REDACTED PROTOCOL

Title: A Phase III Randomised, Double-Blind, Placebo-Controlled, Parallel, Multicentre Study to Assess the Efficacy and Safety of Continuing IRESSA™ 250 mg in addition to Chemotherapy versus Chemotherapy alone in Patients who have Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) and have progressed on First-Line IRESSA™.

IMPRESS (IRESSA™ Mutation Positive Multicentre Treatment Beyond ProgRESsion Study)

Study No: D791LC00001

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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Source material:

Sections taken from the Clinical Study Protocol (study code D791LC00001) dated 9 November 2011, with exception of sections marked *, which are from the Clinical Study Protocol (study code D791LC00001) Addendum dated 9 November 2011.

1. SELECTION OF PATIENTS

1.1 Inclusion criteria

For inclusion in the study, subjects should fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures.
2. Male or female patients aged 18 years or older (**for Japan only –** male or female patients aged 20 years or older).
3. Cytological or histological confirmation of NSCLC other than predominantly squamous cell histology with an activating EGFR tyrosine kinase (TK) mutation as determined locally.
4. 'Acquired resistance' on first-line gefitinib as defined by the following clinical endpoints:
    a. Radiological documentation of disease progression while on continuous treatment with first-line gefitinib within 4 weeks prior to randomisation into the study.
        i. Evidence of central nervous system (CNS) recurrence only while on first-line gefitinib is not considered a sign of developing 'acquired resistance' and therefore those patients are not eligible for the study.
        ii. Evidence of CNS recurrence with other systematic progression while on first-line gefitinib is considered 'acquired resistance'. Those patients are eligible if CNS lesion treated with surgery and/or radiation and stable without steroid for at least 10 days within 4 weeks of randomisation into the study.
    b. Prior objective clinical benefit defined by either partial or complete radiological response or durable stable disease (SD; >6 months) after initiation of first-line gefitinib.
    c. Minimum duration on first-line gefitinib treatment of 6 months.
5. WHO Performance Status 0, 1.
6. Life expectancy of at least 12 weeks or longer.
7. Patients suitable to start cisplatin plus pemetrexed combination chemotherapy.
8. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

1.2 Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

2. Previous enrolment or randomisation in the present study.
3. Prior chemotherapy or other systemic anti-cancer treatment (excluding gefitinib). Palliative radiotherapy must be completed at least 4 weeks before the start of study treatment with no persistent radiation toxicity.
4. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease.
5. Neutrophils <1.5 x 109/L or platelets <100 x 109/L.
6. Serum bilirubin >1.5 x the upper limit of normal (ULN).
7. Creatinine clearance <45 mL/min calculated by either Cockcroft–Gault, 24-hour urine collection, ethylenediaminetetraacetic acid (EDTA) scan or other validated methods.
8. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x ULN in the absence of liver metastases, or >5 x ULN in the presence of liver metastases.
9. As judged by the investigator, any evidence of severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, renal or hepatic disease).
10. Treatment with an investigational drug within 4 weeks before randomisation (first-line gefitinib received via a clinical study or other access programme is allowed).
11. Other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or cervical cancer in situ or completely resected intramucosal gastric cancer.
12. Women of childbearing potential who do not comply with the following:
    a. Use an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study in such a manner that the risk of pregnancy is minimised. Adequate methods of contraception are: oral contraceptives; Norplant implants; Depo-Provera injections; intrauterine devices; barrier methods (diaphragm, cervical cap or condom) when used in combination with a spermicide.
    b. Have a negative pregnancy test.

1.3 Procedures for handling subjects incorrectly enrolled or randomised

Subjects who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised to receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are enrolled in error or incorrectly randomised and started on double-blind treatment, or where patients subsequently fail to meet the study criteria post-randomisation, a discussion should occur between the AstraZeneca Study Team Physician and

the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca Study Delivery Team Physician is to ensure that all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have study therapy stopped.

2. STUDY PLAN AND PROCEDURES

2.1 Overall study design

This is a double-blind, placebo-controlled, parallel, multicentre study to assess the efficacy and safety of continuing gefitinib 250 mg (gefitinib) in addition to chemotherapy versus chemotherapy alone in patients who have *EGFR* mutation-positive locally advanced or metastatic NSCLC and have progressed on first-line gefitinib.

The study will randomise approximately 250 patients with locally advanced or metastatic *EGFR* mutation-positive NSCLC who have received gefitinib as first-line treatment. All eligible patients should have either responded or achieved a durable stable SD (at least 6 months) on their first-line gefitinib treatment and subsequently developed radiological disease progression. To be eligible for the study, all patients will be required to have received a minimum duration of 6 months' first-line gefitinib. At this point, eligible patients will be randomised to either continue blinded gefitinib or blinded placebo in addition to treatment with cisplatin plus pemetrexed combination chemotherapy. Patients should be randomised into the study as soon as possible after radiological progression on first-line gefitinib treatment (as assessed by the investigator according to principles outlined in RECIST 1.1). The time between documented radiological progression (the date of scan performed) on first-line gefitinib and randomisation into the study should be within 4 weeks.

All patients will receive maximum of six cycles of cisplatin plus pemetrexed chemotherapy with standard dose in addition to the randomised treatment (gefitinib or placebo). After completion of chemotherapy, patients will continue their randomised treatment until disease progression or other discontinuation criterion is met. Pre-treatment to pemetrexed, such as vitamin supplementation, should be started immediately after obtaining informed consent from patients; this is expected to support the start of pemetrexed-based chemotherapy on the day of randomisation (which should be within 4 weeks from the first documented radiological progression). The baseline scan for assessment of the primary endpoint of progression-free survival (PFS) following randomisation must be within 4 weeks prior to randomisation. Following documented radiological progression (but before randomisation), continuation of gefitinib is encouraged. However, if a patient stops taking gefitinib treatment, the maximum allowed time off gefitinib treatment prior to randomisation is 4 weeks.

Treatment compliance between progression and randomisation will be recorded, and any effect on the subsequent treatment effect will be explored.
All randomised patients will undergo radiological evaluations every 6 weeks from randomisation until documented progression, withdrawal of consent, loss to follow-up, death or the primary data cut off (DCO) for the analysis, whichever occurs first. These radiological evaluations will continue, regardless of treatment decisions and subsequent therapy received. The primary analysis will be based on the tumour assessments recorded on the electronic Case Report Form (eCRF; clinical database, as collected via the investigator). Analysis derived from the central review will be considered to be secondary and confirmatory, and will be derived from the independent review visit responses and the dates of the scan assessment visits. Study treatment will be given until objective disease progression is documented or other criterion for study treatment discontinuation is met. Safety data will continue to be collected for patients still on randomised therapy and within the safety follow-up period.

Following progression (and discontinuation of randomised treatment), patients will enter survival follow-up to assess patient status. Survival contacts will be made every 8 weeks and will continue until documentation of death, withdrawal of consent, loss to follow-up or the final DCO, whichever occurs first. At the point of progression, further subsequent therapy is at the discretion of the investigator. Information on all subsequent anti-cancer therapy received will be documented during the survival follow-up.

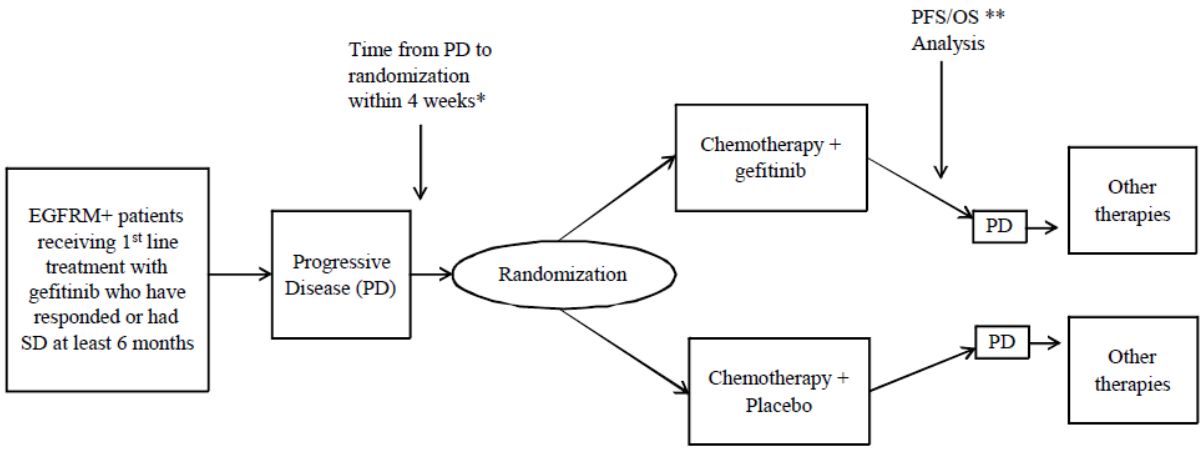
This study is planned to have two data cut-offs, that is 'primary' PFS analysis (at the time of approximately 190 PFS events) and 'final' overall survival (OS) analysis (at the time of approximately 175 OS events). The primary PFS analysis will take place when 190 progression events have occurred (75% PFS maturity) at the time of the primary data cut-off. At the time of the primary PFS analysis, OS will also be analysed, when it is estimated there will be 125 OS events (i.e. approximately 50% have died). After this primary PFS analysis, patients will then continue to be followed up until 175 deaths have occurred (i.e. 70% OS maturity), when the final data cut-off will occur. Following the primary data cut-off for the primary endpoint (when 190 PFS events have occurred), data collection will be limited to survival status and subsequent anti-cancer treatments collected every 8 weeks until the final data cut-off. However, serious adverse events (SAEs) will be collected for those patients continuing on study treatment.

Post-randomisation gefitinib toxicity should be managed by dose interruptions, to allow recovery from the AE or improvement to Common Terminology Criteria for Adverse Events (CTCAE) grade 1. Previous studies have allowed up to 14 days' dose interruption; however, in order to support management of toxicity that patients may experience due to a combination of gefitinib- and pemetrexed-based chemotherapy, and to fit in with the visit schedule, if required interruptions will be

allowed for up to a maximum of 3 weeks on each occasion. Chemotherapy-related toxicity will be managed as per standard clinical practice and pemetrexed/cisplatin prescribing information. Patients who are not able to tolerate the combination of chemotherapy plus study treatment due to repeated CTCAE grade 3–4 toxicity may need to discontinue the randomised treatment (gefitinib or placebo). In these cases, requests for further use of randomised treatment after completion of chemotherapy need to be discussed with an AstraZeneca representative for agreement on management. As all patients have tolerated at least 6 months of gefitinib treatment prior to randomisation, it is expected that patients will recommence randomised treatment (gefitinib or placebo) once chemotherapy is completed.

All randomised patients will be asked to provide a mandatory diagnostic tumour sample where available, optional tumour samples at first progression (i.e. at enrolment) and second progression (i.e. on study), as well as mandatory blood samples for exploratory biomarker analysis to help ascertain the key molecular subtypes which may predict a relative treatment effect.

Figure 1. Study flow chart



*PD based on radiological evaluation, using modified Jackman's criteria to define patients with acquired resistance to prior gefitinib

** Primary DCO for analysis estimated to occur 11 months following the last patient randomized (approximately 190 PFS events, 125 OS events). After primary PFS analysis, patients will then continue to be followed up until final data cut-off (70% OS maturity).

Table 1. Study plan

Visit description	Screening [a]	Randomization	Treatment visits				Discontinuation from treatment	Safety follow-up	Post treatment follow-up until progression [c]	Post-progression survival follow-up [d]	Additional survival follow-up post primary data cut-off
Visit Number	1	2	3	4	5	6+ [b]	50	51	52+	80+	100+
Visit window (days)			± 3	± 3	± 3	± 3		+ 3	± 3	± 3	± 3
Weeks	- 4 to 0	0	3	6	9	12 onwards		(30 days after last dose of study drug)	6 weekly relative to randomization	8 weekly relative to progression	8 weekly relative to progression
Signed informed consent	X										
Inclusion/Exclusion criteria	X										
WHO Performance Status	X										
Medical & Surgical History (incl. demography / smoking history)	X										
Treatment compliance between progression and randomisation [e]		X									
Documented radiological disease progression	X										
Where available, diagnostic slides or blocks from original diagnostic sample (histology or cytology) [f]	X										
Optional Biopsy or Cytology [g]	X						X [h]				
Tumour Assessment using RECIST 1.1 [i]	X			X		X			X		
Extent of disease	X										

Visit description	Screening [a]	Randomization	Treatment visits				Discontinuation from treatment	Safety follow-up	Post treatment follow-up until progression [c]	Post-progression survival follow-up [d]	Additional survival follow-up post primary data cut-off
Visit Number	1	2	3	4	5	6+ [b]	50	51	52+	80+	100+
Visit window (days)			± 3	± 3	± 3	± 3		+ 3	± 3	± 3	± 3
Weeks	- 4 to 0	0	3	6	9	12 onwards		(30 days after last dose of study drug)	6 weekly relative to randomization	8 weekly relative to progression	8 weekly relative to progression
Blood (10ml) sampling for serum exploratory biomarker analysis	X			X		X	X				
Blood (10ml) sampling for plasma exploratory biomarker analysis	X			X		X	X				
Physical Exam	X	◄ As clinically indicated ►									
HRQoL (FACT-L and EQ-5D) [j]		X	X	X	X	X	X		X	X	
Vital signs [k]	X	◄ As clinically indicated ►									
Concomitant medications	X	X	X	X	X	X	X	X			
Clinical chemistry/haematology [l]	X		X	X	X	X	X				
Urine analysis	X	◄ As clinically indicated ►									
Pregnancy test (Female patients with childbearing potential only)	X	◄ As clinically indicated ►									
12- lead ECG	X	◄ As clinically indicated ►									
Adverse Events/ SAEs	X	X	X	X	X	X	X [n]	X [n]			X [o]

Visit description	Screening [a]	Randomization	Treatment visits				Discontinuation from treatment	Safety follow-up	Post treatment follow-up until progression [c]	Post-progression survival follow-up [d]	Additional survival follow-up post primary data cut-off
Visit Number	1	2	3	4	5	6+ [b]	50	51	52+	80+	100+
Visit window (days)			± 3	± 3	± 3	± 3		+ 3	± 3	± 3	± 3
Weeks	- 4 to 0	0	3	6	9	12 onwards		(30 days after last dose of study drug)	6 weekly relative to randomization	8 weekly relative to progression	8 weekly relative to progression
Dispense Study Drug using IWRS/IVRS		X				X					
Drug Accountability/ Compliance						X	X				
Survival data										X [p]	X
Additional study drug [q]	X	◄ Maximum of 6 cycles ►									
Post study treatment - progression cancer therapy								X	X	X	X

[a] Patients should preferably be screened and eligibility decided as quickly as possible to shorten the time from documented radiological progression to start of pemetrexed in combination with cisplatin and randomised study medication. From -28 - 0 days is preferred. Following progression (but before randomization) continuation of gefitinib is encouraged. However, if a patient stops taking gefitinib treatment, the maximum allowed time off treatment prior to randomization is 4 weeks. All other screening assessments must be completed within the specified 28 days.

[b] Patients will have treatment visits every 6 weeks from visit 6 onwards.

[c] Patients who do not have objective disease progression at treatment discontinuation will continue to attend clinic visits every 6 weeks (as per their original visit schedule) until objective disease progression or the data cut-off for analysis, whichever occurs earliest.

[d] Survival information including safety and anti-cancer treatment should be collected after objective disease progression at every 8 weeks until death, withdrawal of consent, loss to follow up or final data cut-off for analysis, whichever occurs earliest.

[e] The information about treatment compliance between first progression and randomization need to be recorded in the medical record (number of days gefitinib used) as obtained from the patient.

[f] Where EGFR diagnosis samples are available, collection is mandatory. Histological samples are preferred, but cytology samples will be accepted. For histology samples blocks are preferred. If blocks were not available, we would accept 10-20 slides.

[g] Biological samples for optional Biomarker Research Informed Consent Form should be signed by the patients before sampling.

[h] The Optional Biopsy or Cytology sample on 2nd progression needs to be collected only if a baseline progression sample has been taken.

[i] RECIST 1.1 assessment will be performed (using CT or MRI scans of chest and abdomen, including liver and adrenal glands). Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 4 weeks before the start of treatment, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 6 weeks after randomization (within a window of +/- 7 days of the scheduled date) until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

[j] HRQoL (FACT-L and EQ-5D) questionnaires will be administered at visits 2-6 by paper and pencil, then every 6 weeks until progression, at progression and 8 weeks after progression.

[k] Please refer CSP section 6.4.8 for vital signs to be recorded in the study.

[l] INR (PT) will be performed locally for patients on warfarin as per the local practice.

[n] SAEs occurring more than 30 days after discontinuation of study treatment should be reported if they are considered to be related to the study treatment by the investigator. These SAEs will be not entered into the study database but should be reported to AstraZeneca within requested timeframe.

[o] Adverse Event information need to be collected during additional survival follow-up post primary data cut-off, only for those patients still on study treatment without disease progression.

[p] Immediately following the primary & final data cut-off all patients remaining in the study should be contacted so that survival status can be confirmed and recorded in the eCRF. This may require an additional unscheduled survival contact.

[q] Pemetrexed in combination with cisplatin treatment will be administered in cycles as instructed on the prescribing information (See section 5.5.3.2 for information on required pre-medication).

2.2 Patient enrolment, randomisation and initiation of double-blind investigational product

The Principal Investigator will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed.
2. Assign a potential subject a unique enrolment number, beginning with 'E#' using the Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS) at screening (Visit 1). The 'E-code' allocated at screening will be used throughout the entire study.

3. Determine subject eligibility.
4. Assign the eligible subject a unique randomisation code/treatment code, using IWRS/IVRS at randomisation visit (Visit 2).
5. Allocate kit ID using IWRS/IVRS and dispense study drug.
6. Re-screening is not allowed in the study.
7. If patients have been withdrawn from participation in the study, they cannot re-enter into the study.
8. If a subject withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

2.2.1 Procedures for randomisation

Eligible patients will be randomised in a 1:1 ratio to receive either:

- Gefitinib 250 mg in addition to cisplatin plus pemetrexed combination chemotherapy
  or
- Matching placebo to gefitinib 250 mg in addition to cisplatin plus pemetrexed combination chemotherapy.

Study site is considered a stratification factor for randomisation.

Once a subject's eligibility has been confirmed, the investigator (or delegated study site staff) will assign the randomisation code/treatment code using IWRS/IVRS at randomisation visit (Visit 2). Patients will be randomised on a 1:1 basis, stratified by centre. The IWRS/IVRS will inform the investigator of the subject randomisation code to be allocated. The subject randomisation code will correspond to a randomised treatment allocation. Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation.

2.3 Blinding and procedures for unblinding the study

2.3.1 Methods for ensuring blinding

All packaging of active tablets and their respective matching placebo (i.e. gefitinib 250 mg) will be identical.

2.3.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised subject, will be available to the investigator(s) or pharmacists at the study centre from the IWRS/IVRS. Routines for this will be described in the IWRS/IVRS user manual that will be provided to each centre.

2.4 Treatments

2.4.1 Identity of investigational product(s)

AstraZeneca will supply gefitinib to the investigator as brown, film-coated, round-shaped tablets. Descriptive information for gefitinib can be found in the Investigator Brochure (IB; **for Japan only –** it can be found in the package insert).

Table 2. Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Gefitinib	250 mg tablet	AstraZeneca
Placebo to match gefitinib	250 mg tablet	AstraZeneca

The above mentioned gefitinib or matching placebo to gefitinib will be provided to subjects as per their randomisation code in addition to cisplatin plus pemetrexed combination chemotherapy.

2.4.2 Doses and treatment regimens

Eligible patients will be treated with either gefitinib 250 mg or placebo (once daily administration) continuously from Visit 2 (start of study treatment) until criterion for discontinuation is met (see **Section 3**). Gefitinib tablets will be taken about the same time each day.

After the study analysis for PFS and OS, patients will have their treatment unblinded. Patients receiving gefitinib and still considered to be gaining benefit will be provided with an option for continued gefitinib treatment. This will be via standard commercial and reimbursement routes or via open-label clinical study supply if the commercial supply route is not possible.

2.4.3 Additional study drug

Cisplatin plus pemetrexed combination chemotherapy is considered an additional study drug as it will be administered along with either gefitinib 250 mg or matching placebo. The recommended dose of pemetrexed is 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each cycle. The recommended dose of cisplatin is 75 mg/m^2 BSA infused over two hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each cycle (see also cisplatin prescribing information for specific dosing advice).

This additional study drug (cisplatin plus pemetrexed combination chemotherapy) will be handled by the investigator at the study site as per the prescribing information available in each country and sites should follow their local prescribing policies for required pre-medication. It is preferred to start the pre-treatment to pemetrexed, such as vitamin supplementation, immediately after obtaining informed consent from patients; this is expected to support the start of pemetrexed-based chemotherapy on the day of randomisation.

After a maximum of six cycles of cisplatin plus pemetrexed combination chemotherapy, subjects will continue on blinded gefitinib/matching placebo to gefitinib monotherapy until progression. Pemetrexed maintenance is not allowed after completion of chemotherapy. It is preferred that gefitinib should be taken in the morning either before a meal or with a meal. On Day 1 of each cycle, subjects must wait to take their gefitinib/matching placebo to gefitinib tablets until after the blood sample has been collected.

If the subject inadvertently does not take the dose of investigational product in the morning, he or she may take that day's dose any time up to 10 p.m. that same day. However, if a subject misses taking their scheduled dose and is unable to take the missed dose on the same day, he or she must take the next scheduled dose and the missed dose will not be made up. The missed dose must be documented on the appropriate eCRF. The dose of study treatment may be repeated if vomiting occurs within 30 minutes of taking the study treatment.

The investigator sites need to locally purchase the accepted standard brand of available and commonly used cisplatin plus pemetrexed combination chemotherapy. If required by local country regulations or procedures, AstraZeneca will provide reimbursement for the cost incurred of this additional study drug.

2.4.4 Pre-medication for cisplatin plus pemetrexed combination chemotherapy

All pre-medication for cisplatin plus pemetrexed combination chemotherapy should be collected in the eCRF.

2.4.5 Premedication regimen of cisplatin plus pemetrexed combination chemotherapy

Patients must receive adequate anti-emetic treatment and appropriate hydration prior to and/or after receiving cisplatin. To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration.

To reduce toxicity, patients treated with pemetrexed must also receive vitamin supplementation as per local prescribing guidelines. It is preferred to start vitamin supplementation immediately after obtaining informed consent from patients; this is expected to support the start of pemetrexed-based chemotherapy on the day of randomisation.

- Patients must take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis.
- At least five doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Patients must also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every three cycles thereafter.
- Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

2.4.6 Monitoring of cisplatin plus pemetrexed combination chemotherapy

Patients receiving pemetrexed should be monitored before each dose with a complete blood count, including a differential white cell count (WCC) and platelet count. Prior to each chemotherapy administration, blood chemistry tests should be collected to evaluate renal and hepatic function. Before the start of any cycle of chemotherapy, patients are required to have the following: absolute neutrophil count (ANC) should be $\geq$1500 cells/mm^3 and platelets should be $\geq$100,000 cells/mm^3. Creatinine clearance should be $\geq$45 mL/min. The total bilirubin should be $\leq$1.5 times the ULN. Alkaline phosphatase (AP), aspartate transaminase (AST or SGOT) and alanine transaminase (ALT or SGPT) should be $\leq$3 times the ULN. Alkaline phosphatase, AST and ALT $\leq$5 times the ULN is acceptable if the liver has tumour involvement. Treatment decisions should be based on local laboratory results.

2.5 Concomitant and post-study treatment(s)

2.5.1 Pre-study treatment for cancer

Prior chemotherapy or other systemic anti-cancer treatment (excluding gefitinib) is not allowed. Palliative radiotherapy must be completed at least 4 weeks before start of study treatment with no persistent radiation toxicity.

2.5.2 Concomitant anti-cancer treatment

- No additional systemic anti-cancer treatment may be used prior to discontinuation of study treatment.
- Bisphosphonates for treatment of bone pain or hypercalcaemia are allowed during study treatment.
- Palliative radiotherapy for painful bone metastases or to other non-pulmonary metastatic sites is allowed during study treatment and there is no need to discontinue study treatment.
- Any systemic anti-cancer treatment, radiotherapy or cancer surgery conducted during study treatment or after discontinuation of gefitinib will be collected until death, loss to follow-up, withdrawal of consent or until the data cut-off for analysis is reached.

2.5.3 Other concomitant treatment

Phenytoin, carbamazepine, rifampicin, barbiturates or St John's Wort induce CYP3A4 and may decrease the levels of gefitinib. Co-administration of drugs that cause significant sustained elevations in gastric pH >5 may reduce plasma concentrations of gefitinib and therefore may reduce its efficacy. In order to maintain a homogeneous population to measure efficacy in this study, concomitant use of these drugs is not allowed during study treatment. Patients taking warfarin (coumarin) should be monitored regularly for changes in their prothrombin time (PT) or International Normalised Ratio (INR).

2.5.4 Prohibited medications

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and all concomitant treatments given from screening until 30 days after last dose of study drug should be recorded in the appropriate sections of the eCRF.

2.6 Treatment compliance

The administration of all study drugs (both investigational products and additional study drug) should be recorded in the appropriate sections of the eCRF. Subjects will be asked to return all unused gefitinib investigational product and empty bottles to the investigator at each scheduled visit during treatment period; the investigator will retain these until they are collected by AstraZeneca Pharmaceuticals authorised personnel, along with any study treatments not dispensed. The subject will be asked about gefitinib compliance at each study visit. Gefitinib compliance will also be assessed based on returned tablet counts.

Tablet counts will be recorded in the eCRF. Patients judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of investigational product) may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

3. REASONS FOR EARLY CESSATION OF TRIAL THERAPY

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject who has finished six cycles of chemotherapy should continue on gefitinib or placebo until objective disease progression according to RECIST 1.1
- Subject decision; the subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to study protocol
- Objective disease progression, confirmed by RECIST 1.1, at any time during chemotherapy along with gefitinib/placebo or gefitinib/placebo alone. Symptomatic deterioration needs to be confirmed by radiological evaluation through unscheduled RECIST 1.1
- Incorrect enrolment of the subject (i.e. the subject does not meet the required inclusion/exclusion criteria)
- Subject lost to follow-up

3.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s).
AEs will be followed up, and health-related quality of life (HRQoL) questionnaires and all study

drugs should be returned by the subject. The discontinuation visit should take place after the last dose of gefitinib/placebo or cisplatin plus pemetrexed combination chemotherapy, whichever comes last.

Patients who do not have objective disease progression at treatment discontinuation will continue to attend clinic visits every 6 weeks (as per their original visit schedule) until objective disease progression or the data cut-off for analysis, whichever occurs earliest. Discontinuation visit (Visit 50) will be performed for all of those subjects who discontinued their treatment before objective disease progression.

Subjects who discontinue study treatment due to disease progression should be contacted for survival status every 8 weeks to collect survival information including safety and anti-cancer treatment until death, withdrawal of consent, loss to follow-up or final data cut off, whichever occurs earliest following the treatment discontinuation visit. Survival status may be collected by telephone contact with the subject, subject's family, or by contact with the subject's current physician. The names and dates of first and subsequent therapies for cancer will be collected after discontinuation of treatment.

Patients who discontinue study treatment prior to progression will continue with visits every 6 weeks until documented progression, withdrawal of consent, loss to follow-up or data cut off for primary PFS analysis, whichever occurs earliest. Following the primary data cut-off (when 190 PFS events have occurred), data collection will be limited to survival status and subsequent anti-cancer treatments collected every 8 weeks. However, SAEs will be collected for those patients continuing on study treatment.

Following discontinuation of all study treatment, subjects may receive any subsequent therapy for NSCLC at the discretion of the investigator. After discontinuation of study treatment, all systemic anti-cancer treatment, radiotherapy or cancer surgery will be collected until death, loss to follow-up, withdrawal of consent or until the final data cut-off for analysis is reached.

New-onset AEs, including SAEs, will be recorded into the eCRF until 30 days after discontinuation of the investigational product. The patient will be followed up for progression in line with the study plan, unless he/she has withdrawn consent to both study treatment and study assessments, or has died.

All AEs and SAEs ongoing at 30 days after discontinuation of study treatment must be followed until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. SAEs occurring more than 30 days after discontinuation of study treatment should be reported if they are considered to be related to the study treatment by the investigator. These SAEs

will be not entered into the study database but should be reported to AstraZeneca within the requested timeframe.

Provision will be made for subjects who are not progressed at the time of the data cut-off and/or have benefit from the study drug to continue to be treated with gefitinib outside this CSP (e.g. named patient programme or other supply).

Treatment discontinuation should be reported via IWRS/IVRS by the investigator or delegate.

For Japan − the first paragraph of this section will be replaced with the following:
A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s), as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. AEs will be followed up (see **Sections 4.4.3** and **4.4.4**); and health-related quality of life (HRQoL) questionnaires and all study drugs should be returned by the subject. The discontinuation visit should take place after the last dose of gefitinib/placebo or cisplatin plus pemetrexed combination chemotherapy, whichever comes last.

3.2. Withdrawal from study

3.2.1 Randomised patients

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Events will be followed up; HRQoL questionnaires and all study drugs should be returned by the subject. Withdrawn subjects will not be replaced. Pregnant patients confirmed by a pregnancy test or otherwise verified will be withdrawn from the study.

It will be established if the subject is only withdrawing from study treatments and is willing to remain in follow-up with full or limited assessments or if they are withdrawing completely from the study.

The reason for withdrawal from the study should be recorded on the eCRF. Patients will be considered to have withdrawn from the study only due to the following reason:

- Subject decision (patients withdraws consent from participating in the study)
- Death
- Subject lost to follow-up.

Patients who withdraw from the study should always be asked specifically whether they are withdrawing or continuing their consent for the optional biomarker research. The investigator or delegate should inform AstraZeneca of the withdrawal from this aspect of the study.

3.2.2 Screening failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study and are therefore not randomised. These patients should have their reason for study withdrawal recorded as 'Incorrect enrolment'.

4. COLLECTION OF STUDY VARIABLES

4.1 Recording of data

The Rave Web-Based Data-Capture (WBDC) system will be used for data collection and query handling. Data must be entered into the WBDC system at the investigational centre within 72 hours after the scheduled visit (except for SAEs that should be entered within 1 calendar day). When data have been entered, reviewed, edited and Source Data Verification has been performed by an AstraZeneca representative, the data will be frozen to prevent further editing.

4.2 Data collection at enrolment and follow-up

Data management determines the format of the data to be received from external vendors and co-ordinates the flow of data to an external environment or clinical database (if applicable). The study Data Management Plan will describe in greater detail the methods used to collect, check and process clinical data.

AEs and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All the SAEs in the clinical database will be

reconciled with the safety database and any discrepancy between the clinical and safety database will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

4.2.1 Enrolment procedures

As subjects are screened for the study at Visit 1, they must be allocated an E-code. The E-code is a 7-digit number. The first step to assign an E-code is obtaining consent from the subject without mentioning the E-code. Subsequently, perform an enrolment call by using the IWRS/IVRS system, where the system will assign the E-code for the subject. Then enter the same E-code in two original sets of the Informed Consent Form, both signed and dated (one of them must be given to the subject and the other filed at the study centre). This number is the subject's unique identifier and is used to identify the subject in the study. All screened subjects are assigned an E-code irrespective of whether or not they are subsequently randomised to receive study treatment. The actual treatment given to individual subjects will be determined by their randomisation code. The randomisation scheme will be stratified by centre. If a subject discontinues from the study, the subject E-code number will not be reused, and the subject will not be allowed to re-enter the study.

Subject eligibility will be established before treatment randomisation. Subjects will be randomised strictly sequentially, as subjects are eligible for randomisation. Once the eligibility of a subject has been confirmed, the investigator (or nominated assistant) should assign the subject randomisation code and allocate randomised therapy using the IWRS/IVRS. Subjects will be identified to the IWRS/IVRS by using subject initials, E-code and date of birth. The IWRS/IVRS system will inform the investigator of the subject randomisation number and treatment to be allocated. The subject randomisation code will correspond to either cisplatin plus pemetrexed combination chemotherapy plus gefitinib or cisplatin plus pemetrexed combination chemotherapy plus placebo.

4.2.2 Follow-up procedures

Patients who discontinue study treatment for reasons other than objective disease progression will be scheduled for post-treatment follow-up until progression. Upon documentation of objective disease progression, all patients will enter survival follow-up. Survival information should be collected every 8 weeks until death, withdrawal of consent, loss to follow-up or final data cut-off for analysis, whichever occurs earliest. For AE reporting during follow-up, please refer to **Sections 4.4.3** and **4.4.4**.

4.3 Efficacy

4.3.1 Tumour assessments by imaging techniques using RECIST

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS times, objective response rates (ORR), disease control rate (DCR). The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions (NTLs) and the objective tumour response criteria (complete response [CR], partial response [PR], SD or progression of disease [PD]) are presented in **Appendix F.**

The methods of assessment of tumour burden used at baseline – CT or MRI scans of chest and abdomen, including liver and adrenal glands – must be used at each subsequent follow-up assessment. Any other areas of the disease involvement should be additionally investigated based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 4 weeks before the start of treatment, and ideally should be performed as close as possible to the start of study treatment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 6 weeks after randomisation (within a window of +/- 7 days of the scheduled date) until objective disease progression as defined by RECIST 1.1. Any other sites at which new disease is suspected should be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled

assessment, or sooner if clinically indicated, and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status. Following progression, patients should continue to be followed up for survival every 8 weeks as outlined in the study plan.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in **Section 2**.

Central reading of scans

An independent review of all scans used in the assessment of tumours using RECIST 1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

The primary analysis of the RECIST-derived outcome variables will be based on the tumour assessments recorded on the eCRF (clinical database; as collected via the investigator). Analysis derived from the central review will be considered to be secondary and confirmatory, and will be derived from the independent review visit responses and the dates of the scan assessment visits.

4.3.2 Efficacy variable

Primary variable

The primary endpoint is PFS in patients who have 'acquired resistance' to first-line gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone by using the tool RECIST 1.1 (see **Section 2** for more details on the study plan).

Key secondary variables are to evaluate the following variables in patients who have 'acquired resistance' to gefitinib (see Section 2 for more details on the study plan)

- Overall survival (OS).
- ORR by using RECIST 1.1.
- DCR by using RECIST 1.1.
- Delay in time to worsening and improvement rates measured by the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire Trial Outcome Index (TOI).

4.3.3 Key exploratory variable

- **Biomarker analysis –** Biomarker analysis of putative resistance factors, including but not limited to T790M, cMET amplification and *EGFR* amplification, at baseline to be viewed in isolation as well as to compare to analysis of optional tumour samples at progression in order to assess any changes in biomarker status upon treatment.
- **Change in utility value –** as measured by the EQ-5D questionnaire.

4.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

4.4.1 Definition of AEs

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an

investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

4.4.2 Definition of a serious adverse event (SAE)

A SAE is an AE occurring during any study phase (i.e. run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Any event that results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Any events that are unequivocally due to PD must not be reported as an SAE.

For further guidance on the definition of a SAE, see **Appendix B** to the Clinical Study Protocol.

4.4.3 Recording of AEs

Time period for collection of AEs

AEs and SAEs will be collected from time of signature of informed consent, on Visit 1, throughout the treatment period until 30 days of discontinuation of gefitinib treatment.

Follow-up of unresolved AEs

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

SAEs occurring more than 30 days after discontinuation of study treatment should be reported if they are considered to be related to the study treatment by the investigator. These SAEs will not be entered into the study database but should be reported to AstraZeneca within the requested timeframe (see **Section 4.4.4**). The requirement to follow-up AEs is not intended to delay database lock or production of the Clinical Study Report. These activities should proceed as planned with ongoing AEs if necessary. Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade according to the National Cancer Institute (NCI) CTCAE Version 4.0 and changes of CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Concomitant medications
- AE caused patient's discontinuation from study treatment/withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to...
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to additional study drug
- Description of AE.

Intensity rating scale

The grading scales found in the revised NCI CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in **Section 4.4.2**. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The investigator will assess causal relationship between the investigational product and each AE, and answer 'yes' or 'no' to the question, 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?' For SAEs, causal relationship will also be assessed for other medication and study procedures and additional study drug. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'. A guide to the interpretation of the causality question is found in **Appendix B** to the Clinical Study Protocol.

AEs based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you/the child had any health problems since the previous visit/you were last asked?'*, or revealed by observation, will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

AEs based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values/vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical rather than the laboratory term (e.g. anaemia vs. low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Potential Hy's law cases: laboratory values consistent with Hy's law (AST or ALT at least 3 x ULN or total bilirubin at least 2 x ULN) are usually reported as SAEs in AstraZeneca studies. This is not necessary for gefitinib because the safety profile is well established and already contains hepatitis with fatal outcomes among the listed possible adverse drug reactions. Abnormal laboratory results will not be reported as SAEs in this study unless they are associated with an event that fulfils serious criteria, in which case the event will reported according to the instructions provided above.

Disease progression

Disease progression can be considered as a worsening of a subject’s condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing, metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

Lack of efficacy

When there is deterioration in the condition for which the study treatment is being used (i.e. NSCLC), there may be uncertainty whether this is lack of efficacy or an AE. In such cases, unless AstraZeneca or the reporting physician considers that the study treatment contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Handling of deaths

Deaths that occur during the study will be reported as follows:

- Death, which is clearly as a result of disease progression, should not be reported as an SAE. It will be documented in the 'Death module' of the eCRF within 72 hours and it should be communicated to the study monitor at the next monitoring visit.
- Where death is not due (or not clearly due) to PD under the study, the AE causing the death must be reported as an SAE within 1 calendar day (see **Section 4.4.4** for instructions). The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign a single primary cause of death together with any contributory causes. 'Death module' of the eCRF should be completed within 72 hours.
- Deaths with an unknown cause should always be reported as an SAE (see **Section 4.4.4**), but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death and, if performed, a copy of the post-mortem results (with translation of important parts into English) should be forwarded to AstraZeneca, Patient Safety within the usual timeframes. 'Death module' of the eCRF should be completed within 72 hours.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be disease progression.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the defined medical procedures to be followed by the investigator**,** regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

4.4.4 Reporting SAEs

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within 1 day, i.e. immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, i.e. immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone or by faxing the paper SAE report.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

For EU: the reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as ‘immediately but no later than the end of the next business day’) of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the SAEs in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s): study code, site number, enrolment code, AE, seriousness, start date.

The following detailed information should be sent to AstraZeneca as soon as it becomes available: severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of AE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and, if applicable, date and cause of death.

In addition, AstraZeneca will provide details of any serious adverse drug reactions reported in this study with regard to the test product for a double-blind study to the head of the study site, Principal Investigator and the regulatory agency. The head of the study site should submit a written report to the International Review Board (IRB) providing the details of all AE case(s) reported by AstraZeneca.

Procedure for reporting SAEs using the WBDC system

The investigator(s) and other site personnel will access the WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate measures to provide a SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into the eCRF via the WBDC system by the investigator(s).

4.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the study plan (see **Table 1**).

The following laboratory variables should be measured and analysed at the local laboratory:

Clinical chemistry

ALT, AST, alkaline phosphatase, total bilirubin, blood urea nitrogen or urea, serum creatinine, potassium, sodium, calcium.

Haematology

ANC count, white blood cell count (total), haemoglobin, platelet count. For patients receiving warfarin (coumarin derivative) concomitantly with gefitinib, INR monitoring should be conducted and recorded in the eCRF.

Urine analysis

Protein, blood

For blood volume, see **Section 5.1**.

Potential Hy's law cases: laboratory values consistent with Hy's law (AST or ALT at least 3 x ULN or total bilirubin at least 2 x ULN) are usually reported as SAEs in AstraZeneca studies. This is not necessary for gefitinib because the safety profile is well established and already contains hepatitis with fatal outcomes among the listed possible adverse drug reactions.

4.4.6 Physical examination

Full physical examination will be performed at enrolment (Visit 1) and then as clinically indicated during the study. Physical examination includes but is not limited to the following: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen and neurological. After Visit 1, any clinically significant new findings or aggravated pre-existent condition should be reported as an AE unless unequivocally related to disease progression. For timings of assessments refer to the study plan (see **Table 1**).

4.4.7 ECG

4.4.7.1 Resting 12-lead ECG

12 lead ECG will be performed at Enrolment (Visit 1). Follow-up ECG will be performed during study only if clinically indicated.

4.4.8 Vital signs

Resting blood pressure, pulse rate, height and weight will be measured. Height will be measured only at screening visit. For timings of assessments refer to the Study Plan (see **Table 1**).

4.4.9 Management of gefitinib toxicity

The safety/tolerability profile of gefitinib is well established. The most common AEs are gastrointestinal disturbances and skin reactions. These events were usually occurring within the first month of treatment, generally mild to moderate, reversible, noncumulative, and manageable by simple medication or a short cessation of the therapy. In this study, all patients have already been exposed to gefitinib as their first-line treatment.

In all cases where the randomised treatment (gefitinib/placebo) has been interrupted or the patient discontinued due to unexpected severe toxicity considered related to gefitinib/placebo, the investigator must contact the AstraZeneca study physician.

Gefitinib dose interruption

Dose interruptions should be used as the first approach to managing toxicity. Repeat dose interruptions are allowed as required, for a maximum of 3 weeks on each occasion. Dose reductions are not permitted in this study. If the randomised treatment (gefitinib/placebo) is discontinued due to repeated interruptions during chemotherapy, the investigator must contact the AstraZeneca study physician to discuss and reach agreement on further management. As all patients have been exposed to gefitinib for at least 6 months prior to randomisation, it is assumed where possible that the patient would recommence randomised treatment following completion of chemotherapy.

Management of skin toxicity

Subjects with poorly tolerated skin toxicity may be managed by providing a brief (maximum of 3 weeks) interruption of gefitinib; the daily dose of gefitinib should then be reinstated. However, the rash may improve without the need for interrupting gefitinib therapy. There is no standard, known or established treatment proven effective for drug-related skin rashes or skin changes due to gefitinib. Most commonly, a pustular rash has been observed, which frequently improves even when the same dose of gefitinib therapy is continued uninterrupted.

Investigators have had varying degrees of success with a variety of agents used to manage skin rashes. These include mild to moderate strength steroid creams, either topical or systemic antihistamines and occasionally retinoid creams. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. The use of oral steroids for dermatological conditions should be discussed with an AstraZeneca study physician. Dry skin can be managed with simple emollients.

Management of gastrointestinal (GI) toxicity

If GI toxicity is not appropriately managed, this may be associated with the development of dehydration. Subjects should be advised to seek medical advice promptly in the event of developing severe or persistent diarrhoea, nausea, vomiting or anorexia.

Nausea and/or vomiting

In patients who have vomiting and are unable to retain gefitinib, every attempt should be made to control the nausea and vomiting. The dose of gefitinib may be repeated if vomiting occurs within 30 minutes of taking the tablet.

Diarrhoea

Diarrhoea has been successfully managed with anti-diarrhoeal agents such as loperamide.

- CTCAE grade 1−2 diarrhoea: no specific supportive care is usually needed or indicated. Oral fluid intake should be encouraged.
- CTCAE grade 3 or 4 diarrhoea: if this occurs, immediate supportive care measures should be initiated and gefitinib should be interrupted for up to a maximum of 3 weeks until resolution,

or until the diarrhoea has decreased in severity to CTCAE grade 1. If CTCAE grade 3 or 4 diarrhoea recurs, and in the investigator's opinion cannot be controlled by further drug interruptions and optimal symptomatic management, then gefitinib should be discontinued.

- If a CTCAE grade 4 diarrhoea is associated with haemodynamic collapse, gefitinib should be discontinued, the investigator should notify the AstraZeneca study physician, and it should be reported as a SAE.

Liver transaminases

Liver function test abnormalities (including increases in ALT, AST, bilirubin) have been observed, uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure, which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. Gefitinib should be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Ophthalmology

Patients presenting with signs and symptoms suggestive 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 ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with IRESSA™ should be interrupted, and if symptoms do not resolve, or recur on reintroduction of IRESSA™, permanent discontinuation should be considered.

Management of interstitial lung disease (ILD)

ILD, including interstitial pneumonitis, is a common complication of lung diseases including advanced lung cancer, regardless of treatment. It has also been widely observed in clinical studies in which chemotherapy (incidence generally ranges from 3 to 6%) and/or radiotherapy (incidence generally ranges from 10 to 15%) has been used for the treatment of advanced lung cancer.
ILD, which may be acute in onset, has been observed in approximately 1% of patients treated with gefitinib. These patients usually present with a fairly acute onset of dyspnoea, sometimes associated with cough or low-grade fever. This may become quite severe within a short period of time and usually results in hospitalisation. Radiological investigations, often including CT scan, frequently show pulmonary infiltrates or interstitial shadowing with ground glass appearance. There is often respiratory distress with arterial oxygen de-saturation. Cultures are frequently negative for bacterial growth. In a number of cases, the event has responded to steroid therapy but this is not always so and some cases have been fatal. Patients with concurrent idiopathic pulmonary fibrosis, interstitial

pneumonia, pneumoconiosis, radiation pneumonia or drug-induced pneumonia have been observed to have an increased mortality rate from this condition.

If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient promptly investigated for ILD. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

4.4.10 Management of chemotherapy toxicities

The safety/tolerability profile of doublet chemotherapy is also well established. The most common side effects are bone marrow suppression manifested as neutropenia, leukopenia, thrombocytopenia and anaemia; and GI toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, mucositis and stomatitis. Other undesirable effects include renal toxicities, increased transaminases, fatigue, dehydration, rash and neuropathy. Local practice, prescribing information and clinical judgement should be followed for the management of toxicities.

Overlapping toxicities between gefitinib and chemotherapy

GI toxicities, in particular nausea, vomiting, diarrhoea, liver transaminases elevation, interstitial lung disease, are considered the major overlapping toxicities of chemotherapy and gefitinib. Please refer to **Section 4.4.9** for management of these toxicities and **Section 4.4.11** for guidance on the assessment of respiratory symptoms.

The investigator should always consider the interruption of gefitinib first in order to maintain chemotherapy dose and schedule. If a patient develops overlapping toxicities, the chemotherapy dose should be adjusted as appropriate according to packaging insert, local practice and clinical judgement. Gefitinib dose interruption is allowed up to a maximum of 3 weeks on each occasion. If gefitinib is interrupted for longer periods to allow chemotherapy administration, the investigator may still consider re-starting gefitinib when symptoms have improved, toxicities have resolved or chemotherapy has been completed.

4.4.11 Guidelines for the assessment of patients developing new onset or worsening of respiratory symptoms

If, during the course of the study, a patient develops new onset, or worsening of existing respiratory symptoms then gefitinib should be temporarily interrupted and investigations undertaken to define the aetiology of these symptoms. Clinical investigation (radiological studies and pulmonary function

studies) should be strongly considered. Specialist pulmonary consultation should also be considered. Further clinical management will be dictated by the results of these investigations and the patient's clinical condition.

- **Clinical presentation and investigations indicate a diagnosis other than ILD:** patients should receive appropriate therapy, which will vary according to the specific diagnosis made (e.g. intercurrent infection, progressive disease, pulmonary oedema, pulmonary embolus). Depending on the clinical situation, gefitinib may or may not need to be discontinued. This will be at the discretion of the investigator but if there is any uncertainty, the investigator should contact AstraZeneca.

- **Clinical presentation and investigations indicate/suggest a diagnosis of ILD:** gefitinib should be discontinued and an attempt should be made to define the extent of and a specific aetiology for the ILD (e.g. radiation pneumonitis, viral or fungal infections, pulmonary fibrosis). This is likely to require high-resolution CT scanning and full pulmonary function testing, with measurement of transfer factor. Additional investigations such as bronchoalveolar lavage, trans-bronchial biopsy or video-assisted trans-thoracic biopsy should also be undertaken if clinically appropriate. Specialist pulmonary consultation is strongly recommended. The patient should receive all therapeutic and supportive intervention deemed appropriate by the investigator. The use of corticosteroids should be considered.

- **Clinical presentation and investigations inconclusive:** in this situation, the continued administration of gefitinib should be at the discretion of the investigator. However, if there is any uncertainty regarding the continuation of study medication, the investigator should contact AstraZeneca. The patient should be closely monitored for further changes in respiratory symptoms, which may indicate the need for additional or repeat investigations and/or specialist pulmonary consultation. If additional or repeat investigations indicate/suggest a diagnosis of ILD, the patient should be managed as described above.

4.4.12 Other toxicity

For any other CTCAE grade 3 or 4 toxicity or any clinically significant lower-grade toxicity, randomised treatment (gefitinib/placebo) should be interrupted for a maximum of 3 weeks until the subject recovers completely or the toxicity reverts to CTCAE grade 1 or to the baseline grade. In all cases where the subject has been withdrawn due to unusual or unusually severe toxicity considered related to gefitinib, the investigator must contact the AstraZeneca study physician.

4.5 HRQoL

4.5.1 QoL − Functional Assessment of Cancer Therapy − Lung (FACT-L)

Data on QoL will be assessed using the FACT-L. FACT-L has been validated with respect to its psychometric properties and sensitivity to clinical changes (*Cella DF et al 2002; Cella DF et al 1995*). This questionnaire has been used in many clinical studies in patients with advanced lung cancer, including previous AstraZeneca studies, and is appropriate, valid and sensitive to clinical changes in this study population.

4.5.2 EQ-5D

The questionnaire will be completed by patients as per HRQoL in **Table 1**. Further information about the questionnaire can be found in **Section 4.9**.

4.5.3 Administration of HRQoL questionnaires

Each centre must allocate the responsibility for the administration of the HRQoL questionnaire to a specific individual (e.g. a research nurse, study co-ordinator) and if possible assign a back-up person to cover if that individual is absent. The AstraZeneca Study Delivery Team (or delegate) will provide relevant training in administration of the questionnaires. The paper questionnaire must be administered and completed at the clinic as per the study plan (**Table 1**).

HRQoL (FACT-L and EQ-5D) questionnaires will be administered at Visits 2 to 6 by paper and pencil, than every 6 weeks until progression, at progression and 8 weeks after progression. However, during the post-progression survival follow-up before primary data cut-off, it is anticipated that the forms will be completed at home and then posted to the investigator site, following a phone call from the site. It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the HRQoL questionnaire are as follows:

- It must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions.
- It must be completed in private by the patient.
- The patient should be given sufficient time to complete it at their own speed.

- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire (e.g. is blind or illiterate), the questionnaire may be read out by trained clinic staff and responses recorded.
- On completion of the questionnaire, it should be handed back to the person responsible for questionnaires who should check for completeness.
- Only one answer should be recorded for each question. Data from the paper questionnaire will be transcribed at the investigator site onto the eCRF.

4.6 Pharmacokinetics (not applicable)

4.7 Pharmacodynamics

4.7.1 Collection of biomarkers

The proposed sample collection and proposed exploratory biomarker analyses will help ascertain the key molecular subtypes which may predict for a relative treatment effect. Samples will not be used for heritable DNA analysis. Multiple different sample types will be collected for this purpose as detailed in **Table 3** below.

Table 3 Biomarker sample in the study

Sample	Type/ Condition	Screening/ Visit 1	Visit 4, 6, (then every 6 weeks)	Discontinuation from treatment	Post-treatment follow-up until progression
Diagnostic Biopsy/ Cytology (10-20 sections/ block)	Historical/ Mandatory (where available)	X			
10 mL blood for preparation of serum and 10 mL blood for preparation of plasma	New/ Mandatory	X	X	X	
Optional Biopsy/ Cytology	New/ Optional	X			X Only collect if have 1st progression sample

4.7.1.1 Mandatory collection of diagnostic tumour sample for exploratory biomarker analysis

Collection may enable biomarker analysis of putative resistance factors, including but not limited to T790M, c-Met amplification and *EGFR* amplification at baseline to be viewed in isolation as well as to compare to analysis of optional tumour samples at progression in order to assess any changes in biomarker status upon treatment.

4.7.1.2 Mandatory collection of blood samples for exploratory biomarker analysis

Plasma and serum samples will be collected as a source of cfDNA for mutation analysis. Such analysis may allow for temporal assessment of *EGFR* mutation status, thus monitoring mutation status on treatment to progression.

4.7.1.3 Optional collection of tumour biopsy/cytology sample at progression for exploratory biomarker analysis

Collection may enable biomarker analysis of putative resistance factors, including but not limited to T790M and c-Met amplification, at point of first progression, i.e. at enrolment, and second progression, i.e. on study to be viewed in isolation as well as to compare to baseline analysis of diagnostic sample and first progression sample, respectively. Treatment arms will not be unblinded at the second progression, since it may impact on the survival and standard care is available for both arms. However, T790M result of those patients who require such information for further therapy guidance, and who provide a valid sample, may be provided to investigators after the second progression sample is received.

4.8 Pharmacogenetics (not applicable)

4.9 Health economics

The EQ-5D questionnaire is a standardised measure of health status, developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The information can be converted into a single index value of health status, generally ranging from 0, representing a health state of being dead, to 1, representing a health state of full health. It consists of the EQ-5D descriptive system (comprising 5 dimensions – mobility, self-care, usual activities, pain/discomfort and anxiety/depression) plus an overall rating of health status measured on a Visual Analogue Scale. Collection of EQ-5D data is discussed in **Section 4.5.2**.

5. BIOLOGICAL SAMPLING PROCEDURES

5.1 Volume of blood

The total volume of blood that will be drawn from each subject in this study is as follows (**Table 4**).

Table 4 Definitions of Analysis Populations

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical Chemistry	5 approximately a	15	75 c
	Haematology	3 approximately a	15	45 c
Mandatory blood samples for exploratory biomarker (2 x 10ml)		20	8 b	160
Total		28	15	280

5.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here. Biological samples for future research might be retained at AstraZeneca and/or at Central Laboratory, on behalf of AstraZeneca, for a maximum of 25 years following the last subject's last visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately.

5.2.1 Pharmacodynamic samples

5.2.1.1 Biomarker samples

Biomarker samples will be shipped to a central laboratory for co-ordination of exploratory sample analysis as detailed below.

5.2.1.2 Mandatory collection of diagnostic tumour sample for exploratory biomarker analysis

Where available, blocks or slides from original diagnostic histology or cytology samples will be collected at enrolment. Cytology samples may include, but not limited to: pleural fluids, fine needle aspirations (FNA) and bronchoalveolar lavage (BL).

The investigator will be asked to provide one of the following for each consenting patient, in order of preference:

1. Formalin-fixed, paraffin-embedded tumour tissue blocks, or cytology blocks where no histological samples are available.
2. 10–20 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 µm thick.
3. 10–20 re-cut unstained sections from formalin-fixed paraffin-embedded cytology block, presented on slides. Each section is to be 5 µm thick.
4. Cytology smears.
5. Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual.

5.2.1.3 Mandatory collection of blood samples for exploratory biomarker analysis

All consenting patients will be asked to provide mandatory blood samples for exploratory biomarker research. The investigator will be asked to provide the following for each consenting patient:

- 10 mL blood for preparation of serum
- 10 mL blood for preparation of plasma.

Samples will be collected at screening as well as throughout the study up to and including second progression according to the study plan (see **Table 1**). Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual. For blood volume, see **Section 5.1**.

5.2.1.4 Optional collection of tumour biopsy/cytology sample at progression for exploratory biomarker analysis

Patients will be asked to undertake an optional study-specific procedure to collect tumour samples at first progression, i.e. at enrolment, as well as second progression, i.e. on study. Optional biopsy or cytology samples at the time of second progression will only be collected if a first-progression sample has been taken. Cytology samples may include, but not limited to: pleural fluids, FNA and BL.

The investigator will be asked to provide one of the following for each consenting patient, in order of preference:

1. Formalin-fixed, paraffin-embedded tumour tissue blocks, or cytology blocks where no histological samples are available.
2. 10–20 re-cut unstained sections from formalin-fixed paraffin-embedded tumour tissue block, presented on slides. Each section is to be 5 μm thick.
3. 10–20 re-cut unstained sections from formalin-fixed paraffin-embedded cytology block, presented on slides. Each section is to be 5 μm thick.
4. Cytology smears.

Patients who decline optional collection of tumour biopsy/cytology sample are still free to remain in the study. Samples will be collected, labelled, stored and shipped as detailed in the laboratory manual.

6. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

6.1 Calculation or derivation of efficacy variable(s)

RECIST 1.1 assessments

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST 1.1 (see **Appendix F**). At each visit, patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

If a patient has had a tumour assessment, which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE), unless there is evidence of progression, in which case the response will be assigned as PD.

For a visit to be evaluable then all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A NTL visit response of PD is recorded

- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥5mm, from nadir even assuming the non-recorded TLs have disappeared.

6.1.1 Primary endpoint

Progression-free survival (PFS)

The primary endpoint of PFS is defined as the time from randomisation until objective disease progression as defined by RECIST 1.1 based on the investigator measurements or death (by any cause in the absence of progression).

Patients who have not progressed or died at the time of the statistical analysis will be censored at the time of their last evaluable RECIST assessment. However, if the subject progresses or dies after two or more missed visits, the subject will be censored at the time of the latest evaluable RECIST assessment. If the subject has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within two visits of baseline.

The primary analysis of PFS will be based on RECIST results programmatically determined from investigators assessments.

6.1.2 Secondary endpoints

Overall survival (OS)

OS is defined as the time from the date of randomisation until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Objective Response Rate (ORR)

ORR rate is defined as the number (%) of subjects with at least one visit response of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR.

Disease Control Rate (DCR)

DCR is defined as the percentage of patients who achieved disease control at 6 weeks following randomisation. Disease control at 6 weeks is defined as a best objective response of CR, PR or SD ≥6 weeks. If a patient experiences a CR/PR very shortly after starting treatment but then progresses or becomes NE by 6 weeks, then they will not be included as having disease control at 6 weeks. The DCR will be calculated as the percentage of patients with CR or PR or SD ≥6 weeks.

6.1.3 Exploratory endpoints

Refer to **Section 6.4**.

6.2 Calculation or derivation of safety variable(s)

All AEs will be listed for each patient and summarised according to the system organ class (SOC) and preferred term assigned to the event using MedDRA. AEs will be graded according to the NCI CTCAE; the CTCAE grade will be assigned by the investigator.

At the point of the data cut-off for the statistical analysis, any patients still on treatment and gaining benefit can continue to receive study treatment. However, no further data will be entered on to the clinical database. The sites must continue to report any SAEs for pharmacovigilance purposes.

Changes from baseline (i.e. latest available value pre-first dose of study treatment) will be calculated for laboratory and vital signs outcome variables. Laboratory values outside laboratory reference ranges will be identified.

6.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and Discontinuation of Investigational Product due to Adverse Event (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

6.2.2 Calculation or derivation of patient-reported outcome variables

The methods for collecting patient-reported outcomes data are presented below.

6.2.3 QoL – FACT-L

Please refer **Section 4.5**.

6.2.4 Derivation or calculation of variable

The following subscale scores will be derived from the FACT-L questionnaire:

- The physical well-being (PWB), functional well-being (FWB), social/family wellbeing (SWB), emotional well-being (EWB) and Lung Cancer Subscale (LCS) domain scores from the FACT-L questionnaire
- TOI which is the sum of the PWB, FWB and LCS domain scores
- The 7-item LCS total score
- The overall score for the questionnaire (FACT-L) which is the sum of the PWB, FWB, SWB, EWB and LCS domain scores.

If <50% of the subscale items is missing, the subscale score will be divided by the number of non-missing items and multiplied by the total number of items by the subscale. If 50% or more of the data items are missing, that subscale will be treated as missing. The reason for any missing data will be identified. If data is missing at random, the above techniques will be used. If there is evidence that the missing data is systematic, missing values will be handled to ensure that any possible bias is minimised.

6.2.4.1 Change in QoL

Overall improvement will be calculated for FACT-L, TOI and LCS scores based on the changes from baseline. At a given visit, the criteria for a clinically relevant change (*Cella DF et al 2002*) will be used to assign a visit response for each score (see **Table 5**).

Table 5 **FACT-L total score, TOI and LCS: Visit score**

Score	Change from baseline	Visit response
TOI, FACT-L	≥ + 6	Improved
	≤ - 6	Worsened
	Otherwise	No change
LCS	≥ + 2	Improved
	≤ - 2	Worsened
	Otherwise	No Change

FACT-L: Functional Assessment of Cancer Therapy - Lung; LCS: Lung Cancer Subscale, TOI: Trial Outcome Index

At the conclusion of the study, the criteria listed in **Table 6** will be used for each score, based on the individual visit responses, to assign a best overall score response.

Table 6 **FACT-L total score, TOI and LCS overall response**

Best overall response	Criteria [a]
Improved	Two visit responses of "improved" a minimum of 21 days apart without an intervening visit response of "worsened"
No change	Does not qualify for overall score response of "improved". Two visit responses of either "no change", or "improved" and "no change" a minimum of 21 days apart without an intervening visit response of "worsened"
Worsened	Does not qualify for overall score response of "improved" or "no change". A visit response of "worsened" without a response of "improved" or "no change" within 21 days
Other	Does not qualify for one of the above

FACT-L: Functional Assessment of Cancer Therapy - Lung; LCS: Lung Cancer Subscale, TOI: Trial Outcome Index

[a] Based upon the visit response derived from change from baseline.

The 'improvement rate' will be calculated as the percentage of all analysed patients with an overall response of improved.

Time to worsening will be defined for FACT-L, TOI and LCS as the interval from the date of randomisation to the first visit response of worsened without a subsequent response of improved or no change within 21 days, or to the date of death if no more than 12 weeks after the last evaluable QOL assessment. If a visit score of worsened has not been observed at the time of analysis, time to worsening will be censored at the last non-missing assessment visit.

Note that the FACT-L questionnaire will be completed at the post-progression follow-up visit for patients progressing up until the time of the PFS (primary) data cut off.

6.3 Calculation or derivation of pharmacokinetic variables (not applicable)

6.4 Calculation or derivation of biomarkers

Exploratory biomarkers may be analysed for patients who have evaluable tumour samples. Such analyses may include, but not limited to:

1. The *EGFR* mutation status detected from the original diagnostic tumour samples will be recorded in the CRF.
2. Tumour samples may be analysed for T790M, c-Met amplification and *EGFR* amplification.
3. Blood samples may be analysed for *EGFR* mutation status.

6.5 Calculation or derivation of pharmacogenetic variables (not applicable)

6.6 Calculation or derivation of health economic variables

The EQ-5D descriptive system comprises five questions which generate possible health states which can be converted into a weighted health status index by applying scores from the appropriate available 'value sets'. The responses on EQ-5D will be used to derive a unique EuroQoL health state. For each EuroQoL health state there exists a corresponding valuation. This valuation will be used for health economic calculations.

Note that the EQ-5D questionnaire will be completed at the post-progression follow-up visit for patients progressing up until the time of the PFS data cut-off.

7. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

7.1 Description of analysis sets

Please refer to **Table 7** for a definition of analysis populations.

Table 7 Definitions of Analysis Populations.

Analysis Set	Definition
Full Analysis Set (FAS)	This will follow the intention to treat (ITT) principle and will include all enrolled patients. This is the primary analysis set for the efficacy outcome variables
Evaluable-For-Safety (EFS)	This will include all patients who received at least one dose of gefitinib. This is the primary analysis set for the safety outcome variables.
Evaluable for Quality of Life (QoL) (EFQ)	This is a subset of the Full Analysis Set (FAS) population with a baseline QoL assessment and at least one post-baseline QoL assessment.

7.1.1 Full analysis set

The Full Analysis Set will follow the intention-to-treat (ITT) principle and will include all enrolled patients and will compare the treatment groups on the basis of randomised treatment, regardless of treatment actually received. Subjects who were randomised but did not go on to receive study treatment are included in this population. This analysis set will be the primary analysis set and efficacy outcome variables will be summarised using this analysis set.

7.1.2 Safety analysis set

All subjects who received at least one dose of randomised investigational product, and for whom any post-dose data are available, will be included in the safety population. Throughout the safety results sections, erroneously treated subjects (e.g. those randomised to gefitinib but actually given placebo) will be accounted for in the actual treatment group.

7.2 Methods of statistical analyses

RECIST results will be programmatically determined from investigators' assessment. In addition, a sensitivity analysis will be performed based on independent blinded review assessments.
Demographic data including vital signs and ECG will be summarised descriptively by treatment.

7.2.1 Primary outcome variable

PFS is defined in **Section 6.1.1**.

The analysis population for PFS will be the Full Analysis Set. The primary analysis of PFS will compare the PFS between treatment arms using a proportional hazards model adjusted for age (<65, ≥65), and prior response to gefitinib (SD vs. PR and CR combined). The hazard ratio (HR; gefitinib: placebo) will be estimated together with its 95% confidence interval and p-value. Confidence intervals will be profile likelihood intervals.

Several sensitivity analyses will be performed:

- Interval censored analysis to assess evaluation time bias
- Using methodology described by *Sun et al 2005* to calculate the p-value and calculating HR and its confidence interval from a Cox regression based on the midpoint of the intervals
- Analysis to assess attrition bias
- Assessed by censoring subjects who take subsequent anti-cancer therapy prior to progression and not censoring subjects who miss >1 assessment visit
- Additionally, a Kaplan-Meier plot of time censoring, where the roles of events and censored observations are reversed, will be produced
- Analysis using data from the central scan review to assess ascertainment bias
- The consistency of treatment effect between subgroups will be assessed using a global interaction test and forest plot showing HRs and 95% confidence intervals for each strata in the following subgroups:
    - Region (Asia, EU)
    - Time from progression to randomisation
    - Smoking history (never vs. current/former)
    - Prior response to gefitinib (SD vs. PR and CR combined)
    - Exon 19 deletion versus L858R mutation
    - Age (<65, ≥65)
    - Gender
    - Disease stage at diagnosis (locally advanced vs. metastatic).

PFS will also be displayed graphically using Kaplan-Meier plots. Median PFS will be summarised for each arm.

7.2.2 Secondary outcome variables

Secondary outcome variables are defined in **Section 4.3**. No adjustment will be made for multiplicity.

Overall survival (OS)

The analysis population for OS will be the Full Analysis Set. The analysis of OS will compare the OS between treatment arms using proportional hazards model adjusted for age (<65, ≥65), and prior response to gefitinib. The HR (gefitinib: placebo) will be estimated together with its 95% confidence interval and p-value. Confidence intervals will be profile likelihood intervals.

A Kaplan-Meier plot of OS will be presented. The median survival time from the Kaplan-Meier curve will be presented.

The OS analysis will take place at the same time as the PFS analysis (at which time it is expected that the OS data will have reached 50% maturity). A second analysis of OS (using the same methodology) will take place when 175 deaths have occurred.

Objective Response Rate (ORR)

The ORR will be summarised for all patients in the Full Analysis Set. The ORR will be analysed using logistic regression adjusted for the following:

- Prior response to gefitinib (SD vs. PR and CR combined)
- Age (<65, ≥65)

The results of the analysis will be expressed in terms of an odds ratio and its associated confidence interval and p-value. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates detailed above. Confidence intervals will be profile likelihood intervals.

If the number of responses is low (<20) then alternative analyses such as Fisher's exact test will be considered.

Disease Control Rate (DCR)

The DCR will be summarised in patients included in the Full Analysis Set. DCR will be analysed using the same methodology as ORR.

7.2.3 QoL – FACT-L

The analysis population for QoL data will be the Evaluable for Quality of Life (QoL) (EFQ) Analysis Set.

The analysis of the TOI improvement rates will be regarded as the primary analysis of the FACT-L questionnaire with the other outcomes (LCS and Total FACT-L) as supportive. The TOI is considered to be focused at physical well-being which can be directly correlated with signs and symptoms and AEs.

The time to worsening data will be analysed using a proportional hazards model including terms for treatment received and the covariates as defined for PFS. Kaplan-Meier curves will also plotted and the HR along with its 95% confidence interval and p-value will be presented.

QoL improvement rates (as defined in **Section 6.2.2**) will be summarised descriptively by treatment arm and analysed using the same methodology as ORR.

7.2.4 Exploratory endpoints

The data from the EQ-5D questionnaire will be listed as part of the main report of this study.Simple summaries of these data will also be included by providing the frequency of response to each of the five questions by protocol-led visit. A summary at each protocol-led visit of the expected number of questionnaires and the actual number of questionnaires received will also be presented. This will also include the actual number of questionnaires received as a percentage of the expected number at each protocol-led visit.

7.2.5 Safety

Assessment of safety will be based on the safety population. For listings and summaries of changes from baseline, the latest available value pre-first dose of study treatment will be used. All AEs will be listed for each patient and summarised according to the SOC and preferred term assigned to the event

using MedDRA. AEs will be graded according to the NCI CTCAE; the investigator will assign the CTCAE grade.

Any AEs occurring after the first dose of study treatment and within 30 days of the last dose of study treatment will be included in the AE summaries. AEs occurring before the first dose of study treatment or more than 30 days after the last dose of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

Clinical chemistry, haematology and vital signs (pulse rate and blood pressure) data will be listed for each patient and summarised with descriptive statistics (mean, standard deviation, median, minimum, maximum, number of patients) by scheduled visit. Both absolute values and changes from baseline will be presented. ECG results (normal and abnormal) will be summarised by visit using frequency counts and percentage of patients for each treatment group.

7.3 Interim analyses (not applicable)

7.4 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis.

The study is designed to have 190 PFS events based on 90% power to demonstrate superiority of gefitinib in combination with cisplatin plus pemetrexed combination chemotherapy versus chemotherapy alone at a two-sided 5% significance level assuming a HR of 0.63. It is expected that 250 patients will need to be randomised to achieve the 190 PFS events (i.e. 75% PFS maturity). The recruitment is estimated to take 2 years and follow-up would be around 11 months, giving a total study time of around 35 months.

As an illustration of this, if the median on the control arm was 6 months with a HR of 0.63 and assuming an exponential distribution, this translates to a 3.5-month median improvement in PFS. However, the largest observed HR for which statistical significance can be declared (i.e. $p<0.05$) would be a HR=0.75, which translates to a minimum median improvement in PFS of 2 months.

At the time of the PFS analysis it is estimated that there will be ~125 OS events (i.e. 50% OS maturity). As an illustration of what might be seen if there was a similar difference in medians of 3.5 months between treatment groups as assumed for PFS, then this would translate to a HR of ~0.82 in OS (assuming chemotherapy alone gives a 16-month median improvement which is an

approximation based on previous studies). If a HR of 0.82 was seen in this study, this would yield a 95% upper confidence interval of 1.16 or a 0.87 probability that the HR <1.

A second analysis of OS will be carried out when 175 OS events have occurred (i.e 70% OS maturity). If a HR of 0.82 was seen in this study at this second OS cut-off, this would yield a 95% upper confidence interval of 1.1 or a 0.90 probability that the HR <1. This would also yield a 0.95 probability that the HR <1.05, where a HR of 1.05 is equivalent to a 3-week worsening of OS.

7.5 Data monitoring committee (DMC)

This study will use an external IDMC which is composed of therapeutic area experts and statistician(s), who are not employed by AstraZeneca, and do not have any major conflict of interest. The IDMC will work to an agreed charter. The first IDMC meeting will review the safety data of approximately the first 10% of patients randomised to this study. Further reviews will be based on IDMC recommendations. No unblinded information will be shared with AstraZeneca. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation (to proceed unchanged, to proceed with amendments to the protocol, or to terminate the study) and any potential protocol amendments and will not contain any unblinded information. A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

8. LIST OF REFERENCES

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9. APPENDIX

Appendix F

Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines for the D791LC00001 study with regards to investigator assessment of tumour burden, including protocol-specific requirements for this study.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion, which has not been previously irradiated.

Measurable

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions.**

* Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTL).

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

Special cases

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TL).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TL at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as non-TL (NTL) at baseline.

3. METHODS OF ASSESSMENT

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

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, chest x-ray	x-ray, chest x-ray
		Ultrasound
		Bone scan FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment, assess NTL and identify any new lesions.

In the D791LC00001 study, it is recommended that CT examinations of the chest and abdomen will be used to assess tumour burden at baseline and follow-up visits.
CT examination with intravenous (IV) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contraindicated.
For brain lesion assessment, MRI is the preferred method.

3.2 Clinical examination

In the D791LC00001 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TL if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest x-ray

In the D791LC00001 study, chest x-ray will not be used for assessment of TL as they will be assessed by CT or MRI examination. Chest x-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain x-ray

In the D791LC00001 study, plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In the D791LC00001 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size, and is subjective and operator-dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D791LC00001 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D791LC00001 study, tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study, the following marker(s) T790M and cMET amplification are being collected for separate analysis. However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

3.7 Cytology and histology

In the D791LC00001 study, histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or x-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D791LC00001 study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D791LC00001 study, FDG-PET scans may be used as a method for identifying new lesions, according to the following algorithm: new lesions will be recorded where there is positive FDG uptake* not present on a baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinically indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based

on signs and symptoms of individual patients. They should be performed no more than 28 days (see the study plan from the study protocol) before the start of study treatment. Follow-up assessments will be performed every 6 weeks +/- 3 days after randomisation. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of TL

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. TL should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits, the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention, e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of TL

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 2 Evaluation of TL

Complete response (CR)	Disappearance of all TL since baseline. Any pathological lymph nodes selected as TL must have a reduction in short axis to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of TL, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not evaluable (NE)	Only relevant if any of the TL were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the PD criteria, PD overrides not evaluable as a target lesion response.

4.3 Non-target lesions (NTL)

4.3.1 Evaluation of NTL

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 Evaluation of NTL

CR	Disappearance of all NTL since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTL
PD	Unequivocal progression of existing NTL. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
NE	Only relevant when one or some of the NTL were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TL at baseline, this is relevant if any of the NTL were not assessed at this visit and the progression criteria have not been met.

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

4.4 New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence

of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example, because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall visit

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/non PD	No	SD (Non CR/non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

NE = not evaluable, NA = not applicable.

5. CENTRAL REVIEW

The Contract Research Organisation (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

5.1 CT scan

CT scans of the chest, abdomen and pelvis should be contiguous throughout all the anatomic regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness and reconstruction interval.

a. **Anatomic coverage:** optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that

may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. **IV contrast administration:** optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TL on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax, abdomen and pelvis examination.

c. Slice thickness and reconstruction interval: it is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater

than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

5.2 MRI scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake

period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared, thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post-injection. PET camera specifications are variable and manufacturer-specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low-dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Appendix B

Additional safety information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that they did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the subject or may require medical intervention to prevent one or more outcomes listed in the definition of

serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g. neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. Has a specific laboratory investigation (if performed) confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.