15th October 2009

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National Institute for Health and Clinical Excellence

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Dear [redacted] and [redacted],

Re: Single Technology Appraisal – Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer

The Evidence Review Group Liverpool Reviews and Implementation Group (LRiG) and the technical team at NICE have now had an opportunity to take a look at submission received on the 24th September by AstraZeneca. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports, and you may want to respond to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, 29th October 2009**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Fay McCracken – Technical Lead (Fay.Mccracken@nice.org.uk) Any procedural questions should be addressed to Jeremy Powell – Project Manager (Jeremy.Powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Section 4.5 – Issues relating to current UK clinical practice

A1. **Priority question:** Please provide further details of actual EGFR-TK mutation testing currently taking place within the UK (e.g. number of tests conducted in each centre, type of test used, number/proportion of EGFR mutation positive, mutation negative, and mutation unknown patients etc).

EGFR Testing

	Tests Performed	M+ve identified
Birmingham	23	3
Aberdeen	10	0
Leeds	4	0
Christie	4	0
Cardiff	14	2
Lab21	10	2
	65	7
EGFR mutation rate		10.7%

To date the majority of EGFR mutation testing takes place in commercial laboratories (e.g. Lab21) and multiple regional hospital laboratories (e.g. those listed on http://www.egfr-info.com/EGFR-exon/egfr-mutation-lab/).

A2. **Priority question:** Please clarify whether the ARMS test (as used in the IPASS study) is the same test as is proposed by AstraZeneca for use in UK clinical practice.

The short-term strategy is test patients with available methodologies that are "well-validated and robust" in line with the SmPC approved by the EMEA. This will include the EGFR29 Therascreen kit (DxS), PCR/Sequencing and Pyrosequencing using quality processes which have been well validated within the laboratories supplying them operated by trained scientists (Quality Systems and Training Records are required, and membership of a regional quality network is advantageous).

Commercial laboratories, e.g. Lab21 will provide testing using the EGFR29 Therascreen Kit (DxS). This method is a one-step, CE marked kit, which is more sensitive than PCR/Sequencing. Please refer to A29 for details on the sensitivity of the techniques currently being used.

At present, AstraZeneca is not actively seeking to advocate any one testing methodology, rather, it is seeking to optimise the number and quality of tumour samples which are suitable for EGFR Mutation testing.

Laboratories are invited to become testing facilities through the website http://www.egfr-info.com/Becoming-testing-laboratory/

A3. Please clarify how patient compliance with gefitinib therapy was monitored during the IPASS trial.

Patients self-administered gefitinib and compliance was assessed by tablet count. Patients were queried for treatment compliance at each visit. All patients returned the bottle of gefitinib at each scheduled visit when a new bottle was dispensed. Any remaining tablets in the bottle were counted to determine if the patient was following their treatment dose schedule.

A4. Please clarify the rate of patient compliance with gefitinib therapy during the IPASS trial.

Treatment compliance with gefitinib was high. The mean compliance was 98.3%. See Table 11.3.1.8. The footnote to this summary table gives the definition of the compliance derivation for each patient.

A5. Please clarify whether patients received monthly packs/bottles of gefitinib tablets.

Study treatment was dispensed to patients on Day 1 and every 84 days (12 weeks) thereafter during the treatment period, until the patient had documented objective PD or other criteria for discontinuation were met.

A6. Please clarify the proportion of patients in the IPASS trial who received second-line treatment by treatment arm. The MS states that patients whose tumour progressed after first line treatment were offered the opportunity to switch to other treatments.

The number and type of subsequent anti-cancer therapies following discontinuation were well balanced between the two groups at the data cut off (Table below). The protocol intended that patients in the gefitinib treatment arm should receive carboplatin / paclitaxel following progression with gefitinib. Investigators could, however, decide to treat with another approved therapy if carboplatin / paclitaxel therapy was considered unsuitable. However, only 234 (38.4%) patients received carboplatin / paclitaxel as second-line therapy following gefitinib first-line therapy In the carboplatin / paclitaxel treatment group, 240 (39.5%) patients received EGFR TKIs following first-line carboplatin / paclitaxel treatment. Whilst there was a large degree of crossover of treatments, the number and type of subsequent anti-cancer therapies taken at any time after discontinuation were well-balanced between the 2 randomised treatment groups (see CSR Table 21).

A7. Please specify the post-progression chemotherapies given by treatment arm in the IPASS trial and the proportions of patients receiving each of these post-progression chemotherapies.

Patients may have taken additional treatments after having discontinued randomised treatment for any reason. Table 11.1.16.1 summarises by treatment arm the chemotherapy treatments taken by patients after discontinuation. Additionally, Tables 11.1.16.2 to 11.1.16.4 summarise EGFR-TKIs and other systemic anti-cancer therapies taken by patients after discontinuation. These summary tables include the detail of these therapies. Table 11.1.16.6 gives a simplified, grouped summary of these therapies, and it includes summary numbers of patients who received chemotherapy after discontinuation.

A8. The MS states that forty patients were non-compliant with the trial protocol in the IPASS trial and others “did not significantly deviate at entry” (pg 20 of the MS). Please provide the number of patients in each arm of the IPASS trial broken down by type of protocol deviation.

Summary Table 11.1.3 gives the reasons for the 40 major protocol deviations, which were specified prior to the database lock and to unblinding of study for analysis. A major deviation was defined as one that caused the patient to be unrepresentative of the intended patient population for analysis or had the potential to affect the efficacy of the investigational product.

In fact, few patients in either treatment group had major deviations: 12 (2%) in the gefitinib arm and 28 (4.6%) in the carboplatin / paclitaxel arm (Table 11.1.3). All individual patients with major protocol deviations are listed in Table 12.2.3.1 (appended). The number of each type of protocol deviation was generally balanced between the 2 treatment groups with the exception of the number of patients who failed to receive randomised treatment: 19 patients in the carboplatin/paclitaxel group compared with 2 patients in the gefitinib group, with the reason for treatment discontinuation being 'subject not willing to continue treatment'.

A9. Please provide the number of patients who deviated from the IPASS trial protocol by treatment arm and were included in the analysis data set.

As was pre-planned and documented in the Statistical Analysis Plan (SAP) before data were unblinded for analysis, the primary analysis dataset was the intention to treat (ITT) patient population. This ITT dataset contained all patients who were randomised to this study, and hence excluded no patients who deviated from the protocol. The SAP also specified that a sensitivity analysis for PFS would be performed in the per-protocol (PP) patient population. The PP population excluded patients who were defined prior to unblinding for analysis as having a major protocol deviation. The list of all patients who had a protocol deviation was reviewed by the Study Team in advance of unblinding for analysis in order to specify whether each deviation could be considered as being major. Details of major and all deviations are provided in response to item A10 below.

A10. Please provide a full list of protocol deviations for the IPASS trial.

Please see the embedded pdf below for details of all the major and minor protocol deviations. Some patients had both minor and major protocol deviations

"Question A9-A10 - Deviation Listings - E

A11. Please clarify the assumptions undertaken to incorporate data points from patients who deviated from the IPASS trial protocol.

As noted in response to item A9 above, the primary analysis data set was ITT, which included all randomised patients

The SAP specified (Section 2.2) particular reasons as being important to identify protocol deviations. SAP Section 2.2.4 discussed how violation of certain entry criteria relevant (or where characteristics are unknown or missing) for the statistical analysis would be handled in the analysis. In addition, SAP Sections 3.1 and 10 specified how patients having deviations concerning RECIST assessment (non-assessment; or issues with its timing) would be dealt with for the endpoints of PFS and ORR.

A12. Please clarify at what point during the IPASS trial patients were tested for mutation status.

Mutation status was determined retrospectively i.e. after the patient was recruited to the trial, but prior to database lock.

In detail; on recruitment to the trial, the patients were asked to provide consent for biomarker analysis. If the patient consented, then a request was placed to obtain a block of tissue (or 10-20 slides from this block) for biomarker analysis. If tissue was unavailable, cytology was accepted. (Please note: the cytology samples were not put forward for mutation testing). The samples were sent to one of two central laboratories (Genzyme for non-China samples; Q-LAB/PUMCH for China samples). Mutation status was determined, recorded and the data transferred to AstraZeneca.

A13. Please clarify whether patients were tested for mutation status of their tumours more than once during the IPASS trial. If yes, please provide details on whether the mutation status of tumours changed over time.

Patients samples were tested only once during the IPASS trial. Only those that consented to biomarker analysis, had a biomarker sample available, passed pathology review were eligible for mutation analysis.

A14. Please clarify the number of centres in which patients were invited to provide samples for testing.

The biomarker consent form was approved by ethics committees at all 87 centres involved in the trial.

A15. Please clarify the number of patients in each centre who were invited to provide samples.

It was the responsibility of the Investigator to discuss the biomarker consent form with the patient. Details of the number of patients who provided biomarker consent in each centre can be found the in the embedded pdf below.

"Question A15 - A17 - ERG clarification.pd

A16. Please clarify the number of patients in each centre who agreed to provide samples.

See Tables in A15

A17. Please clarify the number of patients who were EGFR M+, M- and M unknown in each of the centres.

It is important to note that by presenting the data according to centre, there may appear to be imbalances between centres, in the number of patients who are M+, M- or M unknown, as a result of the number of patients included in each centre being extremely small. See Tables in A15.

A18. Please provide additional information on why so few IPASS trial patients provided samples.

Biomarker consent was optional, not mandatory, in this study and 85% (n=1038) patients provided consent. Of these 66% (n=683, or 56% total study population) provided samples. There are a number of reasons for this, including the following;

- Investigators did not ask patients to consent to the optional exploratory biomarker study

- Pleural Effusion samples were available but not considered suitable for biomarker analysis. Tissue or cytology was unavailable.

- Despite having consented to optional exploratory biomarker analysis, the sample may not have been available;

    - At another hospital site, different to the investigator site and difficult to retrieve

    - Insufficient tissue available (no block, or insufficient slides (<10))

A19. Please clarify why so few samples were evaluable for IPASS trial patients.

Of the 683 patients who provided biomarker samples, 118 provided cytology (17%) and 565 were tissue (83%) (CSR, Section 7.1.4). All 683 samples were reviewed by a pathologist. Pathology review assessed a number of factors including quality of the tissue, sufficient tissue and >100 tumour cells present. Only those that passed pathology went forward for analysis of three exploratory biomarkers, in order of priority, EGFR mutation, EGFR copy number by FISH, and EGFR protein expression by IHC. None of the cytology samples were analysed for EGFR mutation due to the fact that the DxS EGFR29 RUO kit was not validated on DNA derived from samples other than Formalin Fixed and Paraffin Embedded (FFPE) Tissue.

These criteria were put in place at the beginning of the trial in order to streamline the process, and exploratory biomarkers were analysed blinded prior to database lock. However, we now know the importance of EGFR mutations. If EGFR mutation analysis only was being performed, not EGFR copy number of EGFR protein expression, the threshold could have been reduced from 100 tumour cells to 50 tumour cells which would have increased the number of evaluable samples. Key learning for future trials.

It is important to note that although the analysis of biomarker data was an exploratory objective in this study, the dataset studied was large, with more than 400 patients with known tumour status for at least one biomarker. It is of note that the subgroup of 261 EGFR mutation positive patients is the largest group by far ever studied in a randomised controlled trial in NSCLC.

A20. Please provide a per protocol analysis for the overall population in the IPASS trial. In the analysis of a non-inferiority trial, it is usual to perform an intention to treat (ITT) analysis and a per protocol (PP) analysis.

Table 11.2.1.2.1 included results of the analysis of the primary endpoint of PFS in the overall ITT population: HR=0.741 with 95% CI of 0.651 to 0.845; $p < 0.0001$. Table 11.2.1.2.2 shows the results of the PFS analysis in the overall PP population: HR=0.743 with 95% CI of 0.652 to 0.848; $p < 0.0001$. The result of the PFS analysis in the PP population is entirely consistent with that of the primary pre-planned analysis of PFS in the ITT patient population.

A21. Please provide a per protocol analysis for EGFR M+ patients in the IPASS trial.

Table 11.5.1.2.1 included results of the PFS analysis in EGFR M+ ITT patients: HR=0.482 with 95% CI of 0.362 to 0.642; p < 0.0001.

Table 1 (appended) (which is a copy of the table shown on the following page) shows the results of the PFS analysis in the EGFR M+ PP population. It should be noted that only 1 patient of the 40 patients with a major deviation was in fact EGFR M+.

Table 1

Analysis of Progression-Free Survival by EGFR Mutation Status
by Fitting a Cox Proportional Hazard Model
Population : PP

EGFR Mutation Status	n (Patients)	n (Progressions)	% (Progressions)	Hazard Ratio*	Lower 95% CL	Upper 95% CL	p-value
Positive	260	207	79.6	0.477	0.357	0.636	<0.0001

* Gefitinib : Carboplatin/Paclitaxel
CL = Confidence Limit
A Hazard Ratio <1 implies a Lower Risk of Progression on Gefitinib
Cox Proportional Hazard model includes terms for Randomised Treatment, Sex, WHO Performance Status and Smoking History
Analysis includes all Progression Events, or Deaths in the Absence of Progression, Regardless of when they Occur

Section 6.6 - Indirect/mixed treatment comparisons

A22. **Priority question:** Please provide a network diagram for each outcome of interest (overall survival, progression free survival and objective response rate). The network of randomised controlled trials comparing doublet chemotherapies in the first-line treatment of advanced NSCLC (MS, Figure 16) is not sufficiently informative since it is not presented by the outcome of interest.

As requested, network diagrams are presented in Figures 1, 2 and 3 for overall survival, progression-free survival, and objective response, respectively (please see the end of this document).

A23. **Priority question:** Please provide all data points used in the mixed treatment comparison (MTC) analyses including WinBUGS codes used for each analysis. The MS does not explicitly present the data points used in each analysis (direct evidence) and it is not clear what assumptions were made on the prior distributions.

Tables of data for each outcome are presented at the end of this document. No assumptions were made with regards to prior distributions (i.e. they were specified as uninformed or “flat” priors).

The WinBUGS code used for each outcome was dependent on whether the outcome was calculated as a hazard ratio or an odds ratio; i.e. a different set of code was not used dependent on each outcome but rather on the outcome measure.

Example of WinBUGS code used for hazard ratios (fixed effects)

```
model{
```

```
for(i in 1:ndp){
        prec[i]<- 1/(se[i]*se[i])
        lhr[i]~dnorm(md[i],prec[i])
        md[i] <- d[t[i]] - d[b[i]]

    rhat[i] <- lhr[i] * prec[i]
    dev[i] <- (lhr[i] - md[i])*(lhr[i] - md[i])/(se[i]*se[i])
        }
        resdev <- sum(dev[])

        d[1]<-0
        for (k in 2:nt){
        d[k] ~ dnorm(0,.001)
        }

for(k in 1:nt){
        rk[k]<- rank(d[],k)
        best[k]<-equals(rk[k],1)
        }

for (c in 1:nt-1){
        for (k in (c+1):nt){
                lhzr[c,k] <- d[k] - d[c]
                HR[c,k] <- exp(lhzr[c,k])
                }
        }
}
```

Example of WinBUGS code used for odds ratios (fixed effects)

```
model{

for(i in 1:ns){

        delta[i,t[i,1]]<-0
        mu[i] ~ dnorm(0,0.0001)

        for (k in 1:na[i]) {
                r[i,t[i,k]] ~ dbin(p[i,t[i,k]],n[i,t[i,k]])
                logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

        rhat[i,t[i,k]]<- p[i,t[i,k]] * n[i,t[i,k]]

        resdev[i,k]<- 2 * (r[i,t[i,k]] * (log(r[i,t[i,k]]) - log(rhat[i,t[i,k]])) + (n[i,t[i,k]] - r[i,t[i,k]]) *
(log(n[i,t[i,k]] - r[i,t[i,k]]) - log(n[i,t[i,k]] - rhat[i,t[i,k]])))
        }
        sumdev[i]<-sum(resdev[i,1:na[i]])

for (k in 2:na[i]) {
        delta[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]]
        }
}

sumdevtot<- sum(sumdev[])

d[1]<-0
for (k in 2:nt){
        d[k] ~ dnorm(0,0.0001)
        }
```

```
for (k in 1:nt) {
        logit(T[k])<- sum(mu1[])/nb +d[k]
        }

for (k in 1:nt) {
        rk[k]<-(nt+1)-rank(T[],k)
        best[k]<-equals(rk[k],1)
        }

for (c in 1:(nt-1)) { for (k in (c+1):nt) { or[c,k] <- exp(d[k] - d[c] ) }}
}
```

A24. **Priority question:** Please provide the rationale for selecting the following adverse events to be included in the MTC: anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting, and neutropenia (pg 48 of the MS) and not including adverse events such as rash/acne, neurotoxicity, haematologic toxicity, hair loss etc.

A primary objective of the MTC was to generate relative risks for CTC grade III/IV AE that would inform the gefitinib cost-utility analysis. The adverse events that were selected had been identified in the pemetrexed and erlotinib aNSCLC STA submissions as being associated with high healthcare costs and/or decrements in utility.

Section 7.2.3 – Comparator technology

A25. Please provide clarification for the exclusion of docetaxel as a comparator. The scope for the appraisal specified 'platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine); or pemetrexed in combination with platinum based chemotherapy (carboplatin or cisplatin); or best supportive care'.

Taxane (docetaxel and paclitaxel) based platinum doublet chemotherapy is seldom used as a 1st line treatment for aNSCLC in England and Wales (< 5% of 1st line initiations). A decision was taken to restrict the number of comparators to a manageable number considered of most relevance to the decision problem. Paclitaxel/carboplatin was chosen over docetaxel/(cisplatin or carboplatin) as this comparator was used in IPASS to assess the efficacy and tolerability of gefitinib as a 1st line treatment for aNSCLC. Paclitaxel/carboplatin provided the baseline against which all the other interventions in the economic evaluation were compared

Section 7.2.9.7 – Additional infrastructure for the technology

A26. **Priority question:** Please clarify the description of EGFR-TK mutation testing by providing more detailed information on the infrastructure required to set up a universal and standardised method of testing in England and Wales.

AstraZeneca is facilitating the uptake of EGFR testing in the UK. Much of this is being carried out through interactions with NHS hospital laboratory networks and through commercial laboratories. Regional quality networks are being established to monitor the quality of testing through efforts such as round-robin testing (same sample, multiple labs, testing concordance of results, followed by troubleshooting if necessary).

Discussions with laboratories have indicated that a standardised methodology is not preferable, as occasionally test kits or specific reagents may become unavailable and this would result in patients not being able to access the service. Regional quality networks are the preferred way therefore, of ensuring continuity of high quality testing across the UK.

A27. **Priority question:** Please outline the anticipated length of time it would take to set up a universal and standardised method of testing for EGFR-TK mutations in England and Wales.

Each laboratory will require 3-4 months to establish its testing service, validate its methodology and ensure that the testing methodology is robust and sensitive. An additional 2-3 months may be required to set up a whole network, however the framework for this already exists in the UK, so this second step may happen more quickly.

Where a laboratory chooses to use a commercially available kit, the set-up time may be much faster as the validation step is much more straightforward.

A28. **Priority question:** Please provide details of the different types of EGFR-TK mutation tests currently available.

The EGFR29 Therascreen kit, an ARMS technology, is the only EGFR mutation test available in kit form. There are many other molecular techniques available; please see http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/ for further details on the range of tests available.

- EGFR29 Therascreen: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/TheraScreen-Mutation-Kit/

- PCR/Sequencing: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/egfr-Sequencing/

- Other Methods: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/mutation-detection-methods/

A29. **Priority question:** Please clarify what the associated accuracy rates of the different EGFR-TK mutation tests are.

EGFR29 Therascreen quotes a sensitivity of 1% mutant DNA in normal background (given input of sufficient DNA). PCR/Sequencing is less sensitive, being able to detect 20% mutation in normal DNA background, while the other available methods are likely to be in between this range.

Each test is heavily dependent on the **quality** and **quantity** of tumour tissue used for DNA extraction. For this reason, part of AstraZeneca's strategy is to work with pathologists to maximise the quality of the biopsy sample being taken. At present, the following issues have been identified and steps taken (including provision of information on a dedicated website) to address them.

- The type and as a consequence the **quantity** of sample obtained for the diagnosis of NSCLC is variable. Guidance:http://www.egfr-info.com/EGFR-mutation-analysis/).

- The **quality** of DNA from Formalin Fixed and Paraffin Embedded (FFPE) tissue is often poor due to the degradation that occurs during fixation. It is important to use established methods for DNA extraction to increase yield (http://www.egfr-info.com/EGFR-exon/DNA-extraction-methods/) and mutation assays that are designed against small fragments of DNA to increase assay success rates.

- Because tumours are heterogenous in nature, one way of increasing the chances of detecting a true positive result is to perform macrodissection to enrich for tumour cells prior to DNA extraction (http://www.egfr-info.com/EGFR-exon/egfr-tumour-cells/).

A30. **Priority question:** Please clarify whether any of the EGFR-TK mutation tests can use cytology rather than histology specimens.

Currently the analysis of FFPE Biopsy/Resected Tissue is considered the "gold-standard" for mutation analysis. However, work is ongoing on surrogate tissues including cytology particularly in regions where this type of sample is used for diagnosis. The challenge is to obtain sufficient tumour cells of sufficient quality for downstream mutation analysis (http://www.egfr-info.com/EGFR-exon/egfr-mutation-future-analysis/). Although this has been demonstrated to be successful in a research setting*, at present cytology is not routinely used in clinical practice. (Once additional work has been carried out, our position will be reassessed and guidance for use of these samples may be released.)

"Molina_Vila et al. 2008.pdf"

A31. **Priority question:** Please provide details on how AstraZeneca will ensure that the EGFR test proposed for use in UK clinical practice is robust. In the Summary of Product Characteristics leaflet for gefitinib, under special warnings and precautions, it states: "When assessing the EGFR-TK mutation status of a patient, it is important that a well validated and robust methodology is chosen to avoid false negative or false positive determinations".

AstraZeneca has launched a website (http://www.egfr-info.com/) which is aimed at both patients, healthcare professionals and importantly, molecular pathologists. This is a key part of AstraZeneca's strategy to ensure high quality, consistent testing. The website covers many areas of EGFR mutation testing including the generalised process for EGFR testing integrated with therapeutic decisions (http://www.egfr-info.com/EGFR-exon/). The key to success is to increase awareness of the need for quality samples, and quality testing using robust methodologies to ensure a robust result. Quality Systems and Training Records are required, and membership of a regional quality network is advantageous

- Standardisation of the EGFR29 Therascreen kit is achieved through the clear guidance on their kit insert (http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/TheraScreen-Mutation-Kit/).

- Standardisation of PCR/Sequencing and similar methods is more difficult, although aided by Quality Networks which influence laboratories to utilise best practice. In addition, AstraZeneca are providing guidance notes to kick-start best practice of EGFR mutation detection with PCR/Sequencing (Please see downloadable document on Best Practice at http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/egfr-Sequencing/). AstraZeneca is working with the Clinical Molecular Genetics Society (CMGS) to encourage this process.

A32. Please provide the same description of baseline characteristics for the EGFR M+ population in the IPASS trial as is presented for the overall population i.e. ethnic group, tumour histology, disease stage at entry, time from diagnosis to randomisation, stage classification at diagnosis.

Table 2: Demographics and Baseline Characteristics (Intent-to-Treat Population) of the EGFR-TK mutation positive patients in IPASS.

	Gefitinib (n=132)	**Carboplatin/ Paclitaxel (n=129)**
Age (years)		
Median	57	59
Range	34-82	32-80
Sex, n (%)		
Male	24 (18.2)	26 (20.2)
Female	108 (81.8)	103 (79.8)
Ethnic group, n (%)		
Chinese	41 (31.1)	35 (27.1)
Japanese	68 (51.5)	61 (47.3)
Other East Asian[a]	23 (17.4)	33 (25.6)
Other	0 (0)	0 (0)
Smoking history, n (%)		
Never smoked	124 (93.9)	122 (94.6)
Light ex-smoker	7 (5.3)	7(5.4)

	Gefitinib (n=132)	Carboplatin/ Paclitaxel (n=129)
Ex-smoker (non-light)	1(0.8)	0
WHO performance status, n (%)		
0	30 (22.7)	39 (30.2)
1	89 (67.4)	83 (64.3)
2	13 (9.8)	7 (5.4)
Tumor histology, n (%)		
Adenocarcinoma	122 (92.4)	125 (96.9)
Bronchoalveolar carcinoma	10 (7.6)	4 (3.1)
Unknown	0 (0)	0 (0)
Disease stage at entry, n (%)		
Locally advanced	19 (14.8)	29 (22.5)
Metastatic	113 (85.6)	100 (77.5)
Unknown	0 (0)	0 (0)
Time from diagnosis to randomisation, n (%)		
<6 months	123 (93.2)	117 (90.7)
>=6 months	9 (6.8)	34 (9.3)
Unknown	0 (0)	0 (0)
Stage classification at diagnosis [b], n (%)		
IA	1 (0.8)	6 (4.7)
IB	1 (0.8)	4 (3.1)
IIA	1 (0.8)	0 (0)
IIB	0 (0)	2 (1.6)
IIIA	2 (1.5)	1 (0.8)
IIIB	25 (18.9)	28 (21.7)
IV	102 (77.3)	88 (68.2)
Unknown	0 (0)	0 (0)

[a]Patients belonging to East Asian ethnic groups other than Chinese and Japanese.
[b]All patients had Stage IIIB or IV disease at entry.
WHO, World Health Organization.

Section B: Clarification on cost-effectiveness data

Section 7.2.6 - Framework

B1. Please provide the frequency distribution of number of cycles of chemotherapy received by patients for each treatment arm in the IPASS trial.

Gefitinib is an oral treatment that is taken daily and not in cycles. Summaries of exposure to gefitinib are given in Tables 11.3.1.1 to 11.3.1.8.

Table 11.3.1.9 summarises the number of cycles of randomised carboplatin / paclitaxel received by patients in the overall population. The median (mean) number of cycles received was 6.0 (4.6).

In addition, Table 3 (appended) (which is a copy of the table shown below) is a summary of the number of cycles of carboplatin / paclitaxel received by EGFR M+ patients. The median (mean) number of cycles received was 6.0 (4.8), which is consistent with the overall patient population.

Table 3

Summary of the Total Number of Cycles Received for Mutation + patients - Carboplatin/Paclitaxel
Population : Evaluable-for-Safety - Mutation + patients

Completed Number of Cycles	Treatment Received		
	Carboplatin/Paclitaxel		
	n=129		
	n	%	Cumulative %
Mean Number of Cycles	4.8	NC	NC
SD	1.6	NC	NC
Median	6.0	NC	NC
1	7.0	5.4	100.0
2	10.0	7.8	94.6
3	7.0	5.4	86.8
4	22.0	17.1	81.4
5	11.0	8.5	64.3
6	72.0	55.8	55.8

A cycle Equals 21 Days
Subjects who receive only Carboplatin or Paclitaxel are counted as a complete cycle
NC = Not Calculated

B2. Please clarify how the disultility decrement for certain adverse events (e.g. hair loss, fatigue, anaemia, rash) may impact on HRQoL throughout the course of treatment. The assumption outlined in Table 22 (pg 85 of the MS) states that the disutility associated with the adverse events was applied only for a single cycle (21 days).

Although fatigue, anaemia and hair loss are common problems for patients receiving chemotherapy; information about how these adverse events impact on HRQoL throughout the course of treatment is fragmentary and scarce.

It has been reported that chemotherapy induced fatigue can have long-term effects. A study (Jacobsen 1999) observed that patients with breast cancer who were treated with adjuvant chemotherapy or autologous bone marrow transplantation complained of significant levels of fatigue for months or even years after they had completed their treatment[1].

Chemotherapy induced hair loss is temporary but is a source of distress to patients, particularly women [2], and has been ranked among the three most troublesome side effects of chemotherapy, together with nausea and vomiting[3]

Hair regrowth is unpredictable and sometimes new hair can have a different colour or texture. Patients with severe hair loss or complete baldness can expect to have several centimetres of hair within 6 months after completing chemotherapy[3].

Given these findings, it is likely that applying a 21 day disutility for these adverse events may have underestimated their burden on HRQoL.

Economic model - Individual patient data (IPD)

B3. **Priority question:** Please provide access to anonymised individual patient data for the IPASS trial in order to validate key aspects of the submitted model including the modelling of overall survival and progression-free survival, the choice of parameter values, and structural assumptions.

B4. **Priority question:** Please also provide individual patient data for the following data fields for each EGFR mutation status positive patient in the IPASS trial:

- unique anonymised patient identifier
- gender (male / female)
- smoking status (never / ever)
- histology (adeno / other)
- disease stage at entry (IIIB / IV)
- trial arm (gefitinib or paclitaxel)
- performance status at entry (0 / 1 / 2)
- responder to first-line therapy (yes / no)
- days from randomisation to disease progression/withdrawal or to censoring re-progression/withdrawal
- censoring for progression/withdrawal (yes / no)
- days from randomisation to death or to censoring re-death
- censoring for death (yes / no)
- cycles of trial medication administered
- cycles of second line chemotherapy administered
- type of second line chemotherapy administered (agent(s) or “none”)
- days from randomisation to start of second line chemotherapy

AstraZeneca owns the individual patient data associated with IPASS as a global company and does not routinely share this data with third parties. However AstraZeneca is more than happy to respond to any further requests for analyses from ERG including analyses pertaining to this STA in the future.

Economic model - MTC results

B5. **Priority question:** The submitted model (row 54 of 'Parameters' worksheet) that the MTC included evidence relating to pemetrexed/cisplatin as a comparator, yielding a value for the hazard ratio for overall survival of 0.745. Please provide the corresponding hazard ratios for pemetrexed/cisplatin for progression free survival and adverse events.

The pemetrexed/cisplatin overall survival hazard ratio of 0.745 was not derived from the MTC that was submitted to NICE. This hidden row was part of an exploratory analysis that was conducted following the decision by NICE in August 2009 to recommend pemetrexed/cisplatin for the 1st line use in non-squamous aNSCLC.

An estimate for the OS HR for pemetrexed/cisplatin in EGFR-TK M+ was derived by applying an OS HR of 0.81 reported by Scagliotti (2008) in non-squamous patients to the OS HR 0.92 for gemcitabine/cisplatin that was determined in the MTC (OS HR 0.745 = 0.81 x 0.82)[4].

Following the NICE submission, the MTC and economic model have been updated to incorporate pemetrexed/cisplatin in non-squamous aNSCLC (Scagliotti 2008) as a relevant comparator[4]:

Overall Survival

		95% Credible Interval		Probability
Treatment	Mean	Lower	Upper	"best"
Paclitaxel/Carboplatin	1.00	-	-	0.1%
Vinorelbine/Cisplatin	1.08	0.90	1.28	0.0%
Paclitaxel/Cisplatin	0.91	0.80	1.04	3.6%
Docetaxel/Cisplatin	0.94	0.78	1.14	1.9%
Docetaxel/Carboplatin	1.03	0.80	1.33	1.5%
Gemcitabine/Carboplatin	0.96	0.73	1.23	6.2%
Gemcitabine/Cisplatin	0.92	0.81	1.04	0.1%
Pemetrexed/Cisplatin	0.78	0.65	0.93	86.6%

Progression-Free Survival

		95% Credible Interval		Probability
Treatment	Mean	Lower	Upper	"best"
Paclitaxel/Carboplatin	1.00	-	-	3.6%
Vinorelbine/Cisplatin	0.99	0.80	1.21	6.4%
Paclitaxel/Cisplatin	1.14	0.93	1.39	0.1%
Docetaxel/Cisplatin	1.06	0.85	1.33	1.9%
Gemcitabine/Carboplatin	1.25	0.69	2.08	12.2%
Gemcitabine/Cisplatin	0.92	0.81	1.06	10.8%
Pemetrexed/Cisplatin	0.88	0.74	1.05	65.0%

Objective Response

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	0.1%
Vinorelbine/Cisplatin	1.09	0.89	1.34	0.1%
Paclitaxel/Cisplatin	1.16	0.92	1.44	1.5%
Docetaxel/Cisplatin	1.25	0.96	1.62	4.9%
Docetaxel/Carboplatin	0.95	0.66	1.32	0.1%
Vinorelbine/Carboplatin	1.09	0.31	2.80	16.1%
Gemcitabine/Carboplatin	0.85	0.65	1.09	0.0%
Gemcitabine/Cisplatin	1.16	0.93	1.44	0.1%
Pemetrexed/Cisplatin	1.64	1.15	2.27	77.2%

Anaemia

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	24.3%
Vinorelbine/Cisplatin	2.75	1.71	4.21	0.0%
Paclitaxel/Cisplatin	1.11	0.64	1.80	18.0%
Docetaxel/Cisplatin	1.18	0.62	2.11	14.5%
Docetaxel/Carboplatin	1.42	0.53	3.17	14.4%
Vinorelbine/Carboplatin	1.84	0.39	5.34	18.4%
Gemcitabine/Carboplatin	6.31	2.67	13.02	0.0%
Gemcitabine/Cisplatin	2.73	1.73	4.06	0.0%
Pemetrexed/Cisplatin	1.62	0.54	3.75	10.5%

Diarrhoea

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	8.9%
Vinorelbine/Cisplatin	1.38	0.23	4.46	5.7%
Paclitaxel/Cisplatin	2.66	0.51	8.00	0.9%
Docetaxel/Cisplatin	7.48	1.41	30.98	0.0%
Docetaxel/Carboplatin	6.04	0.38	28.20	0.3%
Vinorelbine/Carboplatin	1.47	0.00	7.65	76.4%
Gemcitabine/Cisplatin	1.38	0.26	4.65	7.8%

No data available for Gemcitabine/Carboplatin or Pemetrexed/Cisplatin

Fatigue

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	30.3%
Vinorelbine/Cisplatin	1.28	0.77	2.03	0.6%
Paclitaxel/Cisplatin	1.27	0.80	1.94	6.6%
Docetaxel/Cisplatin	1.14	0.59	2.03	10.9%
Docetaxel/Carboplatin	0.95	0.47	1.73	51.6%
Gemcitabine/Cisplatin	1.85	1.10	2.90	0.0%

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Pemetrexed/Cisplatin	2.62	1.30	4.65	0.0%

No data available for Gemcitabine/Carboplatin and Vinorelbine/Carboplatin

Febrile Neutropenia

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	0.0%
Vinorelbine/Cisplatin	1.99	0.71	4.51	0.0%
Paclitaxel/Cisplatin	1.00	0.29	2.44	0.1%
Docetaxel/Cisplatin	1.38	0.41	3.52	0.0%
Docetaxel/Carboplatin	1.65	0.19	6.29	0.8%
Gemcitabine/Carboplatin	0.25	0.02	0.97	40.2%
Gemcitabine/Cisplatin	0.39	0.12	0.94	2.0%
Pemetrexed/Cisplatin	0.19	0.01	0.84	56.9%

No data available for Vinorelbine/Carboplatin

Nausea and Vomiting

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	64.5%
Vinorelbine/Cisplatin	4.19	1.78	8.86	0.0%
Paclitaxel/Cisplatin	4.08	1.44	9.88	0.2%
Docetaxel/Cisplatin	5.87	1.83	15.80	0.0%
Docetaxel/Carboplatin	3.76	0.48	14.64	10.3%
Gemcitabine/Carboplatin	1.61	0.45	3.92	23.5%
Gemcitabine/Cisplatin	5.51	2.43	10.85	0.0%
Pemetrexed/Cisplatin	10.92	1.11	41.94	1.4%

No data available for Vinorelbine/Carboplatin

Neutropenia

Treatment	Mean	95% Credible Interval		Probability "best"
		Lower	Upper	
Paclitaxel/Carboplatin	1.00	-	-	0.3%
Vinorelbine/Cisplatin	2.26	1.12	4.06	0.0%
Paclitaxel/Cisplatin	0.76	0.31	1.55	9.0%
Docetaxel/Cisplatin	1.29	0.49	2.93	0.6%
Docetaxel/Carboplatin	1.79	0.32	5.86	3.6%
Gemcitabine/Carboplatin	0.85	0.30	1.94	9.6%
Gemcitabine/Cisplatin	0.70	0.36	1.25	4.4%
Pemetrexed/Cisplatin	0.46	0.07	1.62	72.5%

No data available for Vinorelbine/Carboplatin

Section C: Textual clarifications and additional points

References

C1. Some referenced and unreferenced data in the submission resides in documents not in the public domain or only available in abstract form. For purposes of clarification and verification please provide the following:

- **Priority:** An electronic copy of the full Clinical Study Report for the IPASS trial including the trial protocol (original and amended) and all figures, tables and other results pertaining to the EGFR M+ population.

Two copies have been supplied to the Project Manager for the gefitinib STA process by special delivery on 23rd October.

- **Priority:** The original source of the data which describes the North East Japan Gefitinib Study Group trial (Reference 20) (Kobayashi 2009). Please also clarify why data from the abstract reported in Tables 4 and 5 (pg 40) and Figure 14 (pg 44) of the MS do not match the data reported in the referenced abstract (e.g. there are fewer patients described in the abstract).

The ASCO poster was used as a primary source as it was deemed to be most up to date, unfortunately this was not updated in our referencing software. This has now been attached below for your information. The study was also presented at the European Society for Medical Oncology in Berlin (20-24 September 2009) and the presentation has been included for your information too.


"NEJ002 ESMOver4.ppt"


"Kobayashi 2009 Poster.pdf"

C2. **Priority question:** Please provide more details on the First-SIGNAL trial (reference 21).

Please find attached the abstract that was presented at the World Congress on Lung Cancer 2009 held in San Francisco and also a copy of the presentation itself.


"SIGNAL 1L abstract WCLC 2009.pdf"


"2009WCLC Final Version.ppt"

C3. Please provide a full set of electronic references.

Unfortunately due to the copyright license under which AstraZeneca operates, it is unable to provide electronic copies of references to third parties other than regulatory bodies. At the time of the submission of the MS, a full set of hardcopy references was also submitted.

References

(1) Jacobsen PB, Stein K. Is Fatigue a Long-term Side Effect of Breast Cancer Treatment? Cancer Control 1999 May;6(3):256-263.

(2) Dubey S, Brown RL, Esmond SL, Bowers BJ, Healy JM, Schiller JH. Patient preferences in choosing chemotherapy regimens for advanced non-small cell lung cancer. J.Support.Oncol. 2005 03;3(1544-6794; 2):149-154.

(3) Mols F, van den Hurk CJ, Vingerhoets AJ, Breed WP. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations. Support.Care Cancer 2009 Feb;17(2):181-189.

(4) Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J.Clin.Oncol. 2008 Jul 20;26(21):3543-3551.

Figure 1. Network of randomised controlled trials for Overall Survival

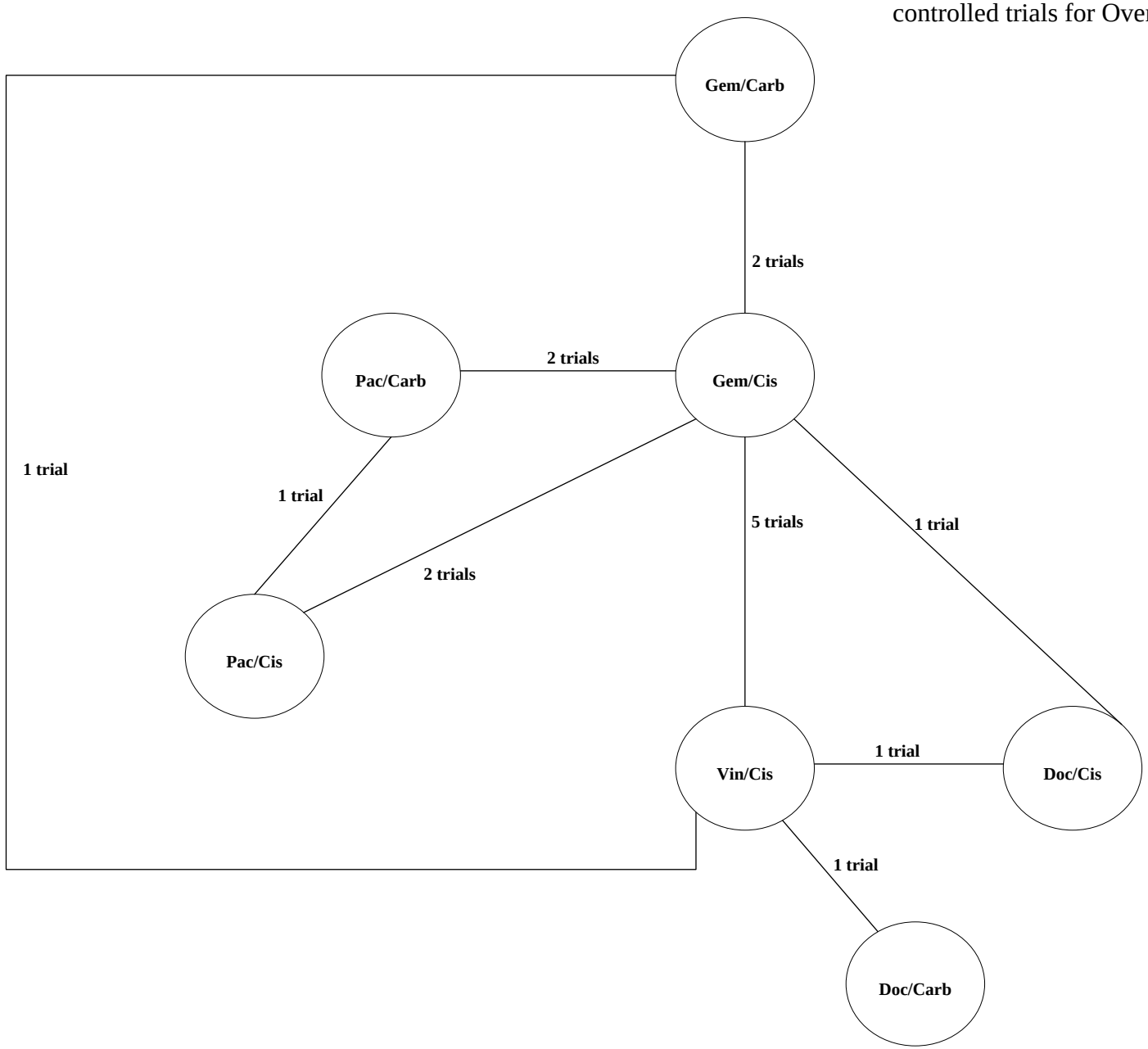
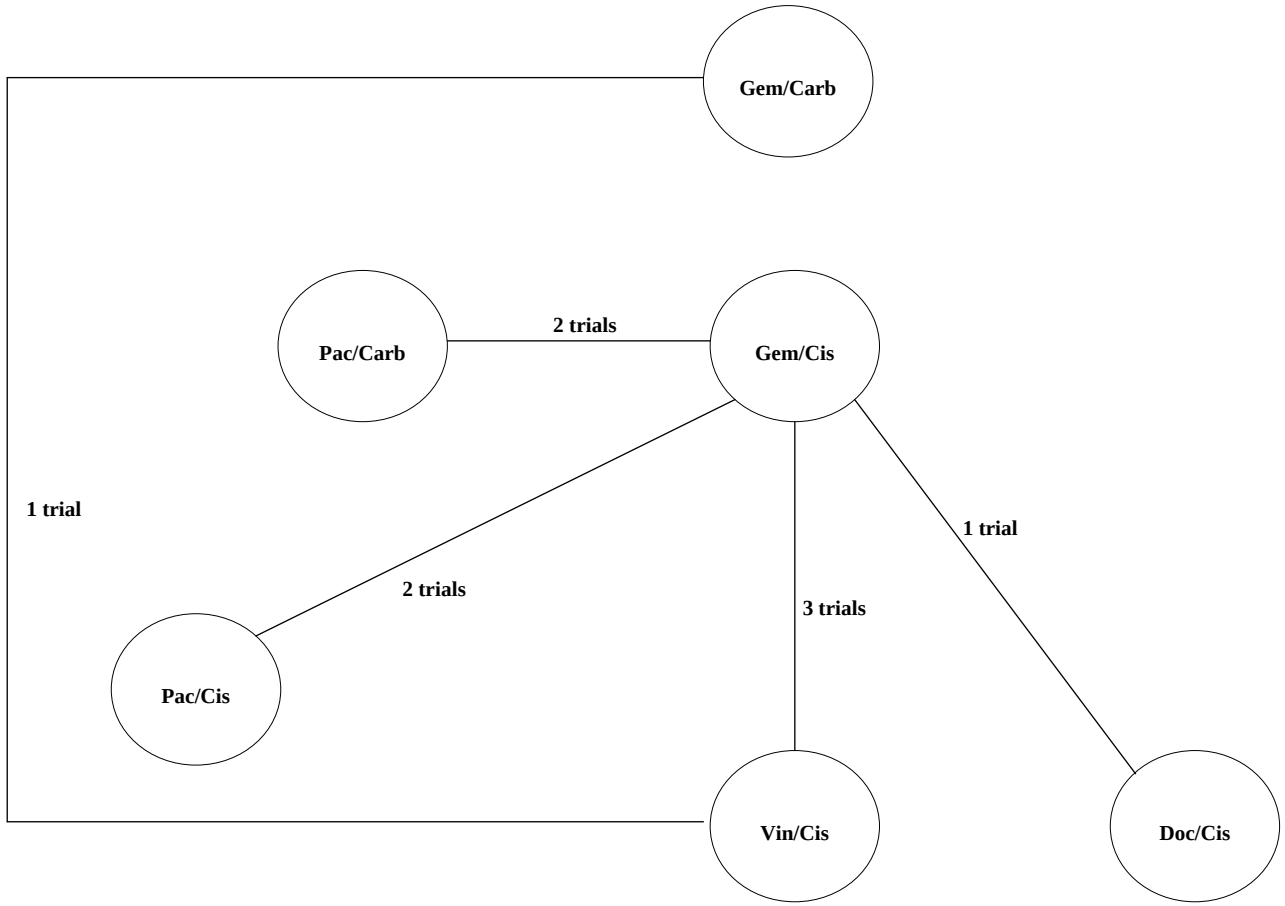


Figure 2. Network of randomised controlled trials for Progression-Free Survival



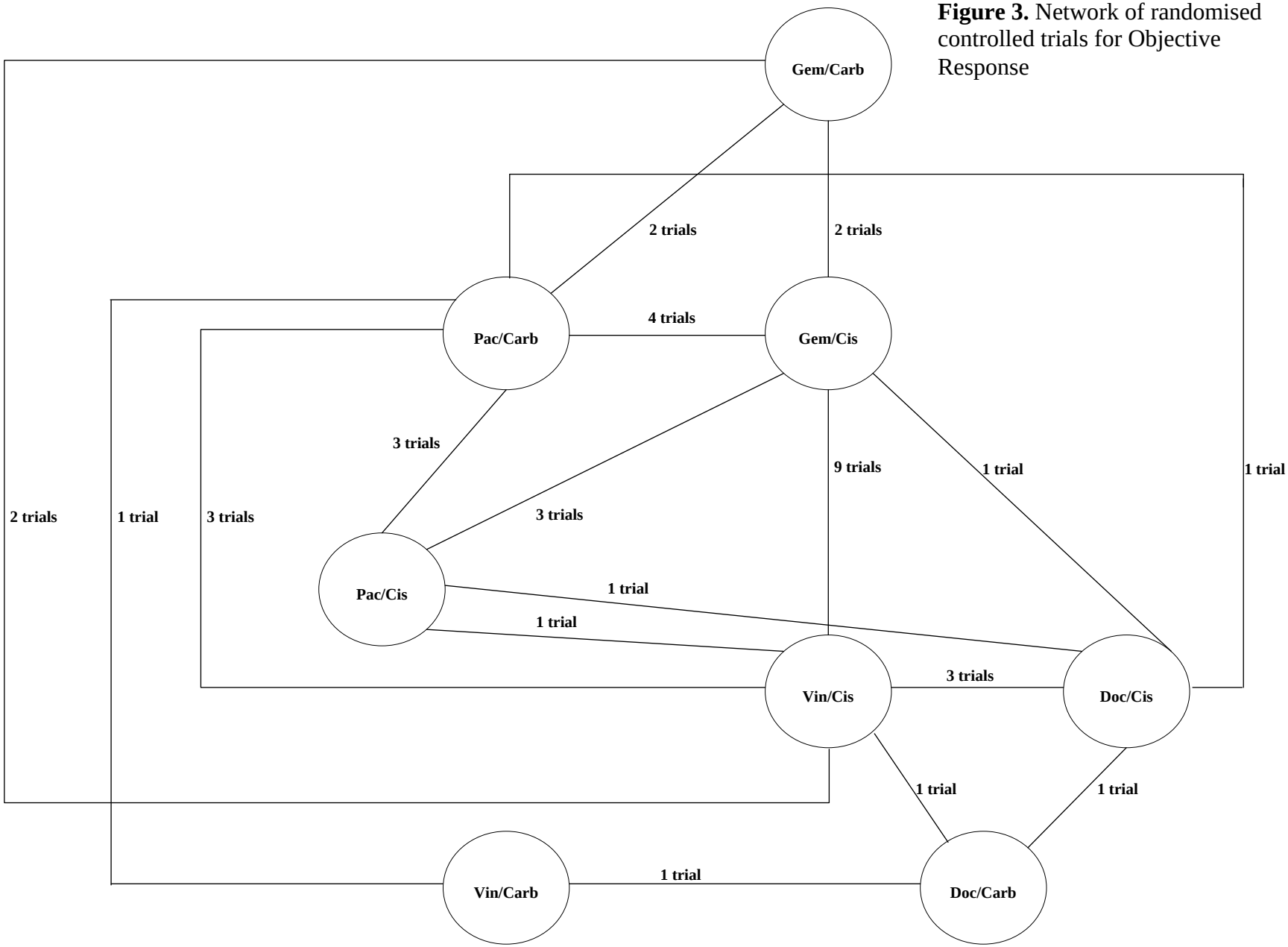


Figure 3. Network of randomised controlled trials for Objective Response

Tables of data used in the mixed treatment comparison

Overall Survival

			Mean	95% Confidence Interval	
Trial	**Treatment A**	**Treatment B**	**Hazard Ratio**	**Lower**	**Upper**
Fossella 2003	Vin/Cis	Doc/Cis	1.183	0.989	1.416
	Vin/Cis	Doc/Carb	1.048	0.877	1.253
Rosell 2002	Pac/Carb	Pac/Cis	1.22	1.03	1.43
Zatloukal 2003	Gem/Carb	Gem/Cis	0.98	0.69	1.39
Mazzanti 2003	Gem/Carb	Gem/Cis	1.09	0.75	1.59
Schiller 2002	Gem/Cis	Doc/Cis	0.94	0.79	1.14
	Gem/Cis	Pac/Cis	0.92	0.76	1.10
	Gem/Cis	Pac/Carb	0.96	0.8	1.15
Chang 2001	Gem/Cis	Vin/Cis	0.93	0.4	2.16
Comella 2000	Gem/Cis	Vin/Cis	0.71	0.45	1.13
Gridelli 2002	Gem/Cis	Vin/Cis	1.02	0.76	1.35
Melo 2002	Gem/Cis	Vin/Cis	0.71	0.41	1.22
Scagliotti 2002	Gem/Cis	Vin/Cis	0.87	0.69	1.09
	Gem/Cis	Pac/Carb	1.04	0.83	1.31
Thomas 2002	Gem/Carb	Vin/Cis	0.89	0.53	1.49
Smit 2003	Gem/Cis	Pac/Cis	0.9	0.65	1.25

Progression-Free Survival

			Mean	95% Confidence Interval	
Trial	**Treatment A**	**Treatment B**	**Hazard Ratio**	**Lower**	**Upper**
Schiller 2002	Gem/Cis	Doc/Cis	0.87	0.73	1.04
	Gem/Cis	Pac/Cis	0.79	0.66	0.94
	Gem/Cis	Pac/Carb	0.84	0.70	0.997
Chang 2001	Gem/Cis	Vin/Cis	0.94	0.50	1.78
Gridelli 2002	Gem/Cis	Vin/Cis	0.91	0.70	1.18
Scagliotti 2002	Gem/Cis	Vin/Cis	0.95	0.77	1.17
	Gem/Cis	Pac/Car	1.05	0.85	1.29
Thomas 2002	Gem/Carb	Vin/Cis	1.21	0.72	2.03
Smit 2003	Gem/Cis	Pac/Cis	0.89	0.65	1.22

Objective Response

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	27	70	27	70				
Chen 2006	Pac/Carb vs Pac/Cis	16	40	16	41				
Chen 2007	Doc/Cis vs Vin/Cis	20	46	22	48				
Comella 2000	Gem/Cis vs Vin/Cis	18	60	15	60				
Douillard 2005	Doc/Cis vs Vin/Cis	39	115	31	118				
Edelman 2004	Gem/Carb vs Vin/Cis	20	95	23	83				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	129	408	97	406	99	404		
Gebbia 2003	Gem/Carb vs Vin/Cis	46	138	62	140				
Gou 2007	Pac/Cis vs Gem/Cis	18	39	16	38				
Jiang 2003	Gem/Carb vs Pac/Carb	16	30	20	34				
Kelly 2001	Pac/Carb vs Vin/Cis	52	206	56	202				
Langer 2007	Gem/Carb vs Pac/Carb	11	47	7	51				
Martoni 2005	Gem/Cis vs Vin/Cis	36	135	44	137				
Mazzanti 2003	Gem/Cis vs Gem/Carb	26	62	18	58				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	47	145	44	146	48	145		
Rosell 2002	Pac/Cis vs Pac/Carb	70	279			80	284		
Rubio 2003	Doc/Carb vs Vin/Carb	13	29	14	31				
Scagliotti 2002	Gem/Cis vs Pac/Carb vs Vin/Cis	64	201	61	201	62	205		
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	63	288	49	289	49	290	60	288
Smit 2003	Gem/Cis vs Pac/Cis	56	152	48	151				
Thomas 2006	Gem/Carb vs Vin/Cis	10	51	14	48				
Treat 2003	Gem/Carb vs Pac/Carb	33	102	34	98				
Tsai 2003	Gem/Cis vs Vin/Cis	19	40	18	40				
Zatloukal 2003	Gem/Cis vs Gem/Carb	36	87	26	89				

Anaemia

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	7	70	10	70				
Chen 2006	Pac/Carb vs Pac/Cis	5	40	4	41				
Chen 2007	Doc/Cis vs Vin/Cis	4	46	0	48				
Comella 2000	Gem/Cis vs Vin/Cis	8	60	8	60				
Douillard 2005	Doc/Cis vs Vin/Cis	17	115	41	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	28	408	42	406	94	404		
Gebbia 2003	Gem/Carb vs Vin/Cis	27	138	19	140				
Helbekkmo 2007	Gem/Carb vs Vin/Carb	42	216	13	210				
Jiang 2003	Gem/Carb vs Pac/Carb	0	30	0	34				
Kelly 2001	Pac/Carb vs Vin/Cis	26	203	33	197				
Langer 2007	Gem/Carb vs Pac/Carb	6	47	5	51				
Martoni 2005	Gem/Cis vs Vin/Cis	5	128	9	127				
Mazzanti 2003	Gem/Cis vs Gem/Carb	3	62	6	58				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	22	145	41	146	44	145		
Rosell 2002	Pac/Cis vs Pac/Carb	21	306	27	302				
Scagliotti 2002	Gem/Cis vs Pac/Carb vs Vin/Cis	12	194	38	198	35	197		
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	82	293	45	297	29	293	39	300
Smit 2003	Gem/Cis vs Pac/Cis	19	160	5	159				
Treat 2003	Gem/Carb vs Pac/Carb	30	151	5	155				
Zatloukal 2003	Gem/Cis vs Gem/Carb	11	87	16	89				

Diarrhoea

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	1	70	1	70				
Chen 2007	Doc/Cis vs Vin/Cis	5	46	0	48				
Comella 2000	Gem/Cis vs Vin/Cis	2	60	1	60				
Douillard 2005	Doc/Cis vs Vin/Cis	5	115	0	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	27	408	21	406	11	404		
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	4	145	3	146	6	145		
Rosell 2002	Pac/Cis vs Pac/Carb	6	306			6	302		
Rubio 2003	Doc/Carb vs Vin/Carb	7	29	1	31				
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	9	293	30	297	6	293	21	300

Fatigue

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2006	Pac/Carb vs Pac/Cis	1	40	7	41				
Chen 2007	Doc/Cis vs Vin/Cis	0	46	0	48				
Comella 2000	Gem/Cis vs Vin/Cis	6	60	9	60				
Douillard 2005	Doc/Cis vs Vin/Cis	13	115	14	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	50	408	43	406	57	404		
Gebbia 2003	Gem/Carb vs Vin/Cis	69	138	49	140				
Kelly 2001	Pac/Carb vs Vin/Cis	16	203	22	197				
Langer 2007	Gem/Carb vs Pac/Carb	10	47	7	51				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	4	145	5	146	4	145		
Rosell 2002	Pac/Cis vs Pac/Carb	31	306	30	302				
Smit 2003	Gem/Cis vs Pac/Cis	19	160	15	159				
Thomas 2006	Gem/Carb vs Vin/Cis	7	51	1	48				

Febrile Neutropenia

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	0	70	2	70				
Chen 2007	Doc/Cis vs Vin/Cis	6	46	6	48				
Douillard 2005	Doc/Cis vs Vin/Cis	11	115	31	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	20	408	15	406	18	404		
Kelly 2001	Pac/Carb vs Vin/Cis	3	203	2	197				
Langer 2007	Gem/Carb vs Pac/Carb	0	47	1	51				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	27	145	3	146	26	145		
Rosell 2002	Pac/Cis vs Pac/Carb	18	306	12	302				
Scagliotti 2002	Gem/Cis vs Pac/Carb vs Vin/Cis	2	194	6	198	1	197		
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	12	293	33	297	12	293	48	300
Smit 2003	Gem/Cis vs Pac/Cis	4	160	2	159				
Thomas 2006	Gem/Carb vs Vin/Cis	1	51	5	48				
Treat 2003	Gem/Carb vs Pac/Carb	1	151	7	155				

Nausea and Vomiting

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	1	70	1	70				
Chen 2006	Pac/Carb vs Pac/Cis	0	40	2	41				
Chen 2007	Doc/Cis vs Vin/Cis	4	46	2	48				
Comella 2000	Gem/Cis vs Vin/Cis	18	60	30	60				
Douillard 2005	Doc/Cis vs Vin/Cis	39	115	20	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	72	408	42	406	65	404		
Gebbia 2003	Gem/Carb vs Vin/Cis	33	138	30	140				
Jiang 2003	Gem/Carb vs Pac/Carb	2	30	6	34				
Kelly 2001	Pac/Carb vs Vin/Cis	22	203	59	197				
Langer 2007	Gem/Carb vs Pac/Carb	11	47	3	51				
Martoni 2005	Gem/Cis vs Vin/Cis	5	126	4	128				
Mazzanti 2003	Gem/Cis vs Gem/Carb	5	62	11	58				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	23	145	56	146	30	145		
Rosell 2002	Pac/Cis vs Pac/Carb	18	306	42	302				
Scagliotti 2002	Gem/Cis vs Pac/Carb vs Vin/Cis	1	194	25	198	13	197		
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	211	293	133	297	49	293	147	300
Smit 2003	Gem/Cis vs Pac/Cis	40	160	27	159				
Thomas 2006	Gem/Carb vs Vin/Cis	1	51	7	48				
Zatloukal 2003	Gem/Cis vs Gem/Carb	15	87	5	89				

Neutropenia

		Treatment A		Treatment B		Treatment C		Treatment D	
Trial	**Comparison**	**n**	**N**	**n**	**N**	**n**	**N**	**n**	**N**
Chen 2004	Pac/Cis vs Vin/Cis	7	70	37	70				
Chen 2007	Doc/Cis vs Vin/Cis	33	46	35	48				
Comella 2000	Gem/Cis vs Vin/Cis	24	60	45	60				
Douillard 2005	Doc/Cis vs Vin/Cis	74	115	99	118				
Fossella 2003	Doc/Cis vs Doc/Carb vs Vin/Cis	302	408	294	406	309	404		
Gebbia 2003	Gem/Carb vs Vin/Cis	29	138	36	140				
Jiang 2003	Gem/Carb vs Pac/Carb	2	30	5	34				
Kelly 2001	Pac/Carb vs Vin/Cis	116	203	150	197				
Langer 2007	Gem/Carb vs Pac/Carb	16	47	30	51				
Martoni 2005	Gem/Cis vs Vin/Cis	22	124	38	124				
Mazzanti 2003	Gem/Cis vs Gem/Carb	6	62	7	58				
Ohe 2007	Pac/Carb vs Gem/Cis vs Vin/Cis	130	145	95	146	128	145		
Rosell 2002	Pac/Cis vs Pac/Carb	165	306	154	302				
Scagliotti 2002	Gem/Cis vs Pac/Carb vs Vin/Cis	98	194	128	198	75	197		
Schiller 2003	Gem/Cis vs Doc/Cis vs Pac/Carb vs Pac/Cis	185	293	205	297	185	293	225	300
Smit 2003	Gem/Cis vs Pac/Cis	69	160	54	159				
Thomas 2006	Gem/Carb vs Vin/Cis	13	51	35	48				
Treat 2003	Gem/Carb vs Pac/Carb	23	151	10	155				

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
833	10	10	10	2	3	5
834	19	12	8	2	2	15
835	6	5	4	1	1	4
837	14	10	10	5	2	7
838	6	5	3	2	0	4
839	6	5	5	2	0	4
840	8	7	5	1	0	7
841	8	6	5	2	2	4
842	13	9	5	0	3	10
843	4	4	4	1	3	0
844	9	6	4	2	2	5
846	9	9	5	2	2	5
847	9	9	9	6	1	2
848	4	3	3	1	1	2
849	9	4	4	2	2	5

(Continued)

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
850	4	4	4	1	1	2
853	12	2	2	2	0	10
854	11	11	6	4	0	7
855	10	4	4	1	1	8
856	8	8	4	1	2	5
857	3	3	3	2	0	1
858	24	21	10	7	0	17
859	4	2	0	0	0	4
860	8	6	5	3	2	3
861	4	4	4	1	3	0
862	6	4	4	2	1	3
864	5	5	3	1	1	3
1406	51	51	19	5	7	39
1407	14	14	3	2	1	11
1408	11	7	5	1	2	8

(Continued)

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
1409	25	25	17	6	6	13
1410	12	12	5	0	1	11
1411	24	23	12	1	8	15
1412	12	8	2	0	1	11
1414	9	9	7	1	2	6
1415	21	17	13	2	4	15
1416	13	13	2	1	1	11
1417	10	2	2	2	0	8
1418	14	5	0	0	0	14
1419	23	23	3	2	1	20
1420	15	12	8	2	0	13
1421	13	4	1	1	0	12
1422	4	4	1	0	0	4
1423	21	19	11	5	6	10
1424	13	9	6	2	2	9

(Continued)

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
1425	23	21	4	0	1	22
1426	44	44	22	6	5	33
1655	27	27	21	13	5	9
1657	1	1	0	0	0	1
1700	30	30	27	16	6	8
1701	22	6	5	3	1	18
1702	14	4	2	2	0	12
1703	10	8	8	2	3	5
1704	14	12	9	4	3	7
1705	19	17	16	14	2	3
1706	22	22	17	9	4	9
5203	16	16	13	5	3	8
5205	44	44	37	9	20	15
5206	23	23	17	8	3	12
5207	19	19	12	5	4	10

(Continued)

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
5208	19	19	18	5	4	10
5209	2	2	2	0	1	1
5210	47	47	36	22	10	15
5211	9	9	6	4	1	4
5212	5	5	4	3	1	1
5302	3	3	3	0	0	3
5304	11	3	2	1	0	10
5307	7	6	4	0	0	7
5308	19	18	17	3	2	14
5309	9	7	5	1	2	6
5310	9	9	9	3	0	6
5902	2	1	1	1	0	1
5903	8	8	5	2	3	3
5906	10	9	3	2	1	7
5907	6	5	3	1	2	3

(Continued)

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable

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Questions A15, A16 & A17: Summary of Biomarker Collection by Centre

Population : Intent-To-Treat

Centre	Number of Subjects Randomised	Number of Subjects where consent for Biomarker Sample provided	Number of Samples provided by consented Subjects	EGFR Mutation Status Positive	EGFR Mutation Status Negative	EGFR Mutation Status Unknown*
	n	n	n	n	n	n
5908	22	21	7	4	2	16
5909	13	13	9	6	0	7
7000	13	7	6	4	0	9
7001	18	17	13	7	4	7
7002	11	11	6	2	2	7
7003	14	14	12	5	3	6
7802	15	6	5	0	0	15
7803	15	12	10	0	0	15
7804	10	10	7	0	0	10
7805	12	8	7	0	0	12
7806	4	4	1	0	1	3
7807	38	35	22	0	0	38
Total (All Centres)	1217	1038	683	261	176	780

* Unknown Mutation status includes subjects who didn’t consent, provide a sample, or whose sample was not evaluable