AstraZeneca

ODAC Briefing Document
IRESSA (gefitinib) Tablets
January 31, 2005

IRESSA® (ZD1839, gefitinib) Tablets
Oncologic Drugs Advisory Committee (ODAC) Meeting Briefing Document
March 4, 2005

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TABLE OF CONTENTS **PAGE**

ABBREVIATIONS

Abbreviations	Term
AACR	American Association for Cancer Research
ASCO	American Society of Clinical Oncology
Asian	Asian excluding patients of Indian origin
BSC	Best supportive care
CI	Confidence interval
CME	Continuing medical education
CR	Complete response
DDL	Dear doctor letter
EGFR	Epidermal growth factor receptor
EGFR-TK	Epidermal growth factor receptor-tyrosine kinase
FDA	Food and Drug Administration
HR	Hazard ratio
IBREESE	Trial 710
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INTEREST	Trial 721
IRB	Institutional Review Board
ISEL	Trial 709
NCI	National Cancer Institute
NCIC	National Cancer Institute Canada
NDA	New Drug Application
NE	Not evaluable
NSCLC	Non small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
PAP	Patient assistance program
PD	Progressive disease
PI	Package insert
PR	Partial response

QOL	Quality of life
SD	Stable disease
SWOG	Southwest Oncology Group
TTF	Time to treatment failure
WHO	World Health Organization
WCLC	World Congress of Lung Cancer

INTRODUCTION

IRESSA was granted accelerated approval on the basis of response rates, and analysis of the top-line survival data has now shown that one of the confirmatory trials (Trial 709) failed to meet its primary objective. AstraZeneca is trying to better understand why this happened and is continuing analysis and interpretation of the full data set. AstraZeneca is working to provide all relevant evidence on IRESSA to the Food and Drug Administration (FDA) to allow for a proper review so that an informed regulatory decision can be made according to due regulatory process. AstraZeneca believes that this public discussion of what has occurred, the steps taken to date, and the future direction of IRESSA, will lead to important lessons for AstraZeneca and other sponsors where accelerated approval was granted or is being sought.

Similar issues were raised at the March 2003 Oncologic Drugs Advisory Committee (ODAC) meeting, which reviewed the status of the post approval commitments for a number of products where accelerated approval was granted. The initial discussion centered on the importance of timely completion of confirmatory clinical trials associated with accelerated approval. An important question was raised concerning the possible situation when the confirmatory trials had been conducted and were hypothetically associated with a negative outcome. At the time, it was acknowledged that this situation had not yet arisen and there was probably no quick or easy answer. It was discussed at the ODAC that if it did occur the reason for trial failure would need to be analyzed because failure of a trial does not necessarily mean that the drug does not work. Since many trials with active drugs fail to show overall survival effects, it may imply that other studies are needed after the possible reasons for failure have been evaluated.

It is AstraZeneca's understanding that the intent of this special, non-voting session is for early public disclosure and discussion, similar to the March 2003 ODAC meeting, rather than for the purposes of regulatory decision-making.

EXECUTIVE SUMMARY

IRESSA was approved under the accelerated approval regulations in May 2003. The approved indication for IRESSA is as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. Effectiveness for IRESSA was based on objective response rates. At the time of IRESSA's approval, there were no placebo-controlled trials of IRESSA demonstrating clinical benefit, such as improvement in disease-related symptoms or increased survival. One of three full approval (Subpart H) commitments was a randomized, placebo-controlled trial (Trial 709) for patients with locally advanced or metastatic NSCLC, refractory to at least one chemotherapy regimen. This study was designed to evaluate the effect of IRESSA on overall survival. AstraZeneca rapidly undertook the Subpart H responsibilities, notably by beginning Trial 709 in July of 2003, less than three months from the approval date.

Also at the time of IRESSA's approval, there was no approved agent for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. There was one agent, Taxotere® (docetaxel), approved for use in patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Since IRESSA was approved, two additional agents have been approved for locally advanced or metastatic NSCLC, Alimta® (pemetrexed) and Tarceva® (erlotinib).

Pemetrexed, as a single-agent, is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy. It was granted accelerated approval, based on the surrogate endpoint, response rate.

Erlotinib was granted full approval based on a survival improvement in locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen.

With respect to IRESSA's Trial 709, survival analysis was conducted in mid-December 2004. While there was some increase in overall survival in IRESSA relative to placebo, the improvement failed to reach statistical significance in the overall population and in the adenocarcinoma histology populations using the protocol specified log rank analysis; utilizing a different, supportive statistical analysis (Cox regression analysis) as specified in the protocol, statistical significance was reached in both overall and adenocarcinoma histology populations. There were subsets of patients where a survival benefit for IRESSA was seen; those of Asian descent and non-smokers. Analysis of unvalidated secondary endpoint data of objective response rates and time to treatment failure suggests that significant improvements in these outcomes were seen among IRESSA treated patients compared to placebo treated patients.

Because Trial 709 did not demonstrate statistically significant improvement in survival in the patient population for which it is indicated, and in light of positive survival data with other agents treating this population, AstraZeneca determined that physicians should consider other treatment options in the recurrent NSCLC patient population.

AstraZeneca immediately, in consultation with FDA, suspended all promotional activities for IRESSA and broadly distributed a Dear Doctor Letter (DDL) informing physicians, as well as other health care providers, of the initial results of Trial 709. This letter also indicated that alternative therapies are available and should be considered for patients. Numerous other communication activities are also under way, including journal advertising of the contents of the DDL. The steps AstraZeneca has taken, in agreement with the FDA, to communicate these results have produced a substantial reduction in the number of new prescriptions for IRESSA.

On January 6, 2005, AstraZeneca met with the FDA to discuss IRESSA and potential future steps to be taken. The FDA informed AstraZeneca that due to the importance of this trial result, the FDA wanted to have a meeting of its advisory panel prior to availability of all trial data. The earliest opportunity for this discussion is the March 4, 2005 ODAC meeting and AstraZeneca agreed to participate. It is AstraZeneca's understanding that the intent of this special, non-voting session is for early public disclosure and discussion, rather than for the purposes of regulatory decision-making.

AstraZeneca intends to continue to make IRESSA available as an option for patients who are deemed appropriate. In addition, AstraZeneca believes that the decision regarding the continued commercial availability of the product should only be made after the full analysis and interpretation of the Trial 709 is complete and a fully informed regulatory decision can be made. AstraZeneca anticipates that the complete, detailed clinical trial report will be submitted to the FDA in May/June 2005. AstraZeneca believes that the steps taken, in agreement with FDA, to inform physicians about these data and the availability of other agents, are sufficient until all information from this trial can be fully reviewed by FDA and the outcome is better understood.

In the absence of final data and the ongoing evaluation of the trial in terms of its design, placement, conduct and patient population, it is not possible at the present time to draw definitive conclusions with respect to the preliminary data. Additional analyses will include an assessment of prognostic significance of biomarkers derived from tumor samples. They may provide insights to the heterogeneity in outcomes observed and importantly suggest guidance on which patients clearly benefit from EGFR inhibition. A description is provided in Section 4 of this briefing document.

The failure to reach statistical significance for survival in the overall population was completely unexpected. It is clear that IRESSA is an active agent. It produces durable tumor responses and, based on the heterogeneity seen in Trial 709, appears to improve survival in some patient subsets (Asian origin and never smokers). What might be driving this heterogeneity is unknown at the present time, though analyses by EGFR expression and by mutation status may provide some insights. AstraZeneca is also exploring other features of the

trial that could have contributed to its outcome. Those include the dose of IRESSA used and the geographic location. We plan to include these investigations as part of the documentation associated with Trial 709.

This briefing document summarizes the primary analysis of the preliminary survival data from Trial 709, actions taken to date to inform physicians, patients and other parties of the data, actions considered but not taken, and next steps for the way forward. The document will serve as the basis for discussion on March 4, 2005.

1. REGULATORY HISTORY OF IRESSA

1.1 Chronology leading to IRESSA approval

IRESSA® (gefitinib) is an orally active, selective inhibitor of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) with a biologically based mode of action distinct from chemotherapy.

A New Drug Application (NDA 21-399) for IRESSA tablets was submitted to the FDA on August 5, 2002. Accelerated approval was sought for the indication of the treatment of patients with locally advanced or metastatic NSCLC who have previously received platinum-based chemotherapy. At that time, there was no proven effective therapy for patients who had progressed following prior platinum and docetaxel therapies. A novel, biologically based agent with clinically significant anti-tumor activity accompanied by significant disease-related symptom improvement in this patient population, would fulfill an unmet need.

Efficacy and safety data were obtained from two Phase II multicenter, randomized, double-blind, clinical trials (IDEAL I (Trial 0039) and IDEAL II (Trial 0016)). In both trials, patients with locally advanced or metastatic NSCLC after platinum therapy were randomized to receive daily oral doses of 250 mg or 500 mg IRESSA. Efficacy was determined by two co-primary endpoints: a) confirmed objective tumor response, and b) clinically significant improvement in disease-related symptoms for at least one month. Overall, efficacy and safety findings were assessed between the two trials, and the 250 mg dose was considered to be as effective as, and better tolerated than, the 500 mg dose. Clinically significant objective radiographic and symptom improvement responses were seen in both trials at the 250 mg and 500 mg dose levels.

On September 24, 2002, AstraZeneca appeared before the ODAC and presented a summary of the efficacy and safety results from Trials 0039 and 0016 and general information about the IRESSA clinical program in support of a Subpart H approval for IRESSA. Subpart H approval is accelerated approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section is subject to the requirement that the sponsor study the drug further, to verify and describe its clinical benefit, or the observed clinical benefit to ultimate outcome. These further studies are to be carried out with due diligence. The ODAC recommended in favor of the question of accelerated approval for IRESSA.

On May 5, 2003, FDA granted Subpart H approval of IRESSA 250 mg, for use as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies. The status of the Subpart H commitments and Phase IV commitments for IRESSA are summarized in Section 1.2. Not included in this document are other ongoing clinical trials in NSCLC and other tumors, which are not part of the Subpart H and Phase IV commitments.

1.2 Subpart H commitments and Phase IV commitments

1.2.1 Subpart H commitments

1.2.1.1 Trial 709 (ISEL) A Double Blind, Placebo Controlled, Parallel Group, Multicentre, Randomized, Phase III Survival Study Comparing ZD1839 (IRESSA) (250 mg Tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC In Patients With Advanced NSCLC Who Have Received One or Two Prior Chemotherapy Regimens and Are Refractory or Intolerant To Their Most Recent Regimen

Trial 709 (ISEL) was agreed with the FDA under Special Protocol Assessment. This study compared the overall survival of IRESSA to placebo, and the recent preliminary findings from this study are the basis for this special session of ODAC. Details of this study are provided in Section 2.

1.2.1.2 Trial 710 (IBREESE) A Double Blind, Placebo Controlled, Parallel Group, Multicentre, Randomized Phase III Study of Disease-Related Symptoms Comparing ZD1839 (IRESSA™)(250mg tablet) Plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Symptomatic Patients with Advanced NSCLC Who Have Received One or Two Prior Chemotherapy Regimens and are Refractory or Intolerant to Their Most Recent Regimen

Trial 710 (IBREESE) was also agreed with the FDA under Special Protocol Assessment. The study prospectively randomized patients, who had received one or two prior chemotherapy regimens and were refractory or intolerant to their most recent regimen, to IRESSA or best supportive care (BSC). The primary endpoint of the study was improvement in pulmonary symptoms. This study was terminated in September 2004 in agreement with the FDA. After patient enrollment started it was determined that Trial 709 data would be available toward the end of 2004 and that this would compromise the continuation of placebo-controlled trials in refractory NSCLC. It was felt that even with best efforts, total recruitment would fall short of the original total number planned to recruit and the trial would therefore lack statistical power to unequivocally address its stated objectives. At the time of study termination, approximately 30 patients of the planned 324 were enrolled from non-US sites.

1.2.1.3 Trial 721 (INTEREST) A Randomized, Open-Label, Parallel Group, International, Multicenter, Phase III Study of Oral ZD1839 (IRESSA®) Versus Intravenous Docetaxel (TAXOTERE®) in Patients With Locally Advanced or Metastatic Recurrent Non-Small Cell Lung Cancer who have Previously Received Platinum-Based Chemotherapy

Trial 721 (INTEREST) was the third trial agreed with the FDA under Special Protocol Assessment. The study prospectively randomizes patients, who have received a platinum-based first-line doublet chemotherapy regimen, to IRESSA or docetaxel. The primary endpoint of the study is overall survival, powered to show non-inferiority. To date, approximately 600 of 1440 scheduled patients have been randomized. Sites in the US are

involved in this trial. The estimated date for completion of enrollment is August 2005. The final analysis is planned at 1150 deaths overall and an interim analysis is planned once 380 deaths have occurred. Based on the patient recruitment rate seen thus far and assuming a median overall survival of 7 months on docetaxel therapy, it is anticipated that the 380 deaths required for the interim analysis will have accrued by April 2005.

1.2.2 Phase IV commitments

A Phase IV commitment is a post-marketing study of a drug product concerning clinical safety, clinical efficacy, clinical pharmacology or nonclinical toxicity that a sponsor commits to at the time of approval, or after approval of an application for a drug product or a supplement to an application. These studies are conducted after the FDA has granted approval of a product for marketing, but are not linked to the accelerated approval process.

1.2.2.1 NCIC (BR 19) "A Phase III Prospective Randomized, Double-Blind, Placebo-Controlled Trial of the Epidermal Growth Factor Receptor Antagonist, ZD 1839 (IRESSA) in Completely Resected Stage IB, II and IIIA Non-Small Cell Lung Cancer"

This is an NCIC conducted, international controlled trial to assess overall survival with IRESSA as compared to placebo in the adjuvant NSCLC setting after definitive surgery (chemotherapy and radiation are allowed at investigator discretion). To date, approximately 457 of the planned 1242 patients have been recruited. The trial is powered to detect a 33% increase in overall survival. The estimated date for completion of the study report is 2008. Interim analyses are planned at 179 and 358 deaths with a final analysis at 537 deaths.

1.2.2.2 NCI (SWOG 0023) "A Phase III Trial of Cisplatin/Etoposide/Radiotherapy with consolidation docetaxel followed by maintenance therapy with ZD1839 or placebo in patients with inoperable locally advanced Stage III NSCLC"

This NCI cooperative group trial assesses overall survival with IRESSA as compared to placebo in patients with stage III NSCLC who have successfully completed chemoradiation and chemotherapy consolidation therapy. To date, approximately 300 of the planned 672 patients have been randomized. The trial is powered to detect a 33% increase in overall survival. The estimated date for completion of the study report is 2008. Interim analyses are planned at 127 and 305 deaths with a final analysis at 508 deaths.

2. SUMMARY OF TRIAL 709

2.1 Summary of preliminary survival data

2.1.1 Methodology

Trial 709 is a randomized, double-blind, placebo-controlled, Phase III survival study, designed to primarily assess the effect of IRESSA on survival among patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen on a background

of best supportive care (BSC). Patients were required to be either refractory or intolerant to their most recent prior chemotherapy regimen. Refractory to chemotherapy, was defined as patients having either clinical or radiological progressive disease while receiving, or within 90 days of the last dose of their chemotherapy regimen. Patients were randomized to receive either IRESSA or placebo in a 2:1 ratio.

The study was originally designed to test the hypothesis that IRESSA would confer a statistically significant survival advantage in patients with adenocarcinoma histology. However, in the light of the NCIC Trial BR-21 data for erlotinib suggesting survival benefit was independent of histological subtype (Shepherd et al 2004), and the recruitment of substantially more non-adenocarcinoma patients in Trial 709 than expected, the Independent Data Monitoring Committee (IDMC) recommended the overall study population be adopted as a co-primary population. In agreement with FDA, analysis was therefore planned once at least 900 deaths had accrued in the overall trial population in order to provide 90% statistical power to test the hypothesis that, in the overall population, IRESSA increased survival by an amount equivalent to that seen for erlotinib. Since the revised analysis plan now involved two co-primary populations, Hochberg's procedure was to be employed to ensure the overall type I error rate was maintained at 5% (Hochberg Y. 1988).

The primary statistical analysis of overall survival was a log-rank test, stratified for the following factors: histology (adenocarcinoma versus other), gender (male versus female), smoking history (never smoked versus current/former smoker), reason for prior chemotherapy failure (refractory versus intolerant), number of prior chemotherapy regimens (1 versus 2 regimens) and WHO performance status (0 or 1 versus 2 or 3). Supportive Cox regression analyses were also conducted, per protocol, with covariate adjustment using these same factors. Further, various subset analyses were planned, including analyses by racial origin, to reflect those subsets explored in the BR 21 trial.

Secondary endpoints were: time to treatment failure (TTF), objective response rates (ORR), Quality of Life (QOL) including symptoms relating specifically to lung cancer and safety in terms of adverse event reports.

2.1.2 Conduct

A total of 1692 patients were recruited from 210 centers in 28 countries, entirely outside the United States (See Appendix A for a listing of participating countries and patient numbers). Patients were randomized between July 15, 2003 and August 2, 2004 (1129 to IRESSA, 563 to placebo). Data cut-off was October 29, 2004 at which time 969 patients had died – (632 (56%) on the IRESSA arm and 337 (60%) on the placebo arm).

The frequency of patient "cross-over" following failure of randomized study treatment was <10 % in both arms.

2.1.3 Results

2.1.3.1 Demography

As would be expected in a large randomized trial with a stratified randomization, the treatment groups were well balanced at baseline with respect to all the important prognostic factors (Table1).

Table 1 Demographic and disease characteristics: overall population

Characteristic		% of patients	
		IRESSA (N=1129)	Placebo (N=563)
Demography			
Male		67%	67%
WHO performance status 0 or 1 (normal/restricted activity)		66%	69%
Non-smoker (never smoked)		22%	22%
Asian racial origin		21%	19%
Disease characteristics			
Histology	Adenocarcinoma	48%	48%
	Other	52%	52%
Time from diagnosis to randomization	<6 months	26%	25%
	6 to 12 months	37%	39%
	>12 months	37%	36%
Stage at diagnosis	IIIB	31%	26%
	IV	54%	56%
Metastatic disease at randomization		85%	86%
Prior cancer therapy			
One prior line of chemotherapy		49%	49%
Refractory to last chemotherapy		90%	91%
Prior platinum		96%	96%
Best response to prior chemotherapy	CR/PR	18%	19%
	SD	37%	37%
	PD/NE	46%	44%

Asian Patients of Asian origin excluding those of Indian origin
CR Complete response. PR Partial response.
NE Not evaluable. SD Disease stabilization.
PD Disease progression. WHO World Health Organization.

2.1.3.2 Primary variable: overall survival

The improvement seen in IRESSA treated patients, both in the overall trial population and in the adenocarcinoma patient subset, just missed reaching statistical significance in the primary stratified log-rank test (Figures 1 and 2, Tables 2 and 3). In a simple comparison of the proportion of patients dying in each treatment arm, an additional 7 deaths for placebo-treated patients in the overall population and an additional 3 deaths in the adenocarcinoma population for placebo-treated patients would have been sufficient to yield $p<0.05$ in the respective

analyses. This is reflected in the supportive Cox regression analysis, which, after covariate adjustment for the same pre-specified factors as in the stratified log-rank test, achieved statistical significance for both patient populations (overall population: HR 0.86, 95% CI 0.76 to 0.995, p=0.0419; adenocarcinoma population: HR 0.81, 95% CI 0.66 to 0.98, p=0.0298).

Figure 1 Survival in the overall population

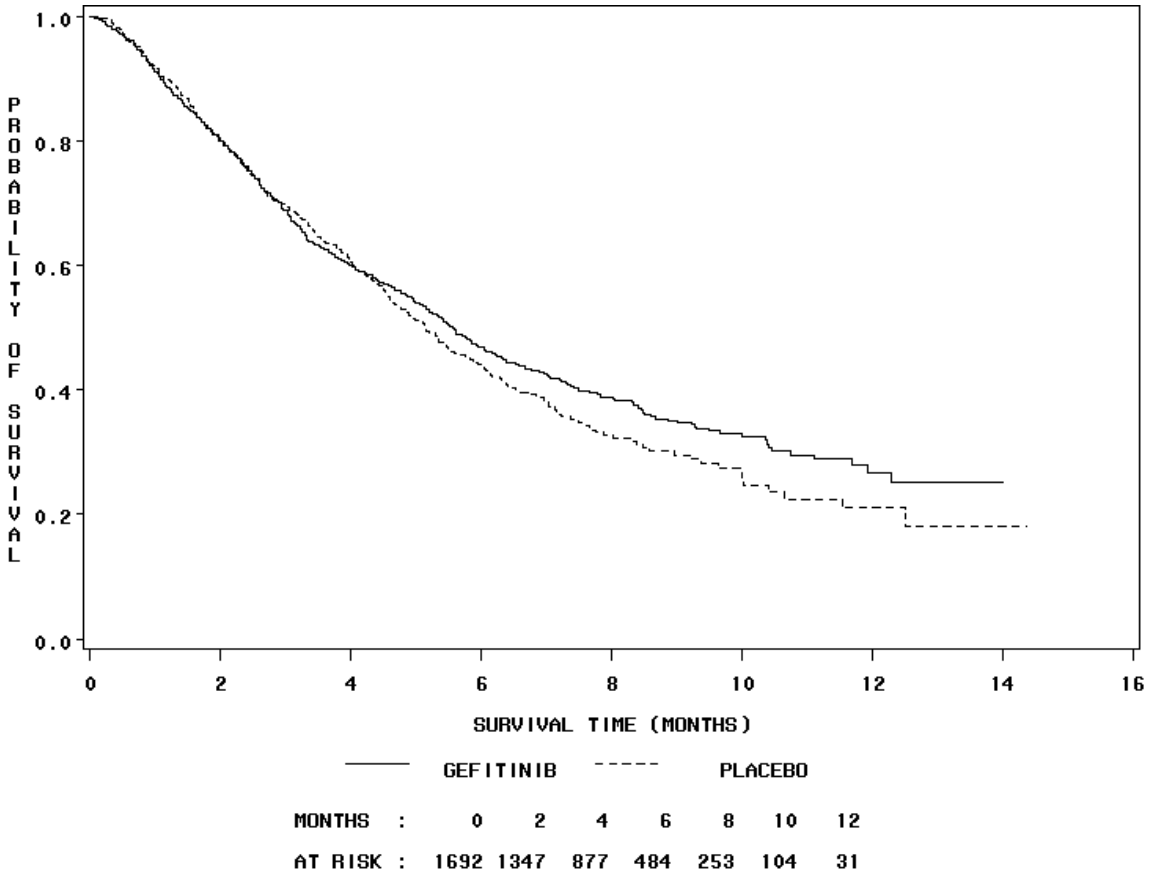


Table 2 Survival in overall population

Treatment group	N	No. (%) deaths	Median (months)	1 year survival (%)	HR (95% CI) (log rank)	p-value (log rank)	p-value (Cox regression)
IRESSA	1129	632 (56.0)	5.6	27%	0.89	0.11	0.042
Placebo	563	337 (59.9)	5.1	22%	(0.78, 1.03)		

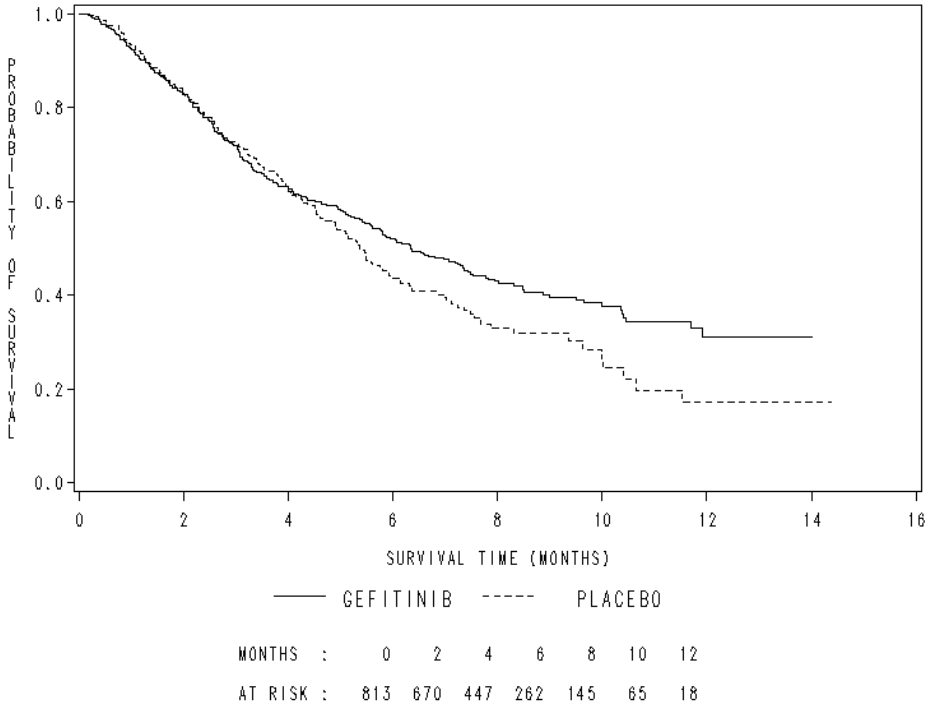
CI Confidence interval.
HR Hazard ratio. HR that is less than 1.00 indicates that survival is better in the IRESSA arm.

Table 3 Survival in patients with adenocarcinoma histology

Treatment group	N	No. (%) deaths	Median (months)	1 year survival (%)	HR (95% CI) (log rank)	p-value (log rank)	p-value (Cox regression)
IRESSA	541	287 (53.0)	6.3	31%	0.83	0.07	0.030
Placebo	272	162 (59.6)	5.4	17%	(0.67, 1.02)		

CI Confidence interval.
HR Hazard ratio. HR that is less than 1.00 indicates that survival is better in the IRESSA arm.

Figure 2: Survival in patients with adenocarcinoma histology



2.1.3.3 Subset analysis

Prior to any unblinded analysis of Trial 709 data, certain prognostic factors and patient groups were identified for subset analysis of survival. These were smoking history (never vs. ever smoker), reasons for chemotherapy failure (refractory vs. intolerant), performance status (0-1 vs. 2-3), number of prior chemotherapy regimens (1 vs. 2 or more), gender (male vs. female),

prior docetaxel therapy (yes vs. no), age at randomization (< 65 yr. vs. ≥ 65 yr.), time from diagnosis to randomization (<6 mo., 6-12 mo., >12 mo.), racial origin (Asian excluding those of Indian origin vs. other) and best response to prior chemotherapy (CR/PR vs. SD vs. PD).

Survival outcomes in subsets are displayed in Figures 3 and 4.

Subset analyses are also planned in Trial 709 in relation to EGFR expression level and EGFR mutation status. These data are not yet available and the analysis is further discussed in Section 4.

Figure 3: Forest plot to show survival in pre-defined prognostic factors

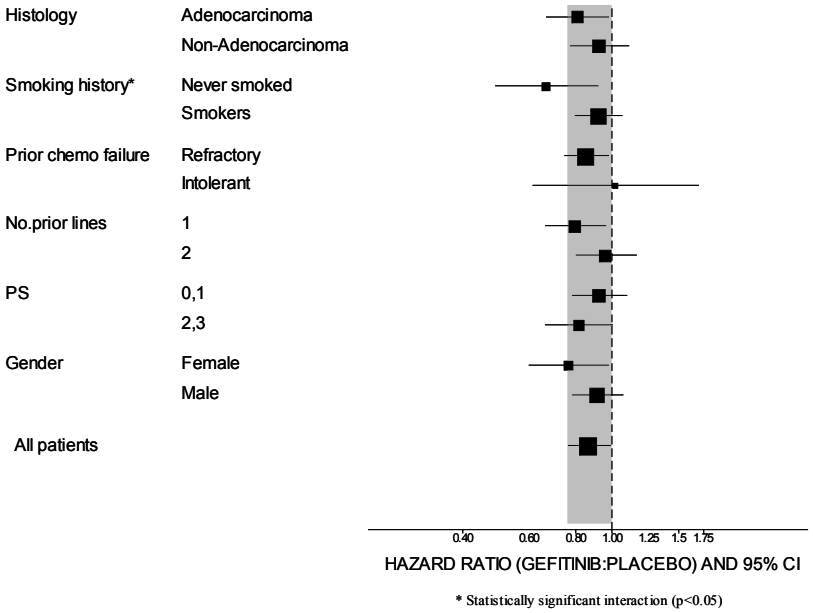
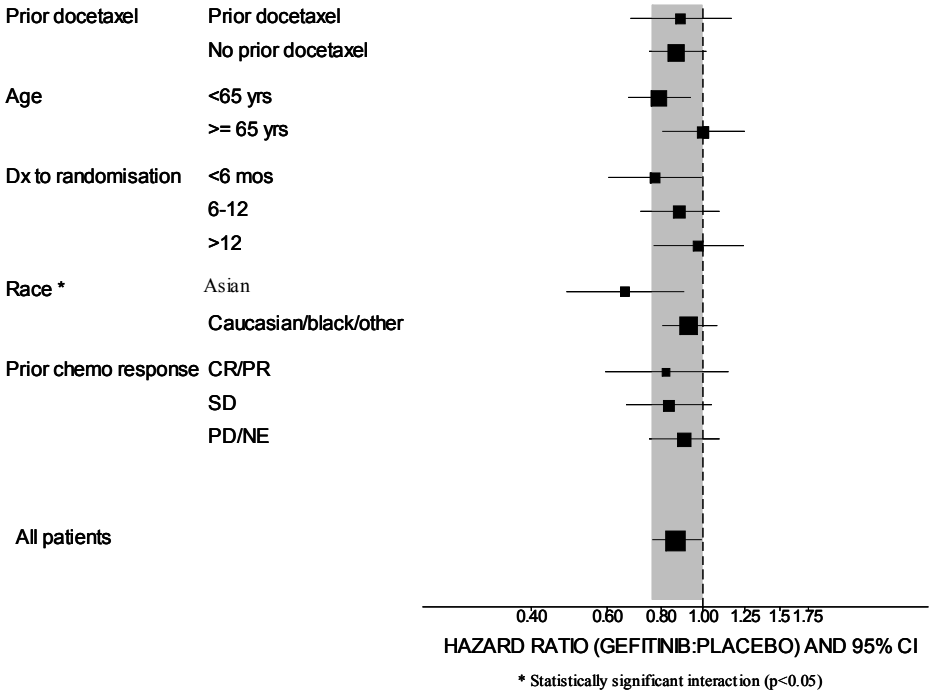


Figure 4: Forest plot to show survival in other important prognostic factors



As indicated in the figures, the only groups where there was evidence that outcomes differed statistically were never vs. ever smokers and Asians vs. non-Asians. For all other subsets, the differences observed were within the play of chance alone.

Patients who never smoked experienced increased survival compared to the corresponding placebo patients (HR=0.67 [0.49,0.91]) whereas, for patients who had ever smoked, there was no difference between treatments (HR=0.93 [0.80,1.07]). Similarly, patients of Asian origin (excluding patients of Indian origin) experienced increased survival compared to the corresponding placebo patients (HR= 0.66 [0.48, 0.91]) whereas, for patients of other racial origin, there was no difference between treatments (HR=0.93 [0.81, 1.08]).

2.1.3.4 Secondary variables

At the time of writing this summary report, preliminary, unvalidated data suggests that TTF and ORR are significantly improved in IRESSA treated patients compared to placebo treated patients (TTF: HR 0.82, 95% CI 0.73 to 0.91, p=0.0005; ORR: ORR 8% on IRESSA and 1% on placebo, odds ratio (OR) 7.03, 95% CI 3.03 to 16.36, p<0.0001).

In terms of safety, preliminary assessment and evaluation of the unvalidated data set indicates that IRESSA was generally well tolerated as expected.

At the time of the writing of this report, the complete analysis is ongoing of the secondary endpoints, being TTF, ORR, QOL and safety in terms of adverse event reports.

In the absence of final data and the ongoing evaluation of the trial in terms of its design, placement, conduct and patient population, it is not possible at the present time to draw definitive conclusions with respect to the preliminary survival data shown above. Data from this trial confirm that IRESSA has anti-tumor activity, which is consistent with the previous clinical trials and with clinical practice. Additional analyses will include updated survival and an assessment of prognostic significance of biomarkers derived from tumor samples. These data may provide insights to the heterogeneity in outcomes observed and importantly suggest guidance on which patients clearly benefit from EGFR inhibition. A description of these further analyses is provided in Section 4 of this briefing document.

3. COMMUNICATIONS ASSOCIATED WITH TRIAL 709

When first made aware of the preliminary survival results for Trial 709, AstraZeneca took prompt action to communicate these results to regulatory authorities (including the FDA), investigators, patients and the broader oncology medical community. These actions were taken to enable physicians to best treat their current and future patients. In light of positive survival data with other agents including another EGFR inhibitor, AstraZeneca urged physicians to consider treatment options, other than IRESSA, for the recurrent NSCLC patient population.

On December 16, 2004, shortly after being informed of the Trial 709 preliminary survival results, AstraZeneca informed the FDA of the results. An open dialogue followed as AstraZeneca and FDA collaborated on the necessary actions, in addition to the steps that AstraZeneca voluntarily took to communicate the trial results to the oncology medical community and patients. A DDL was drafted by AstraZeneca and agreed with the FDA. On December 17, 2004, Dr. Pazdur sent an e-mail of the DDL to American Society of Clinical Oncology (ASCO) members. That same day, the FDA separately posted a statement concerning the Trial 709 preliminary survival data on its web site. AstraZeneca and the FDA also collaborated on the other communication pieces outlined in Table 4.

AstraZeneca provided the FDA with a communication plan outlining the actions AstraZeneca planned to take to further inform the oncology medical community of these results on a continuing basis and to ensure that physicians consider other treatment options. Elements of this communication plan are provided in Sections 3.1 and 3.2.

AstraZeneca agreed to monitor new prescriptions for IRESSA on a weekly basis to measure the effectiveness of the communication plan. A report is provided to the FDA on a bi-weekly basis and a monthly summary is included with every other report.

AstraZeneca believes that these steps are sufficient to ensure physicians and patients can make informed decisions on the appropriate use of IRESSA until such a time as the analysis of the full Trial 709 data can occur.

Table 4 Summary of activities following the announcement of Trial 709 preliminary survival results	
December 14, 2004	Trial 709 preliminary survival results disclosed to AstraZeneca Senior Management
December 16, 2004	AstraZeneca informed the FDA of Trial 709 preliminary results
December 17, 2004	IDMC met to review Trial 709 survival data
December 17, 2004	Communication of preliminary Trial 709 survival results: • External announcement via press release • DDL distribution started to approximately 141,000 health care providers • AstraZeneca's company web site and the IRESSA's web site updated with posting of DDL • AstraZeneca voluntarily suspended IRESSA promotion • DDMAC notified • Teleconference between AstraZeneca and patient advocate groups • Clinical investigators notified via a separate mailing
December 17, 2004	FDA actions: • FDA sent e-mail to ASCO members • FDA posted statement on its web site regarding Trial 709 preliminary results
January 3, 2005	IDMC issued Trial 709 recommendations
January 4, 2005	Teleconference between AstraZeneca and NCI, NCIC, FDA and cooperative group investigators regarding preliminary Trial 709 survival results
January 6, 2005	Meeting between FDA and AstraZeneca to discuss preliminary Trial 709 survival results
January 17, 2004	Letters sent to physicians informing them of a refund program for the benefit of patients whose therapy was changed as a result of the preliminary survival results of Trial 709
January 2005	Letter to patients who have recently contacted AstraZeneca regarding IRESSA, and all

	patients who have previously been mailed an IRESSA promotional booklet
January 31, 2005	Submit Trial 709 abstract to World Congress Lung Cancer (WCLC)
Activities to be taken in the next few months	
February/March (this activity will continue on a monthly basis until agreed upon by FDA)	Journal ads of the DDL with a prominent header placed in the top 10 journals reaching oncologists (based on readership)
February 15, 2005	Submit Trial 709 abstract to American Association of Cancer Researchers (AACR)
February 2005	Letters sent to patients receiving IRESSA via the Patient Assistance Program
February 2005	E-mail referring to the DDL sent to physicians and consumers who have registered to receive updates to the IRESSA web site
April 2005	Presentation of Trial 709 results at AACR conference (pending abstract acceptance)
May 2005	Submit Trial 709 manuscript for publication
July 2005	Presentation of Trial 709 results at WCLC Conference (pending abstract acceptance)

3.1 Information to physicians and other health care professionals

3.1.1 Dear Doctor Letter (DDL)

Starting December 17, 2004, the DDL was distributed to approximately 141,000 healthcare providers including oncologists, hematologists, internists, pulmonologists, thoracic surgeons, oncology nurses. This letter provided the Trial 709 survival results and urged physicians to take these results into consideration and also consider other treatment options when deciding on the best therapy for their current or future patients. (See Appendix B for a copy of the DDL)

AstraZeneca sales specialists were directed to hand-deliver copies of the DDL to their customers. Since the issuing of the DDL, hundreds of visits have been made by AstraZeneca representatives for the purpose of hand-delivering this letter.

AstraZeneca contacted 60 key lung cancer leaders to ensure awareness of Trial 709 results and information contained in the DDL. All written and verbal responses to unsolicited requests for medical information on IRESSA include a summary of the Trial 709 results, as well as a hard copy of the DDL.

The DDL was distributed to medical directors and other managed care health care professionals. In addition, the DDL was sent to chain drug store headquarters for dissemination to chain drug store pharmacy personnel.

A link to the DDL was provided on the AstraZeneca and IRESSA web sites (www.iressa.com).

3.1.2 Communication to clinical investigators

The Trial 709 data have been communicated to all investigators involved in the conduct of clinical trials using IRESSA. In particular, results have been discussed with the co-principal investigators in the INTEREST (721) trial (Section 1.2.1.3) and members of the steering committee. The unanimous decision was to keep the INTEREST trial open for accrual. Informed consent forms are being updated with information regarding the Trial 709 results and all patients are being re-consented.

3.1.2.1 Communication to the NCI and cooperative groups

Trial 709 data were shared with NCI medical staff responsible for IRESSA development in mid-December immediately following the press release. A teleconference with relevant members of the NCI, NCIC, SWOG, AstraZeneca and the FDA was held on January 4, 2005 to discuss the implications of the Trial 709 data on the conduct and design of the BR 19 and SWOG 0023 trials. The investigators stated they wish to continue with the trials and a final decision by NCI and NCIC regarding these trials is pending. The informed consent forms for the NCI and NCIC trials were updated with information regarding the Trial 709.

3.1.3 Journal communication

The top ten journals reaching oncologists, based on readership, were targeted for further communication of the DDL. Five will have this communication in the February editions (based upon printing deadlines) while all will have it placed in the March editions. This will continue on a monthly basis until AstraZeneca and the FDA agree otherwise. This advertisement contains the DDL with a prominent header ("Physicians are urged to consider treatment options other than IRESSA").

3.1.4 Internet and professional web site

The professional web site was updated and an e-mail notification is being sent to 1,564 healthcare providers who previously registered to receive updates to the IRESSA web site (www.iressa.com). The corporate AstraZeneca web site has also been updated with relevant information (www.AstraZeneca.com).

3.1.5 Oncology conferences

AstraZeneca is submitting an abstract of the Trial 709 data for presentations at the American Association of Cancer Researchers (AACR) Meeting in April 2005 and the World Congress of Lung Cancer (WCLC) in July 2005.

The DDL and IRESSA PI will be made available upon request at AstraZeneca booths/displays at all conventions where AstraZeneca has a presence.

3.1.6 Communication to distribution partners

AstraZeneca sent letters to wholesalers who participate in an Inventory Management Agreement and to other distribution partners. These letters communicate the preliminary results of Trial 709 and the current status of IRESSA as a non-promoted, but commercially available product, to help them appropriately manage their stock of IRESSA.

3.1.7 Communication to other third parties

AstraZeneca immediately communicated Trial 709 results through the DDL to all primary medical communication companies, advertising agencies and CME providers. AstraZeneca is providing the DDL to other third parties as appropriate.

3.1.8 Publication of results

AstraZeneca plans to submit a Trial 709 manuscript in May for publication.

3.1.9 Other actions

A letter is being sent to the physician of record for each IRESSA Patient Assistance Program (PAP) patient notifying the physician that AstraZeneca sent a letter to the patient. Another copy of the DDL will be attached to the physician letter. (The PAP is AstraZeneca's free drug program for uninsured, low-income patients).

AstraZeneca has established a patient refund program through which it is reimbursing patients for their out-of-pocket costs for unused IRESSA tablets if the physician decided to change the patient to alternative therapy after reviewing the Trial 709 results. A Dear Doctor Refund Letter announcing this program was sent to known IRESSA prescribing physicians, plus all relevant physicians called on by AstraZeneca's IRESSA sales staff prior to suspension of promotion. A toll-free phone number for the refund service was provided to the physician.

3.2 Information to patients

3.2.1 Web site

The consumer web site was updated and 2,775 consumers who were registered to receive updates to the IRESSA web site (www.iressa.com) are being notified by e-mail.

3.2.2 Follow-up to patients who recently contacted AstraZeneca about IRESSA

Patients who contacted AstraZeneca before December 17, 2004 for information on IRESSA were sent an IRESSA product brochure along with the PI. A follow up letter was sent to provide an update on the Trial 709 results to those specific patients and referred the patients to their physician for more information. It also provided the AstraZeneca Information Center toll-free phone number to answer questions and directed the patient to the www.iressa.com web site to view the DDL. This letter was sent to all patients who previously were mailed an IRESSA promotional booklet.

3.2.3 Patient Assistance Program (PAP)

Patients receiving IRESSA through the AstraZeneca Foundation PAP are being sent a letter, which will direct them to consult their doctor. The letter will also provide the AstraZeneca Information Center toll-free phone number to answer questions and direct the patient to the www.iressa.com web site to view the DDL. As noted above, the patient's physician of record will also receive a letter.

3.2.4 Patient advocate groups

AstraZeneca held a teleconference on December 17, 2004 to rapidly inform the patient advocate community of the Trial 709 data. Subsequently AstraZeneca provided a copy of the DDL for posting on their groups' web sites. AstraZeneca maintains ongoing contact with the groups to answer their questions and monitors patient concerns.

3.3 Actions considered but not taken

The following section provides details of actions that AstraZeneca evaluated in light of the preliminary Trial 709 results but did not implement, after careful internal consideration and discussion with FDA. AstraZeneca concluded that these measures (withdrawal of NDA or limited distribution) would be premature as the full analysis of Trial 709 data set and understanding of the trial results is pending and actions taken by AstraZeneca are considered sufficient. After discussion with FDA, it was mutually agreed that, at this time, the best way to ensure that IRESSA would be available to patients deemed appropriate by their physicians, is through normal distribution channels. AstraZeneca remains committed to maintaining IRESSA's availability to the medical community until such a review has taken place and a regulatory decision can be made

3.3.1 Limited or restricted distribution

A restricted distribution of IRESSA under an open NDA could involve a specialty pharmacy or similarly described closed distribution network. Physicians would sign documentation that they have considered the results of Trial 709 and certify that other treatment options as well as the risks and benefits of IRESSA were discussed with the patient before prescribing IRESSA. The patient's receipt and understanding of this information would also be documented. This documentation would be faxed to the selected distribution partner(s) along with the prescription, and IRESSA could only be dispensed once the required documentation was obtained. The medication could be delivered to the patient by postal service or another vendor. An evaluation of the limited distribution process, revealed that implementation with minimal impact to physicians and patients would take at least 2 months.

AstraZeneca recognizes that an advantage of a restricted access program would be a potentially heightened level of assurance that physicians and patients were aware of the preliminary Trial 709 survival data. However, AstraZeneca believes that the steps already taken and planned to date are appropriate measures to ensure that physicians and patients can make an informed decision on the use of IRESSA until analysis of the full Trial 709 data set has occurred. AstraZeneca further believes that a restricted access program would impose an

additional burden on physicians before the totality of the Trial 709 data is available, and would represent a potential risk to patients of therapy interruption or not receiving medication that may be of benefit to them.

3.3.2 Withdrawal of NDA

In the event of withdrawal of the NDA, the IRESSA IND would remain open and active and AstraZeneca would work with the FDA to provide drug product only to existing patients if deemed medically appropriate. This could be achieved by either a Treatment IND/compassionate use program or a Group C program for the distribution of IRESSA. Withdrawal of the NDA would ensure that no new patients receive IRESSA other than through these routes; however clinical trials can continue.

For the approximately 15,000 patients that are currently receiving IRESSA in the US, there would be several disadvantages to withdrawing the NDA. There is a sizable set-up time of such a program, significantly longer than would be required for the limited distribution described above. Implementation of a Treatment IND or Group C program includes communication of procedural instructions to physicians, developing a protocol, and IRB submission and approval prior to a patient continuing to receive IRESSA. Many community oncologists would need to obtain IRB approval at their individual centers in order to continue IRESSA for their patients, which could interrupt supply for patients receiving IRESSA. As a practical matter, this could inhibit delivery of a treatment option from which existing patients are benefiting.

AstraZeneca believes that withdrawing the NDA at this time would be premature until the full Trial 709 data set has been analyzed and reviewed by FDA.

4. NEXT STEPS

As outlined above, in agreement with the FDA, AstraZeneca has taken numerous actions to inform physicians and patients of the preliminary Trial 709 survival results so that informed treatment decisions can be made. AstraZeneca is committed to have the full trial results from Trial 709 and other relevant data made available to the FDA quickly in order to allow for proper regulatory review so that an informed regulatory decision can be made. During the review period, AstraZeneca intends to continue to make IRESSA available for patients who are deemed appropriate.

The steps required to complete the associated documentation of Trial 709 are outlined below.

For the secondary endpoints of TTF, response rates, safety and QOL, including symptoms relating specifically to lung cancer, the data base lock date is expected to occur on February 2, 2005 and analysis and documentation will be available to FDA by the end of February 2005.

Further to the ongoing analysis of trial data, the Independent Data Monitoring Committee (IDMC) reviewed the initial survival data in December 2004 and concluded that further trial follow-up with an analysis of more mature survival data was required. Given that, in the

interim analysis that took place in August 2004 upon the cessation of recruitment, the IDMC saw no separation in the Kaplan-Meier survival curves, they were unwilling to rule out the possibility that early deaths were different than later deaths and so felt that further follow-up data was required to come to a definitive conclusion regarding the efficacy of IRESSA. They could not conclude that the trial was wholly negative and, given the significant interaction tests underpinning subgroup analyses by racial origin and smoking status, even a claim of a survival benefit might be possible, though this would likely require further data.

In light of the IDMC recommendation, a further analysis of survival will be conducted following the data cut-off date January 28, 2005, thereby coinciding with the availability of the secondary endpoint data set. The timeline for provision of these further survival data to FDA will therefore be the same as that for the secondary endpoint data.

AstraZeneca is also investigating the association between epidermal growth factor receptor (EGFR) protein expression as well as other related biomarker status with efficacy in those patients where such tumor material was available. While EGFR expression was not found to correlate with response rate in IRESSA Phase II trials, EGFR expression as a predictive marker of benefit was suggested from the analysis of the erlotinib trial BR-21 and is included in the package insert for erlotinib. Results from BR-21 suggest that erlotinib prolonged survival in the EGFR positive subgroup while no prolongation was seen among those in the EGFR negative subgroup. Similar results from Trial 709 could provide corroboration that expression of EGFR is a predictive marker when using EGFR inhibitors. AstraZeneca intends to employ methodology, similar to those used to measure EGFR expression for trial BR-21, in the analysis of tumor samples from Trial 709. EGFR protein expression will be measured by IHC using the DakoCytomation pharmDx^{TM} assay kit. In those patients with evaluable tissue, EGFR+ will be defined as having at least 10% of cells staining at any level for EGFR; patients with fewer than 10% of cells stained will be classified as EGFR-. Patients without tissue or with an unevaluable tissue sample will be classified as EGRF unknown. Survival outcomes, IRESSA relative to placebo, will then be evaluated in these three subsets. Over 500 tumor samples have been collected; based on prior experience, it is estimated that approximately one-third of the samples collected will be inadequate or unusable. Data on EGFR expression will be available on March 15, 2005. Subsequently, the analysis and documentation of its association with treatment outcomes is expected to be available on or about March 21, 2005.

In the past year, research has uncovered a subgroup of patients with NSCLC, with specific mutations in the EGFR gene, which correlate with clinical responsiveness to EGFR inhibitors (Lynch, et. al., 2004). There is a suggestion that these mutations are more frequent among lung cancer patients that are female, of Asian descent, adenocarcinoma histology or are non-smokers. These mutations appear to lead to increased growth factor signaling and thus confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who are more likely to have a response to an EGFR inhibitor. Tissue samples are also being collected for these EGFR mutations and will be analyzed with respect to survival. Data on EGFR mutation will be available in June 2005.

The failure to reach statistical significance for survival in the overall population in Trial 709 was completely unexpected given the results of BR-21and especially in light of prior reported survival results seen with IRESSA in the US population in a non-randomized setting. It is clear that IRESSA is an active agent. It produces durable tumor responses and, based on the heterogeneity seen in Trial 709, appears to improve survival in some patient subsets (Asians and never smokers). The possible factors driving this heterogeneity are unknown at the present time, though analyses by EGFR expression and by mutation status may provide some future insights. In addition, AstraZeneca is exploring other features of Trial 709 that could have contributed to the unexpected survival outcome. These include the dose of IRESSA used and geographic location of sites in this trial, in terms of the potential for regional differences to influence susceptibility to EGFR inhibition. AstraZeneca plans to include these investigations as part of the documentation associated with Trial 709.

5. ISSUES FOR CONSIDERATION AND DISCUSSION

AstraZeneca recognizes that because Trial 709 failed to meet its primary objective, there are issues to be considered concerning IRESSA's accelerated approval. There are clearly a number of important questions raised as a consequence of this trial result, which are specific to IRESSA, but may be applicable to the development of other targeted agents. AstraZeneca submits, however, that before FDA can decide on the regulatory future for IRESSA, all available evidence must be considered. As outlined, a full analysis will be available in May/June 2005. In addition, the results of a randomized Phase II trial against docetaxel in second-line treatment of NSCLC will also be available in late February for consideration. AstraZeneca respectfully asks the ODAC to consider the appropriateness of steps already taken, in agreement with FDA, to inform physicians and patients of the preliminary results of Trial 709. AstraZeneca also seeks guidance on any additional steps that they suggest are necessary while FDA reviews all of the evidence.

6. REFERENCES

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