs. 15%).

7.3 PLANNED ANALYSES

All statistical analyses will be performed using the SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC). Significance level will be set as $p < 0.05$, two-sided. Yale Center for Analytical Sciences will provide statistical support.

Patient demographics and clinical characteristics will be summarized. The primary analysis will use a 2-sided binomial test to compare the ORR with historical control of 10%. 95% confidence interval of ORR will be reported as well. As an exploratory analysis, Logistic regression will be used to identify potential risk factors that are associated with ORR.

The secondary endpoint is progression-free survival and overall survival with 1 year follow-up. We will use Kaplan-Meier survival analysis to estimate the median PFS and OS in the cohort. Additional Cox regression analyses will be carried out to examine the association between demographical or clinical variables and survival outcome.

We expect 10 – 15 HPV + patients will be enrolled. We will compare the demographics and clinical characteristics between HPV + and HPV - subgroup, and then calculate the ORR by HPV status. An exploratory analysis will be conducted to compare the ORR using multivariate logistic regression, and a survival analysis for the secondary endpoint as well.

7.4 HANDLING OF MISSING DATA

We will perform complete case analyses in which those with missing data will be excluded from the relevant analyses. We will not impute missing data. Missing data on one item will not preclude a patient's observed data from being used in other analyses. For example, a patient might have missing response data but observed toxicity data. The toxicity data can be used in appropriate analyses.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant sponsor's Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator must inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

8.1.1 Informed consent

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors or Quality Assurance auditors appointed by the Sponsor or IRB, and by inspectors from regulatory authorities.

8.1.2 Patient registration

The informed consent process must be completed before any study screening procedures may begin. Following consent, patients will have all required screening procedures outlined in Section 6.2.1. The site principal investigator or other approved investigator must document that the patient has met all inclusion criteria and has none of the exclusion criteria.

8.2 DATA QUALITY ASSURANCE

The YCCI Project Manager will distribute all necessary study related materials and regulatory documents with instructions for their completion and submission to YCCI. Upon receipt of all required regulatory documents including the IRB approved protocol and informed consent form and participation in a study initiation meeting, the Project Manager will send a site activation notice to that participating site. Upon receipt of the activation notice patient screening and consent may proceed.

8.2.1 Data monitoring

The study principal investigator and YCCI are responsible for monitoring the performance of all of the participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their institution's initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During these monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial
- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, YCCI, NCCN and Boehringer Ingelheim, as appropriate
- That source documentation matches CRFs
- That required procedures for study drug accountability, distribution, and storage are followed.

YCCI will document the required study monitoring activities in a Study Monitoring Plan.

8.2.2 Safety monitoring

The Study Principal Investigator, biostatistician and study team will monitor toxicity and outcome on a continual basis.

The Yale Cancer Center Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator. The DSMC will review this protocol at a minimum of once every six months. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

If the committee decides that changes should be made to this trial, recommendations will be made in writing to NCCN, Boehringer Ingelheim and Division Medical Director, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

8.2.3 Project team meetings

Scheduled meetings will be held and will include the protocol investigators and research staff involved with the conduct of the protocol.

During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment raterelative to expectation of target accrual, (eligible and ineligible\participants)
- Retention of participants, adherence to the protocol and protocol violations
- Protocol amendments

8.2.4 Audit plan

The YCCI Office of Quality Assurance and Training will audit the trial at least annually or as determined by the YCC DSMC. The overall principal investigator, study coordinator and/or data manager may request access to all source documents and other study documentation for on-site or remote monitoring, audit or inspection.

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Yale. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

8.2.5 Data management

The investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. OnCore will be the designated electronic data capture tool. All data should be entered onto OnCore within 2 weeks of each study visit. AEs need to be entered within 72 hours and SAEs need to the entered within 24 hours of the site becoming aware of the event.

8.3 RECORDS

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the (e)CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For (e)CRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The sponsor will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections. Source documents provided to the coordinating

center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, patient ID number, and patient initials. Upon inquiry, NCCN and Boehringer Ingelheim will be provided access to de-identified source data and documents pertaining to data resulting from patients on this study.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records maintained by the participating investigators, including but not limited to medical records and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

8.3.3 Storage of records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For afatinib this is the current version of the Investigator's Brochure. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), to health authorities and IRB or Ethics Committees will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB or Ethics Committees and the regulatory authorities.

8.6 END OF TRIAL

The trial will end when the last patient has completed the last EOR visit or follow-up for progression visit, depending on whether that last patient progressed on treatment.

8.7 PROTOCOL VIOLATIONS

YCCI will conduct ongoing monitoring of the study records of each participant accrued at each site throughout the course of the study in order to ensure proper conduct of this study and identify in a timely manner any protocol violations, as described in Section 8.2.1. Protocol violations will be reported to site's IRBs in accordance with institutional policy.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

No monetary or financial compensation will be made available to study patients in the event of study related injury. However, reasonable medical care will be provided for treatment related injury. Subjects or their insurance providers will be responsible for costs related to treatment of study related injury.

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10. APPENDICES

10.1 APPENDIX 1

List of potent inhibitors and inducers of P-glycoprotein (MDR1)

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

As the information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess such status on concomitant therapies and in case of questions contact the sponsor.

10.2 APPENDIX 2 COCKCROFT-GAULT FORMULA

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results must be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot [0.85 \; if \; Female]}{72 \cdot \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass (in kilograms)} \cdot \text{Constant}}{\text{Serum Creatinine (in µmol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

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10.3 APPENDIX 3 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

10.4 APPENDIX 4 RECIST 1.1 CRITERIA

The criteria below are based on RECIST 1.1 (9).

The preferred method of assessment is a spiral CT scan with IV and oral contrast, unless IV and/or oral contrast are medically contraindicated. CT scans of the chest, abdomen and other areas of known or newly suspected disease must be performed. Scans of the abdomen, pelvis and other areas of the body, but not chest, may be done with MRI instead of CT.

Skin lesions followed as target lesions must be documented by color digital photography and must include in the image a ruler with millimeter subdivisions and a label that includes the patients ID and date.

Bone scans (using ^{99}m-technetium polyphosphonate scintigraphy) are recommended at baseline if the patient has any signs and symptoms consistent with bone metastasis or a history of bone metastasis. Bone metastasis identified at baseline must be documented and assessed according to RECIST 1.1 at the times of the other tumor measurements indicated in the flow chart. During the study bone scans should be repeated as clinically indicated in patients without bone metastasis at Baseline.

For the purposes of this study, patients should be re-evaluated for response at weeks 8, 16 and every 8 weeks thereafter. In the event of a treatment delay, interruption or discontinuation of treatment, tumor assessment should continue to follow the original schedule.

Follow-up tumor assessments must utilize the same CT/MRI/photographic method and acquisition technique (including use or non-use of IV contrast) as were used for screening assessments to ensure comparability. A chest x-ray or skeletal x-ray which clearly demonstrates a new metastatic lesion may be used to document progression in lieu of CT/MRI/bone scan.

Only those patients who have measurable disease present at baseline, have received at least 3 weeks of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Measurability of tumour at baseline

Measurable lesions

Lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm (by CT scan, MRI, caliper measurement) or ≥ 20 mm (by chest X-ray). Pathological lymph nodes, defined as lymph nodes with a short axis >15mm are also measurable.

Measurable disease

Measurable disease requires the presence of at least one measurable lesion. Measurable lesion if limited to either small (<2cm) solitary visceral lesion or scant (<5cm) lymph nodes only metastasis should be evaluated for additional evidence of malignant nature and discussed with the sponsor before enrolling.

Non-measurable disease

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm with CT scan, MRI or caliper measurement or <20 mm with chest X-ray or pathological lymph nodes with shortest axis ≥10 and <15 mm) as well as truly non-measurable lesions. Lesions considered truly unmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

New lesions in irradiated fields

Previously irradiated lesions should not be used as indicator lesions. However, new lesions occurring in previously irradiated fields can be used to assess the antitumor response.

Methods of measurement

All measurements must be recorded in metric notation, using a ruler or callipers. All baseline evaluations must be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. If a lesion is considered too small to measure, a default measurement of 5mm should be applied. If the lesion is not visible, a default measurement of 0mm should be applied.

The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is obligatory.

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis.

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Ultrasound, endoscopy and laparoscopy should not be used to measure tumour lesions or evaluate tumour response. However, these techniques can be useful to supplement information from other techniques.

Cytology and histology can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours where known residual benign tumours can remain).

Baseline Documentation of Target and Non-target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as target lesions and will be recorded, measured (longest diameter = LD) and numbered at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Lymph nodes must be ≥15mm in order to be considered as target lesions.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease (see Table 10.4:1).

Table 10.4: 1 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions.
Partial Response (PR)	At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD.
Progression (PD)	At least a 20% increase in the sum of LD of target lesions taking as reference the smallest sum LD recorded since the treatment started, together with an absolute increase in the sum of LD of at least 5mm. OR The appearance of one or more new lesions.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR, taking as reference the baseline SoD, nor sufficient increase to qualify for PD taking as reference the smallest SoD since the treatment started.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent” (see Table 10.4:2).

Table 10.4: 2 Evaluation of non-target lesions and new lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesions or/and maintenance of tumour marker level above normal limits.
Progression (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the review panel (or study chair).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Confirmation

In case of tumour response (CR or PR), confirmation will be performed with a repeat assessment no less than 4 weeks after the RECIST criteria for response have been met. In the case of SD, measurement must have met the SD criteria at least once after study entry at an interval of not less than 6 weeks.

Evaluation of best response to study treatment

The best response to study treatment (Table 10.4: 3) is the best response recorded from the start of treatment until disease progression or start of further anti-cancer treatment (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurements and confirmation criteria (Table 10.4: 3).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 10.4: 3 Algorithm for evaluation of overall response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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