NDA Team Leader Review

Application: NDA 21-399
Drug: ZD1839 (IRESSA)
Review date: 10/15/02

Introduction

Please refer to Dr Cohen's review for details of FDA's findings and analysis of NDA 21-399, ZD1839 (IRESSA) for NSCLC. This review provides team leader comments including a regulatory background, discussion of study results, deliberations of the ODAC, and phase 4 post marketing commitments.

AstraZeneca submitted a marketing application for third-line treatment for non-small cell carcinoma (NSCLC) for consideration of accelerated approval. Prior to the Agency's action on this application, results became available from ZD1839 studies in the first-line treatment of NSCLC. Two large randomized trials failed to show clinical benefit from the addition of ZD1839 to standard first-line cisplatin-based regimens. The Agency had expected that if ZD1839 received accelerated approval in refractory NSCLC, these trials would provide the post-approval evidence of ZD1839 clinical benefit necessary for conversion to regular approval status. Given the lack of ZD1839 clinical benefit in patients with previously untreated NSCLC, a dilemma for reviewers was whether a 10% response rate in a 3rd line treatment is reasonably likely to predict clinical benefit. On September 24th, the Oncology Drugs Advisory Committee (ODAC) advised FDA whether available data are reasonably likely to predict clinical benefit for ZD1839 treatment in NSCLC. These issues are discussed in detail at the end of this document.

The New Drug Application (NDA) efficacy results consist of tumor response rate data, supported by QOL and symptoms data, in non-small cell lung canceer (NSCLC) patients who have no available therapy, intended to fulfill FDA's requirements for *accelerated approval*. In the following paragraphs FDA's requirements for *accelerated approval* and *regular approval* of new drugs are discussed.

Regulatory background: regular approval versus accelerated approval

Regular marketing approval of oncology drugs requires substantial evidence of efficacy from well-controlled clinical trials. Guidance promulgated in the 1980's indicated that efficacy should be demonstrated by prolongation of life, a better life, or an established surrogate for at least one of these. In 1992 Subpart H was added to the NDA regulations to allow *accelerated approval* (AA) for diseases that are *serious or life-threatening* where the new drug appears to provide *benefit over available therapy*. AA can be granted on the basis of a *surrogate endpoint* that is *reasonably likely to predict clinical benefit,* an

explicitly lower strength surrogate than would be a basis for regular approval. After AA, the applicant is required to perform a post-marketing study to demonstrate that treatment with the drug is indeed associated with clinical benefit. If the post-marketing study fails to demonstrate clinical benefit or if the applicant does not show *due diligence* in conducting the required study, the regulations describe a process for rapidly removing the drug from the market.

Under AA, tumor response has been used as a surrogate *reasonably likely* to predict clinical benefit for ten oncology drug accelerated approvals:

Oncology drug accelerated approvals based on tumor response

Drug	Indication
Liposomal doxorubicin	Kaposi's sarcoma, second line
Docetaxel	Breast cancer, second line
Irinotecan	Colon cancer, second line
Capecitabine	Breast cancer, refractory
Liposomal cytarabine	Lymphomatis meningitis
Temozolomide	Anaplastic astrocytoma, refractory
Liposomal doxorubicin	Ovarian cancer, refractory
Gemtuzumab ozogamicin	AML, second line, elderly
Imatinib mesylate	CML, blast phase, accel. phase & failing interferon
Oxaliplatin	Colon cancer after failing bolus 5FU/LV and camptosar

The accelerated approval regulations were first applied to the approval of AIDS drugs. These early AAs used a different model of drug approval than that commonly used in oncology. AA was usually based on an interim analysis of a surrogate endpoint (e.g., CD4 count or later, viral load) evaluated in a randomized controlled trial. Subsequent proof of clinical benefit and regular drug approval were usually based on final analyses of the same trial. In contrast, AA in oncology has usually relied on response rate as the surrogate endpoint, usually determined in non-randomized trials with limited patient numbers. Clinical benefit has been demonstrated in randomized trials initiated after drug approval, usually in patients with less refractory tumors.

Although AA has been useful for approving many new anticancer drugs, there are disadvantages to drug development based on non-randomized Phase 2 trials in refractory populations. Once the drug is available, it may be difficult to initiate the required confirmatory RCT in the population for which the drug is approved. The small Phase 2 studies provide only limited safety data, and the drugs are often used after approval in a wider population than the one studied. These possibilities were recognized at the time

the accelerated approval rule was developed, and have often been considered acceptable risks, but they are real.

Evaluation of the ZD1839 data in a regulatory context

As outlined by Dr. Cohen, the applicant's efficacy claim is based on a 10% FDA-verified partial response rate in 139 patients with refractory NSCLC and the applicant's findings of improvements in cancer related symptoms and improvement in quality of life. These latter findings would be evidence of clinical benefit, not an effect on a surrogate.

Response rate results from third-line treatment

Is a 10% response rate in 139 patients sufficient to support AA in refractory NSCLC for a drug that, compared to many cytotoxic anticancer agents, is relatively nontoxic? Low response rates have been predictive of clinical benefit in some settings. Irinotecan received in the treatment of refractory colon cancer based on a relatively low response rate and subsequently demonstrated a survival benefit both in the refractory and the first-line settings.

Preliminary results from first-line treatment

Recently the applicant provided FDA with preliminary analyses of two trials evaluating standard chemotherapy plus or minus ZD1839 in first-line treatment of NSCLC. Despite about 350 patients per arm and adequate follow-up (about 240 events per arm) neither showed a survival benefit for ZD1339.

Study 14 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	365	243	9.9	44%
250 mg ZD1839	365	248	9.9	42%
Placebo	363	236	11.1	45%

Study 17 Survival

	At Risk	Events	Median in Months	1-year
500 mg ZD1839	347	246	8.7	38%
250 mg ZD1839	345	232	9.8	42%
Placebo	345	247	9.9	42%

Similarly there was no improvement in response rate:

	Study 14 Response Rate	Study 17 Response Rate
500 mg ZD1839	49.7%	32.1%
250 mg ZD1839	50.1%	35.0%
Placebo	44.8%	33.6%

Even though these data were generated in the first-line NSCLC treatment setting, they are important for our determination of ZD1839 efficacy in treating refractory NSCLC. Accelerated approval based on the surrogate endpoint of tumor response in the refractory setting has often been followed by clinical trials in first- or second-line treatment settings intending to demonstrate a survival benefit or some other clinical benefit. The FDA oncology group has never received an application for accelerated approval in refractory patients when definitive data in another related setting, such as first line treatment, show a lack of efficacy.

Tumor Symptom and QOL data from third-line treatment

What are the meaning of the analyses of tumor symptoms and QOL in the context of a single arm open study? The applicant has done a thorough job of evaluating symptomatic changes, but uncertainty regarding the meaning of these data cannot easily be resolved without a blinded study with a concurrent control arm. The applicant claims clinical benefit is demonstrated by individuals showing a 28-day, 2-point improvement on the 28-point Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L). The 2-point threshold is based on studies showing that a 2-3 point LCS change in study populations is correlated with changes in performance status, weight loss, and TTP. The applicant finds that about 40% of patients in Study 39 derive such benefit, and that the benefit correlates with response and survival. For instance, the rate of a 2-point response on the LCS was 96% for objective tumor responders, 71% for stable disease patients, and 17% for progressors.

There are fundamental problems with the applicant's symptom benefit claims. Without a concurrent control arm, we cannot know whether these symptom results might not be entirely from placebo effect, from hope associated with starting a promising investigational cancer drug. While a 2-point difference on the LCS determined in study populations may have some meaning in a randomized study, there are no data validating its use as an efficacy endpoint for individuals in a single-arm study. Alternatively, as noted by Dr. Cohen, some symptom improvement could be attributed to concomitant medications given to ameliorate these symptoms; or, in patients recently stopping chemotherapy, symptom improvement might occur with recovery from chemotherapy toxicity.

A correlation of positive symptom findings with response rate would not be unexpected. One might expect that responders would feel better after being informed of their tumor

status. Certainly some analytical bias would be expected; for instance, patients going off study early because of tumor progression might not provide sufficient data for the required 28-day verification of symptom response. Therefore, early progressors could not be symptom responders. The 2-point LCS response associations with tumor response and with survival could be due to shared prognostic factors, e.g., prognostic factors (known or unkown) for response, tumor symptom improvement, and survival may be similar. Rather than causing symptom improvement or survival prolongation, tumor response might merely be associated with symptom changes and longer survival through shared baseline prognostic factors.

In the final analysis, it is unclear that the changes observed on the LCS symptom scale represent significant clinical benefit and that the changes observed can be confidently ascribed to ZD1839 treatment. A randomized, blinded trial will be required to make this determination. Although such data might enter into one's judgement whether a 10% response rate is reasonably likely to predict clinical benefit in the refractory NSCLC setting, they clearly are not sufficient for a clinical benefit claim for full NDA approval.

Deliberations of the Oncologic Drugs Advisory Committee

On September 24, 2002, the ZD1839 NDA results were discussed before the Oncologic Drugs Advisory Committee (ODAC). At the open public hearing, a number of patients treated with ZD1839 on the expanded access protocol presented their anecdotal positive experiences. After applicant and FDA presentations, the ODAC addressed the following questions:

Questions to the Committee:

1. The FDA believes the relevance of the symptom improvement data discussed above cannot be adequately evaluated without a randomized, blinded study with an adequate control arm (the two doses of ZD1839 show no difference in efficacy and are thus not adequate). Do you agree?

   YES – 9 NO – 5

   The Committee felt that the data were supportive, but not definitive, given the lack of a blinded control arm.

2. Given the lack of clinical benefit in two large studies of ZD1839 in combination with standard first-line NSCLC chemotherapy, is the Study 0039 response rate of 10% in 139 patients with resistant or refractory NSCLC reasonably likely to predict ZD1839 clinical benefit in NSCLC?

   YES – 11 NO – 3

It was clear from the discussion that most ODAC members did not see a necessary connection between clinical benefit in the first-line combination setting

and the third-line treatment setting. Committee members did cite examples of agents with a cytostatic mechanism of action appearing to inhibit the beneficial effects of chemotherapy.

Discussion

The ODAC supported FDA's position that the symptom benefit data could not be adequately assessed without a concurrent control arm. These data will not be discussed further.

Whether the 10% response rate in lung cancer from Study 39 is reasonably likely to predict clinical benefit is the critical point for discussion. Clearly, response rates of a similar magnitude in some other tumors, such as metastatic colon cancer, have correctly predicted subsequent clinical benefit and have been the basis for accelerated approval. Obviously this is a judgement based on scientific knowledge and experience, and we must consider all available evidence. In this case, we also have an unprecedented additional consideration. We have two large randomized studies of excellent design that show no benefit for ZD1839 added to chemotherapy in first-line treatment of non-small cell lung cancer. Ironically, had ZD1839 already received accelerated approval, these studies would have served as phase IV post-marketing commitment studies to verify its clinical benefit. Now that these results have become available prior to a regulatory decision, we must weigh the significance of these negative findings on the accelerated approval process.

I believe these issues are in the realm of scientific and clinical judgement as intended by the writers of the 1992 accelerated approval rule. The AA requirements reflect both rigor and judgement, rigor in the demand for substantial evidence from adequate and well controlled clinical trials, and judgement in what constitutes a surrogate reasonably likely to predict clinical benefit. The ODAC represents an appropriate forum for obtaining scientific and clinical judgement, and the ODAC clearly advised that despite the first-line trials showing no survival benefit, clinical benefit in the third-line setting was reasonably likely.

The ODAC advice reinforces my pre-existing clinical opinion that these data are reasonably likely to predict clinical benefit. The following are several plausible views why ZD1839 might not provide clinical benefit in the first-line combination therapy setting and yet might still be reasonably likely to provide clinical benefit in the third-line treatment setting:

- There could be a pharmacodynamic interaction in the first-line treatment setting: ZD1839 could suppress tumor growth and thus protect tumor from the effects of chemotherapy. This explanation is supported by recent data suggesting interactions between hormonal agents (e.g., tamoxifen) and chemotherapy. For example, recent results reported at the May, 2002 meeting of the American Society of Clinical Oncology suggest that simultaneous administration of adjuvant chemotherapy and tamoxifen was less effective

than tandom use of these agents; disease-free survival was 67%, 62%, and 55% for tandom use, simultaneous use, and tamoxifen alone, respectively.

- Data from the first-line trials cannot address whether response rate is an adequate surrogate because the addition of ZD1839 to chemotherapy in first-line treatment did not significantly affect the response rates in either of the 1000 patient first-line trials. This contrasts with the single-agent ZD1839 response rates of 10% and 20% in the third-line and second-line settings, respectively.

- Treatment with chemotherapy could induce EGFR(TK) or other kinases that subsequently lend the tumor responsive to ZD1839 treatment in second-line or third-line settings.

- Third-line patients may represent a select subgroup of patients who are susceptible to ZD1839.

Phase IV Commitments

It may seem premature to discuss phase 4 commitments prior to giving a recommendation; however, phase 4 commitments are an integral part of an AA recommendation. It is conceivable that because of drug approval, clinical trials to establish clinical benefit could not be conducted. In such a circumstance, accelerated approval could not be granted.

The applicant has outlined 5 clinical trials that will be conducted as phase IV commitments under Subpart H. These are described in the following table from Dr. Cohen's review:

Study type	Study pts	Design	1° endpoint	2° endpoint	# patients	Complete date
Adjuvant	Stage IB, II, III Resected	Double-blind Placebo control	OS	DFS	1160	2007
Maintenance	Stage III Inoperable	Double-blind Placebo control	OS & PFS	--	840	2006
First-line	Stage III/IV PS 2-3 LCS ≤20 Medical conditions	Double-blind BSC control	Symptom improvement	OS TTP	207	2006
2nd or 3rd line	Stage III/IV PS 0-3	Double-blind BSC control	OS	PFS Symptoms	624	2006
2nd or 3rd line	Stage III/IV PS 0-2 LCS ≤20	Double-blind BSC control	Symptom improvement	OS TTP	207	2006

BSC=best supportive care; DFS=disease free survival; LCS= Lung cancer subscale; PFS=progression free survival; PS=performance status; OS=overall survival

Collectively, the studies evaluate potential ZD1839 clinical benefit in almost every remaining clinical setting. A survival advantage will be sought for adjuvant therapy following initial diagnosis and for maintenance therapy after optimal treatment of stage III lung cancer. In poor performance status patients, who generally do not tolerate combination chemotherapy, a placebo-controlled study will evaluate lung cancer symptoms on the LCS scale. In patients with refractory lung cancer, two placebo controlled studies at non-U.S. sites will be done. One will enter 624 patients and target survival. The other will enter 207 patients and target lung cancer symptoms.

Reviewer comment: The Division met with the applicant and found that these studies would provide sufficient evidence to determine whether ZD1839 provides clinical benefit in NSCLC. Clearly the adjuvant and maintenance studies will be performed, as they are ongoing cooperative group studies. The other studies will be done at non-U.S. sites, where ZD1839 will not be marketed and where use of a placebo (plus best supportive care) arm will be feasible. The three studies with a survival endpoint clearly have the potential to support regular approval. The two studies evaluating symptoms could provide sufficient evidence of clinical benefit if supported by response rates and time to progression advantages. Given the complexity of the various data, other than a survival advantage, it is not possible to specify exactly what set of such findings would support approval. The applicant could improve two trials designed to evaluate lung cancer symptoms by increasing sample size to provide sufficient power to evaluate TTP (This point will be communicated to the applicant).

Recommendations

I recommend approval of IRESSA® (ZD1839, gefitinib) under Subpart H (accelerated approval) for patients with non-small cell lung cancer that has failed both platinum-based and docetaxel chemotherapies. The five studies discussed above and reviewed by FDA in an October 9th meeting are acceptable Subpart H post-marketing commitments. Completion of these studies according to the schedule provided by the applicant would indicate "due diligence" as required under Subpart H regulations.

/S/

Grant Williams
Deputy Division Director
Division of Oncology Drug Products

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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 29, 2002

FROM: Robert J. Temple, M.D., Director
Office of Drug Evaluation I, HFD-101

SUBJECT: Iressa

TO: Richard Pazdur, M.D., Director
Grant Williams, M.D., Deputy Director
Division of Oncologic Drug Products, HFD-150

Rajeshwari Sridhara, Statistician
Division of Biometrics I, HFD-710

There is plenty to think about with respect to Iressa, but I don't think there is reason to doubt that it causes tumor responses.

1. There are more than 64 patients who are relevant to Iressa use in 3rd line therapy. Dr. Cohen chose to pool the 250 and 500 mg data, finding 14 of 139 responses, a 10% rate. This point estimate is lower than would be found in the 250 mg group alone and the lower bound 95% CI is similar either way (pooled or 250 mg group only). I agree with the choice of pooled data. The Japanese data, albeit in 2nd line patients, show no suggestion of a reduced effect at 500 mg. The relevant data base is therefore 139, not 64.

   Continued reference to the uncertainty (questionable reliability) attached to the estimates of response rate puzzles me. The reliability, I would have thought, is fully reflected in the quite wide 95% CI's for response rate. The CI's are indeed wide, but is there an implication in Dr. Sridhara's review that there is even greater uncertainty then is conveyed by the wide CI's?

2. There are additional data, not in 3rd line patients, that are also relevant to the question of whether Iressa can in fact shrink some tumors (even if it cannot when added to chemotherapy). These data are:

   a. The remaining patients in study 039 (n=77), who also had a RR of about 10%.

   b. The Japanese and Caucasian patients in study 016, who had a RR of about 28% (Japanese) and 9% (Caucasian).

   There is thus further reason to believe that the effect seen in study 039 reflects real activity, even if the RR has a wide confidence interval.

3. There are peculiarities in who the responders were. That most responses were in adeno Ca is not too surprising, as most people in study 039 probably had that histology (Dr. Cohen gives data on this only for the 216, not the 139 he considered relevant).

But most patients were males, and most were smokers, so that the excess of female, non-smoking responders is certainly of interest and should be reflected in labeling. (In the draft I saw, the female and adeno Ca findings were noted, but not, I think, the smoking status.

4. My comments do not reflect updated information on the pulmonary toxicity, but that aside, I am convinced that the response rate of about 10% is real and that, as the ODAC also concluded, this finding is not undermined by the results of first line combination therapy, which showed no response (including tumor response) of any kind.

We have accepted "modest" RR's in 3rd-line colorectal Ca as bases for accelerated approval, considering them "reasonably likely" to predict clinical benefit. If we can be satisfied as to the design and prospects of completion of the confirmatory studies and not considering at this point the pulmonary safety issues, I believe approval is consistent with current and recent policy, with FDA's publicly stated standards for oncology drugs, and with the intent of the accelerated approval regulation and Fast Track provision of FDAMA.

/S/

Robert Temple, M.D.

cc:
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Robert Temple
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MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 19, 2003

FROM: Robert J. Temple, M.D., Director
Office of Drug Evaluation I, HFD-101

SUBJECT: Iressa, Pulmonary Consult

TO: Richard Pazdur, M.D., Director
Grant Williams, M.D., Deputy Director
Division of Oncologic Drug Products, HFD-150

It is pretty striking that the rate of ILD in the large controlled primary therapy trials is pretty close (about 1%) to the rate in other (uncontrolled) data bases but there is no difference between the Iressa-treated and no-Iressa patients. Even if you believe the 2% Japanese rate, the rates are close. Doesn't this raise the question as to whether there is a real drug effect here?

/S/

Robert Temple, M.D.

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Robert Temple
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TELECON MINUTES

TELECON DATE: Feb. 28, 2003 **TIME:** 10:00

IND/NDA: IND [redacted] NDA 21-399

DRUG: Iressa **INDICATION:** NSCLC

SPONSOR: Astra-Zeneca (A-Z) **TYPE of MEETING:** NDA review update

FDA PARTICIPANTS: Grant Williams, M.D., Dep. Dir., DODP
Dotti Pease for Amy Baird, Project Manager, DODP

SPONSOR PARTICIPANTS:
Ron Falcone
Mark Scott
Keneally
O'Brien
U.K. rep.
Japanese rep.
@ 6 others (to be provided by A-Z)

MEETING OBJECTIVES: Discuss the status of pending NDA for Iressa

BACKGROUND: This was another of the weekly telecon updates re: this pending NDA.

DISCUSSION:

1. **Recent submissions by A-Z.**

   a. **Meeting Request** (2-3-03, recpt 2-5-03) re: labeling. A-Z wanted to know if there were any major labeling issues that have arisen thus far. FDA noted that the warning re: interstitial pneumonitis was the only one so far. In this regard, we also noted that A-Z has work to do re: the pharmacogenomic aspects of this safety issue.

   b. **Letter to investigators re: expanded access.** Dr. Pazdur had already said we had no comments on this, and we noted now that it did not directly impact our review of the NDA.

2. **Tradename consult to DMETS.** We will follow-up on progress of this consult.

3. **Any FDA feedback from yesterday's internal meeting?** FDA – no.

4. **The promised protocols.** A-Z has submitted the special protocol assessment for the survival study. (Unfortunately, it was submitted to the NDA and therefore could not be coded as an SPA.) We will try to expedite this review. The other two protocols (symptomatic endpoints) are under development; we noted we would like them ASAP. A-Z requested a written confirmation of what further (phase 4) trials will be required for the approval of Iressa.

ACTION ITEMS:

1. A-Z to call Amy for time for next telecon update and include several agenda items such as DMETs update and SPA update.

2. Amy to follow-up on tradename consult.

3. We will have interaction with A-Z on labeling when our reviewers are ready.

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/s/

Dotti Pease
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CSO

Grant Williams
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MEETING MINUTES

MEETING DATE: January 10, 2000 **TIME:** 2:30pm **LOCATION:** G

IND/NDA IND [redacted]

Meeting Request Submission Date: 8-23-99
Briefing Document Submission Date: 12-15-99
Additional Submission Dates:

DRUG: ZD1839

SPONSOR/APPLICANT: Zeneca Pharmaceuticals

TYPE OF MEETING:

1. Discuss how Zeneca might accelerate development after having been granted fast track designation.

2. **Proposed Indication:**

FDA PARTICIPANTS:

Robert Temple, M.D., Director, ODEI
Rachel Behrman, M.D., Deputy Director, ODEI
Richard Pazdur, M.D., Director, HFD-150
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INDUSTRY PARTICIPANTS:

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Steven D. Averbuch, M.D., Sr. Medical Director
Judith J. Ochs, M.D., Medical Director
Michael K. Wolf, Global Project Statistician
Martin C. Dyroff, Ph.D., International Project Toxicologist
Ronald C. Falcone, Ph.D., Dir., Regulatory Affairs
Sandra Bihary, MSN, Exec. Dir., Regulatory Affairs
Maureen A. Morgan, Regulatory Project Manager

MEETING OBJECTIVES:

1. Discuss sponsor's questions in briefing document dated 12-15-99.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. **The data from trial 16 will be available in advance of the first-line Phase III trials. Assuming an outcome that provides sufficient evidence for meaningful clinical benefit, is the proposed trial design acceptable for registration in patients with chemotherapy refractory NSCLC?**

FDA Response:

The recent approval of Taxotere as second line treatment for NSCLC on the basis of improved survival makes this trial design inadequate for registration for this indication. We would recommend either:

- Restricting eligibility to patients who have been exposed to both a platinum-containing regimen and Taxotere (3rd line indication) in which case response rate would be an acceptable endpoint for accelerated approval. However, we expect the response rate to be quite low.

- We would strongly recommend a randomized trial of Taxotere +/- ZD1839 (500mg, 250 mg, or placebo) with survival as the primary endpoint. Given the mechanism of action of this drug, we believe that a demonstration of improvement in survival is preferable to an improved response rate.

2nd Line Taxotere Trial

Taxotere +/- ZD1839
Controlled trial – 2 doses
Double-blinded trial

<u>After failure of taxane regimen</u>

Carboplatin
+ (or) + Taxol → ZD1839 (2 doses)
Cisplatin
Double-blinded

Primary endpoint is symptomatic improvement or delay in onset of symptoms. Duration of symptomatic response should be at least 4 weeks. These 2 trials could provide a full approval if symptomatic benefit is clearly demonstrated. Accelerated approval is possible if clinically meaningful response rates are seen.

Discussion:

Zeneca will consider this.

2. **Currently, there is no approved chemotherapy for patients with NSCLC who have poor performance status. Therefore, Zeneca has designed trial 16 to include a stratum of patients who have a WHO performance status of 2. We believe that this patient population fits the criteria "for unmet medical need or where there is a need for alternative treatment." This stratum will be subject to independent analyses for the study endpoints. Does the Agency agree that inclusion of this population within this trial will support the inclusion of NSCLC patients with a WHO performance status of 2 in the registration package?**

FDA Response:

- We recognize the desirability of a less toxic agent for use in patients with poor performance status, however the subjectivity of PS 2 criteria (i.e. "unable to work") makes it inadequate for registration as a separate indication. We recommend development of objective clinical criteria such as patients with renal impairment who are ineligible for platinum-based treatment, or patients with clinical characteristics which have been validated as surrogates for poor performance status, such as Hgb, albumin, etc., and that makes them unsuitable for Taxotere. Alternatively, a PS of 3 might be more acceptable as a criterion for significantly impaired performance status.

3. **Zeneca has chosen the Southwest Oncology Group modified WHO criteria adapted to NSCLC as it includes the significant subset of patients with non-measurable evaluable disease and it has been extensively used [Green and Weiss, *Investigational New Drugs* 10:239-53, 1992]. Is this acceptable to the Division?**

FDA Response:

- If a registration study were designed with response as the primary endpoint, we would recommend reporting non-measurable PR's separately from conventional PR's.

4. **Zeneca believes that a maximally tolerated dose is inappropriate for determining the doses for a chronic, continuous, daily, oral therapy of a selective EGFR-TK inhibitor such as ZD1839. Therefore, as described in the Clinical Summary update submitted in this package, the doses in Trial 16 are based on tolerability, pharmacokinetic, and efficacy data from over 200 patients in the Phase 1 trials. Is this acceptable to the Division?**

FDA Response:

- It is reasonable to do a dose response study at this stage in development. However, we don't have sufficient information to recommend specific doses at this time.

5. **Zeneca feels that a weekly symptom checklist, the Lung Cancer Subscale (LCS) component of the validated FACT-L Quality of Life instrument and a monthly Quality of Life (QOL) assessment using FACT-L is preferred for accurately measuring symptom and QOL parameters. Cella DF et al., Journal of Clinical Oncology 11(3):570-579, 1993 and Cella DF et al., Lung Cancer 12(3):199-200, 1995. Does the Division agree?**

FDA Response:

- We agree that measurement of QOL is problematic, and the FACT-L quality of life instrument is an acceptable method for the measurement of QOL changes in lung cancer patients, however we would like to avoid burdening study patients excessively with surveys. Biweekly measurement with this QOL instrument may be adequate. We recommend that you study a prespecified small subset of symptoms if this would facilitate compliance and reduce missing data. QOL analysis will be considered exploratory, based on your proposed plan.

Discussion:

Question will be revisited after submission of protocols.

6. **The correlation of EGF-receptor expression or overexpression to ZD1839 effect on clinical outcome has not been established. Zeneca is committed to studying and understanding this relationship, but does not anticipate having sufficient data to answer this question by the time the NDA is submitted for a refractory NSCLC indication. Is this acceptable to the Division?**

FDA Response:

- Availability of EGF – receptor study results is not required for NDA filing and review.

Discussion:

Results should be submitted as soon as it is available.

7. **Corneal changes have been documented in preclinical toxicology studies. In the clinical trial program to date, Zeneca has conducted extensive serial monitoring of the cornea in over 250 patients and healthy volunteers. Preliminary review of these data does not suggest any clearly associated corneal adverse events or safety trends. While these data are still under review, Zeneca is seeking confirmation that the attached proposed plan is an appropriate and acceptable schematic to refine screening and monitoring of patients for corneal safety. Does the Division agree? (*Corneal safety decision tree attached)***

FDA Response:

- Given the low incidence of corneal pathology reported in the phase 1 trials, we would suggest that a complete monthly ophthalmologic evaluation as specified in table 2 is not necessary for patient safety. Instead an initial complete evaluation, monthly visual acuity, and complete reexamination at the termination of study or as needed for symptoms or changes in acuity would suffice to ensure patient safety. The corneal safety monitoring flow diagram is unclear in terms of how decisions concerning corneal safety are to be made. We suggest that any observed corneal pathology be reported in the usual manner for a significant adverse event.

Question regarding First Line NSCLC Indication

8. **Zeneca is planning to conduct two randomized Phase III clinical trials combining ZD1839 with a commonly used combination chemotherapy regimen compared to placebo combined with chemotherapy. We are planning on utilizing Gemcitabine/Cisplatin (ZD1839IL/0014) and Paclitaxel/Carboplatin (ZD1839IL/0017), respectively, in combination with ZD1839. Does the Division agree that these combinations constitute representative and acceptable standard therapies? Does the Division agree that positive outcomes from these randomized trials would support the use of ZD1839 in combination with standard cytotoxic chemotherapy in patients with advanced NSCLC?**

FDA Response:

- We agree that these regimens represent acceptable standard therapy. In general, survival is preferred as the primary endpoint, however a significant improvement in PFS might support approval if the results are dramatic, and if significant improvement in disease-related symptoms and/or QOL is demonstrated.

- You may wish to study time to symptomatic progression since most patients on this study will be asymptomatic at baseline. We would consider this as evidence of unequivocal clinical benefit.

Statistical Comments:

1. The sample size calculation should be based on an adjusted significance level for the two primary endpoints (survival and DPS) if DPS is an acceptable primary endpoint for NSCLC.

2. We think the noninferiority analysis is not necessary.

Biopharmaceutical Comments:

You plan to perform population pharmacokinetic (PK) analysis on the trough plasma levels (Cmin) that will be obtained from patients during the Phase II trial No. 1839IL/0016. The population PK analysis study should be prospectively designed. Aspects such as objectives, sampling schedules, model building and validation, and covariates that will be tested should be adequately defined in the study protocol. The study protocol should be submitted to the Agency for review.

Additional Biopharmaceutical Comments:

All of the items below (Recommendations) should be addressed in Item 6 of the NDA; Item 6 will be reviewed comprehensively according to the Recommendations. The NDA should be organized to address each of the below recommendations in a single comprehensive section. That is, all studies that bear on an issue should be integrated into a single comprehensive section; a study-by-study description is less useful than the integration of all relevant studies into a whole. As an example, within the comprehensive section for recommendation 3. below, all studies that contribute to an estimation of clearance for each relevant species should be used to derive a single point estimate of clearance and its variability for that species in the patient population that will receive the drug for the approved indication in post-approval clinical use. If a recommendation is not heeded, the comprehensive section of the NDA addressing that recommendation should provide justification for the omission. Individual study reports should be included in the NDA, but should occur at the end of the submission -- after all of the recommendations have been have been addressed as described above.

During the development program, you are encouraged to seek guidance before choosing not to heed a recommendation. In this way, you can learn if the failure to obtain the data under question will likely seriously compromise the NDA.

1. The plasma profile of the drug and its metabolites in humans should be reported. What is desired is a "plasma mass balance" accounting of drug and drug-derived species. This is most often accomplished by administering radiolabelled drug and quantitating both the total radioactivity present in plasma and the radioactivity contained in individually identifiable species present in plasma. The scheme used to develop the plasma profile (i.e., separate parent and any metabolites) should be given.

What is desired is only the scheme used to search for all reasonably quantifiable metabolites -- a detailed description of the analytical methods should not be given here, but in a separate section (see 9. below). The review of this scheme will attempt to assure that reasonable effort was made to fully characterize the metabolic profile of the drug. The plasma profile study should use a dose that approximates the recommended dose in the dosage and administration portion of the proposed package insert. Quantitating the recovery of drug and drug-derived species in feces and urine while acquiring the above information sometimes alleviates the need to determine disposition in patients with renal or hepatic compromise (see 4. below).

2. A description of how the specie(s) selected for measurements in pharmacokinetic studies were selected should be given. All species described in 1. above, are potential candidates for measurement; this section will describe which ones were selected. What is desired in this portion of section 6 is the scheme used to determine what to measure in PK studies -- a detailed description of the methods and results of any pre-clinical screening should not be included in section 6. The results of this determination should guide all PK measurement in section 6 -- not just selected studies.

3. The pharmacokinetics of all relevant species (C_{max}, T_{max}, AUC, terminal half-life, clearance, volume of distribution, etc.) across the recommended dosing range in the targeted population should be reported. For drugs demonstrating saturable protein binding at in vivo concentration, it may be necessary to measure free drug. The PK data should be used to attempt to establish pharmacokinetic/ pharmacodynamic relationships for each species. Desired pharmacodynamic endpoints are both the pharmacologic and toxicologic variables used in assessing the safety and efficacy of the drug. To allow for the entire database to be used (i.e., to include those individuals who were only sparsely sampled), and to obtain estimates of both inter- and intra-individual variability in parameters, a population approach is recommended.

4. The pharmacokinetic database should be analyzed to discern if there are differences in PK or PK/PD due to gender, ethnicity, renal status, hepatic status, or age (geriatric and pediatric). If the demographics of the database are insufficient to produce reasonable power to discern differences in these cohorts, it may be necessary to report the results of individual studies in some or all of these populations. All relevant species should be quantitated.

5. Pharmacokinetic and metabolic interactions with anticipated concomitant medications should be reported. For agents always or often co-administered, a clinical pharmacokinetic study may be necessary. To gain insight on potential drug interactions, a characterization of the enzymatic routes through which biotransformation occurs, especially the cytochrome P450 isozymes involved in biotransformation, is recommended. Similarly, a characterization of in vitro plasma protein binding of the drug and all of its metabolites is recommended.

6. The effect of food on the bioavailability and pharmacokinetics of the drug should be studied. This is best performed with the to-be-marketed formulation and at the maximum labeled dose. A high fat meal should be used (FDA has issued guidance on meal composition), and the composition of the meal(s) should be documented in terms of calories and fat, protein, and carbohydrate content.

7. If the clinical trials and the to-be-marketed formulations are not the same, establishment of bioequivalence between these formulations is required. Also, if the drug product is to be marketed in different strengths and if these strengths are not compositionally proportional, establishment of bioequivalence between the strengths is required. Bioequivalence assessment should be performed on both raw and log transformed data; the two one–sided test procedure (90% confidence intervals) should be used for bioequivalence assessment. Minimally, AUC0-t and C_{maxobs} should be tested for bioequivalence. A detailed statistical report, including ANOVA analysis, should be provided.

8. For the dosage form(s) studied clinically, dissolution profiles should be submitted in simulated gastric fluid (without enzymes) and simulated intestinal fluid (without enzymes). Other media (i.e., different pHs, surfactants, etc.) should be studied as appropriate given the drug's solubility characteristics. In media where sink conditions exist, dissolution profiles should be carried out to where at least 80% of the drug is dissolved. For the water dissolution medium, pH should be determined before and after drug dissolution. Twelve dosage units per dosage form per dissolution medium should be provided. If the solid dosage form can be broken for dose administration, similar in-vitro dissolution information should be provided for the broken dosage form. All dissolution data for all formulations studied clinically in the NDA should be submitted. For the to-be-marketed formulation, a minimum of three lots, with a minimum of twelve units randomly sampled from each lot, need be tested according to the specifications previously agreed to during correspondence between the sponsor and the Agency. All raw data should be included for all dissolution studies submitted. Raw data includes analytical methods data (see 9. below for format), a description of the tablet/capsule studied (formulation, batch size, lot number, date of manufacture, expiration date, etc.) for each tablet or capsule studied and % dissolved at each time point for each tablet or capsule studied.

9. A detailed description of the analytical method used for the quantitation of the drug and its metabolites, its validation, the organization of the analytical run (chronology of the samples, standard curves, within-run standards, blanks, etc.) and the performance of the method should be submitted for each study and for all stability testing. The assay performance sections should contain the following: sensitivity, specificity (cross-reactivity if appropriate), recovery, linearity, % accuracy and precision (within and between runs) for the analysis of the drug/metabolite in serum, urine, and any other relevant biological fluids using quality control standards and

representative standard curves covering the range of the observed concentrations found in the study. Stability data during i) the collection and processing of samples, ii) storage of samples, and iii) the assay procedure itself, should be provided.

10. All batches studied and the proposed production batch should be properly identified in terms of formulation, batch size, lot number, date of manufacture, expiration date etc.

11. Besides hard copies, all raw biopharmaceutic/pharmacokinetic data contained in the NDA should be submitted in electronic format (ASCII or Microsoft EXCEL 5.0 for Windows, or formats readily converted to ASCII or EXCEL 5.0 by tools possessed by the Agency). Patient/subject data should include a number that uniquely identifies each subject, study number, site number, absolute dose administered, batch # and lot # of dose administered, actual sampling time, concentrations, pharmacodynamic/ toxicodynamic measurements and demographic data that might influence parameters (i.e., age, weight, body surface area, gender, ethnicity, co-medications, smoking status, etc.). The name(s) and version(s) of software used in all modeling of the data should be noted, and the actual code used in modeling should be submitted in hard copy and, if reasonable, in electronic format.

12. Besides hard copy, the draft package insert should be submitted in electronic format. ~~The reviewer uses Microsoft Word 7.0 for Windows on an IBM-PC-compatible~~ microcomputer.

13. Besides hard copy, electronic submission of text and figures is strongly encouraged but not strictly required. The reviewer uses WordPerfect 6.1 for Windows on an IBM-PC-compatible microcomputer. The desire for electronic submission of text and figures is distinct from the requests in 11. and 12. above. Since any electronic submission of text and figures is a convenience for the reviewer, mixed electronic formats or submission of only selected studies or portions of selected studies is preferable to no electronic submission.

The meeting was concluded at 4:00 pm.

/S/ CSO
Amy Chapman 2-17-00
Project Manager
Minutes Preparer

Concurrence Chair: /S/
Peter Bross, M.D.
Medical Reviewer

Attachment: A copy of Zeneca's slides presented at the meeting.

cc:
Orig. INDs [redacted]
HFD-150/Div. File
HFD-150/Bross/Justice/Duffy/Liang/Andrews/Zheng/Chen/Rahman/Ibrahim/Pease/Chapman

MEETING MINUTES

MEETING DATE: June 14, 2001 **TIME:** 9:30am **LOCATION:** F

IND/NDA IND [redacted]

Meeting Request Submission Date: 4-20-01
Briefing Document Submission Date: 5-30-01
Additional Submission Dates:

DRUG: Iressa (ZD1839)

SPONSOR/APPLICANT: AstraZeneca Pharmaceuticals

TYPE OF MEETING:

1. Pre-NDA.

2. **Proposed Indication:** [redacted]

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, HFD-150
Grant Williams, M.D., Clinical Team Leader, HFD-150
Peter Bross, M.D., Clinical Reviewer, HFD-150
Eric Duffy, Ph.D., Chemistry Team Leader, HFD-150
Dave Morse, Ph.D., Supv. Pharmacologist, HFD-150
Dave McGuinn, Ph.D., Pharmacology Reviewer, HFD-150
Rajeshwari Sridhara, Ph.D., Statistical Reviewer, HFD-150
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, HFD-150
Sophia Abraham, Ph.D., Biopharmaceutical Reviewer, HFD-150
Amy Baird, Consumer Safety Officer, HFD-150

INDUSTRY PARTICIPANTS:

RAV Milsted, M.D., V.P., Regulatory Affairs Oncology
Gerard Kennealey, M.D., V.P. Clinical Research, Oncology
Mark Rickards, Product Director
Steve Averbuch, M.D., Global Product Team Physician
Judy Ochs, M.D., Sr. Medical Director
Andrea Kay, M.D., Medical Director
Ron Falcone, Ph.D., Director, US Regulatory Affairs
Leonid Freytor, M.S., Associate Director, US Regulatory Affairs
Maureen Morgan, M.S., Project Manager, US Regulatory Affairs
Rick Lampe, M.S., Project Associate, US Regulatory Affairs
E. Jane Valas, Ph.D., Associate Director, US Regulatory Affairs
Frances Kelleher, Ph.D., Director, World Wide Regulatory Affairs
Michael Wolf, M.S., Global Product Statistician
Helen Swaisland, BSc. Clin. PK, Experimental Medicines
Michael Hutchison, Ph.D., Assoc. Director, Development DMPK
Yasuo Kotera, Ph.D., Regulatory Strategy Manager – Japan
Laura Helms, Dr PH, Sr. Statistical Scientist

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated 5-30-01.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Human Pharmacokinetics and Bioavailability

1. **We believe our plan of characterization and quantification of ZD1839 metabolites for the NDA is adequate. Does the Division agree?**

FDA Response:

- Yes.

2. **A study to assess the effect of hepatic impairment of the pharmacokinetics of ZD1839 is underway, (1839IL/0032). However, due to the slow rate of recruitment, this study will not be completed in time for the submission of this NDA. The intention is that this would be reflected in the proposed package insert. The hepatic impairment study is on track to be completed in time for submission with the 1st line NSCLC combination trials as per previous agreements with the Division. Does the Division agree with this approach?**

FDA Response:

- Yes.

Clinical

3. **Based on discussion at the May 18, 2001 meeting we plan to include only studies that are related to ZD1839 monotherapy treatment of patients with NSCLC. There have been 689 patients enrolled in the clinical trials proposed for inclusion in the rolling NDA. Table 1 provides the overall number of patients enrolled in trials contained in the application. Table 2 lists the clinical trials, along with their respective submittal dates, proposed for inclusion in the rolling NDA. Table 3 lists trials that have been initiated for other indications that will not be included in this NDA. Any other trials that are subsequently initiated by AstraZeneca will not be included in the NDA. Trials which are not under IND [redacted] will not be included in the NDA. Does the Division agree with this proposal?**

FDA Response:

- You should submit safety data from other trials, including the expanded access trials (50 and 52), specifically unexpected adverse events.

4. **As there is a single pivotal (ZD1839/0039) and a single supportive trial (ZD1839/0016), AstraZeneca does not believe there is a need for Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE). Efficacy and safety data, including Tables and Listings, will be contained in Clinical Trial Reports for Trials 0039 and 0016, the content of which will conform to the guidelines/checklist provided in an FDA facsimile dated May 21, 2001. Item 3H of the NDA will provide the integration of efficacy and safety data contained within these reports. AstraZeneca believes that this plan is based upon an adequate rationale and provides information traditionally presented in the ISS and ISE. Does the Division agree?**

FDA Response:

- To expedite review of the NDA, we prefer to receive paper and electronic ISS and ISE reports, around the time of submission of trial 39 data. However, the clinical review will begin when trial 16 is submitted.

5. **Based upon the May 18, 2001 discussions with the Division, the quality of responses and specific disease-related symptom improvements observed in Trials 0039 and 0016 will be detailed in patient case histories. In particular the individual disease related symptom scores from baseline will be provided for each responding patient. Changes in the patients responses to the 7 questions**

of the Lung Cancer Subscale (LCS) also will be individually examined. These will be characterized for each patient as follows:

- I have been short of breath.
- I am losing weight.
- My thinking is clear.
- I have been coughing.
- I have a good appetite.
- I feel tightness in my chest.
- Breathing is easy for me.

The baseline characteristics of patients with a response or symptom improvement will be characterized relative to the entire trial population. The radiological studies that show objective response will be submitted to the Division as digitized data for Trial 39 and as a mix of hard copy and digitized data for the other monotherapy NSCLC trials (0016, 0005, 0011, 0012, and V-15-11). (See also Question in Section 3.4)

Case histories will be provided for patients with responses and/or durable stable disease (≥ 6 months) in the Phase 1 program.

Specific examples of patient symptom improvement case histories and radiological responses will be provided to the Division no later than July 15, 2001 for their review and comment to guide the final submission.

AstraZeneca believes that this approach could provide evidence of meaningful clinical benefit. Does the Division agree?

FDA Response:

- No. This data will be considered supportive to the validity of response rate for accelerated approval but is not likely to be included in the labeling.

6. AstraZeneca had requested and received a Written Request for pediatric study from the FDA pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (Pediatric Exclusivity) on December 12, 2000. Summaries of trials which we expect to start in pediatric patients by the end of 2001 can be found in Appendix C. AstraZeneca will present to the FDA its proposed pediatric studies, as part of a pediatric patent exclusivity study program. The proposed program would include safety, pharmacokinetic, and tumor response data in children with advanced solid tumors, neuroblastoma, and glioma.

AstraZeneca considers that such a proposed program would meet the Division's needs for the formal requirement of studying a pediatric population with ZD1839 for a 6-month patient exclusivity extension. Does the Division agree?

FDA Response:

- Yes.

7. AstraZeneca intends to request a waiver for NSCLC in the pediatric population at the time of NDA filing. Does the Division agree?

FDA Response:

- Yes.

Regulatory Issues

8. AstraZeneca proposes to submit Clinical Trial Reports, Datasets with Data Definition Tables and Annotated Case Report Forms, and Case Report Forms for Trials 5, 11, 12, 16, and 39 as Units of Information for each Trial on a rolling basis on the following timeline:

Trial 5	July
Trial 11	August
Trial 12	September
Trial 16	October
Trial 39	December

Case Report Forms will not be available for V-15-11 at the time (September) the Clinical Trial Report and Dataset will be submitted due to translation issues.

Item 2 (Labeling), 4 (CMC), 5 (nonclinical as CTD format) and 6 (HPB) will be provided as complete Items on a rolling basis (October thru December). The remaining parts of Items 8 and 10 (i.e. List of Investigators, Background and Overview; Integrated Summary of Benefits and Risks; and Drug Abuse and Overdose), 11 and 12 will be provided in December. The last contribution to the NDA will contain the administrative Items (13-20) as well as Item 3 which will also be submitted in December. This contribution will include a comprehensive Item 1 for the NDA containing pathnames for all contributions, but without hypertext linking.

Will this proposal for rolling submission be acceptable?

FDA Response:

- You should submit the pre-clinical sections in July so that the NDA process is begun. We prefer that you submit the clinical trials 5, 11, 12, and 16 together in October versus staggering their submission, since review will not begin until we have enough response data in order to make a decision with respect to the priority status of the review.

Discussion:

- Sponsor also to submit a complete list of all testing and manufacturing sites for CMC. List to include contact name, telephone number and addresses.
- Summary of the CMC Section of the NDA is all that is needed in order for inspection to take place. Complete section is not needed.
- Sponsor is aiming for December for submission of CMC section.

9. **Due to the rolling submission, the annotated label will be linked to summary documents (within Item 3) but not to the Technical Items. The Table of Studies in Items 6 and 8 as well as the List of Investigators will not be hypertext-linked to documents cited, but pathnames will be provided for contributions. Lists of formulations presented in Item 3 Chemistry and Item 4 will not be hypertext linked to individual preclinical and clinical study reports.**

   Will this be acceptable?

FDA Response:

- Yes.

10. **The safety cut-off date for the pivotal and supportive trials to be reported in the NDA is planned for August and May 2001, respectively. The amount of additional safety data that is going to be collected between the cut-off date and the date of filing of the NDA in these trials is expected to be minimal and will not affect the conclusions reached regarding the overall safety profile of ZD1839 in this patient population. Thus, the absence of this additional safety data is not expected "to reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling", which is the**

reason provided in 21 CFR 314.50 for the requirement of 4-month safety update. Therefore, pursuant to 21 CFR 314.90 AstraZeneca requests a waiver of the 4-month safety update.

Does the Division agree with AstraZeneca proposal?

FDA Response:

- No. Since the trials were conducted over a relatively short period of time, a 4 month safety update should be submitted for serious adverse events reported for all the monotherapy trials including 50 and 52 plus serious unexpected adverse events reported in the combination trials.

Electronic Submission Questions...Datasets

11. For each data warehouse provided to support CTRs, the following will be provided electronically:

- **Case Report Forms (CRFs) annotated with SAS variable names**
- **Data definition Tables**
- **Datasets will be provided in SAS version 5 transport format.**

The data warehouse will consist of:

- **Raw datasets – These are datasets for each CRF which will include all data which as been recorded on the database management system, which has had minimal manipulation, (i.e. formatting and labeling of variables, merging of terminologies and ranges).**
- **Analysis datasets – These contain data which have been manipulated to contain derived values. They are in a report ready structure and are used to perform the analysis. Each analysis dataset will be merged with a subset of the Demography dataset variables. Examples of datasets of Trial 0039 are presented in Table 4.**

SAS data warehouses will be provided for the following CTRs:

V-15-11
1839IL/0005
1839IL/0011
1839IL/0012
1839IL/0016
1839IL/0039

Details of the analysis dataset structures will be provided at a later time prior to submission, if requested by FDA. Most coded variables will be presented as codes, e.g., Yes and No would be held as Y and N in the database. Where it is not obvious from the variable value what the decode would be (and there is no supporting annotated CRF to refer to), the variable will be presented decoded, e.g., in an analysis dataset (DDEMOG) the derived response variable BESTRESP would have values of 1 = CR, 2 = PR, 3 = SD, 4 = PROG.

AstraZeneca believes that the list of the data sets for Trial 0039 is sufficient for review. Does the Division agree?

FDA Response:

- Yes.

Human Pharmacokinetics & Bioavailability (HPB) Datasets

12. **A data warehouse containing only analysis datasets will be provided to support the HPB. The structure and content of these datasets are still under development by AstraZeneca. The dataset structures will be based on the structures for 1839IL/0039 and are expected to consist of the following datasets:**

DATASET NAME	DATASET DETAILS
DDEMOGV	Demography – Volunteers data
DDEMOGP	Demography – Patients' data
PKV	Pharmacokinetic – Volunteers data – derived parameters
PKP	Pharmacokinetic – Patients' data – derived parameters and pharmacokinetics concentrations

AstraZeneca believes that the list of the data sets is sufficient for review of the HPB Section. Does the Division agree?

FDA Response:

- Yes.

13. As the majority of Non-clinical reports are Legacy reports (written prior to January 1999), AstraZeneca proposes to provide all Non-clinical reports as bookmarked pdf files without hypertext links. Will this be acceptable?

FDA Response:

- Yes.

14. AstraZeneca believes that the contents, as presented in draft Item 1 (Appendix A) and as described in this briefing document, will be sufficient to allow the review of this NDA. Does the Division agree?

FDA Response:

- Yes. However, we request paper copies of the clinical trial reports and the ISS and ISE. Specifically, 1 archive copy and 3 desk copies for trials 16 and 39.

15. A stand-alone electronic film library, which includes all radiological studies from the patients who experienced a complete or partial response from the pivotal trial 1839IL/0039, will be provided as a review aid. This film library will not be hyperlinked to the clinical trial report or the case report forms. The electronic format for the film library is as follows:

The Digital Image Warehouse consists of a stand-alone Windows NT/Windows 2000 workstation which includes the Cheshire software, a validated MS Access database with Patient index information and the CDROM library containing the stored digital images of the patient radiographs.

For all other trials we intend to provide radiological studies from the responders as a review aid.

A Word version of the Package Insert will be provided as a review aid. Will these Review Aids be compatible for use by the Division?

FDA Response:

- Yes.

Additional Comments:

During our last meeting we discussed having early FDA access to the data/films on the responders from trial 039. Our assessment of these responses may determine how we approach the review.

When would you be able to provide FDA review of the response data from 039?

Sponsor Response:

- Approximately July 1, 2001.

The meeting was concluded at 10:45am.

/S/

Amy Baird
Project Manager
Minutes Preparer

Concurrence Chair: /S/

Peter Bross, M.D.
Clinical Reviewer

Attachment: AstraZeneca overheads presented at meeting.

Redacted 9

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secret and/or

confidential

commercial

information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Peter Bross
8/23/01 05:27:49 PM

Office of Drug Safety

MEMO

To: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

From: Jennifer Fan, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

CC: Amy Baird
Project Manager, Division of Oncology Drug Products
HFD-150

Date: April 14, 2003

Re: ODS Consult 02-0171-2; Iressa (Gefitinib Tablets) 250 mg, NDA #: 21-399

This memorandum is in response to the March 13, 2003 request from your Division for a re-review of the proprietary name, Iressa. Comments were also made by the Division of Medication Errors and Technical Support (DMETS) on the submitted draft container label. DMETS originally reviewed the proposed proprietary name, Iressa, and found it unacceptable on September 13, 2002 due to look-alike and sound-alike similarities with the marketed drug, Alesse (ODS Consult 02-0171). DMETS also reviewed the sponsor's rebuttal dated September 30, 2002 and did not recommend the use of the proprietary name, Iressa, on October 23, 2003 (ODS Consult 02-0171-1).

Since these initial reviews, DMETS has identified an additional proprietary name that has the potential for confusion with Iressa.

Evista contains raloxifene hydrochloride and is indicated for the treatment and prevention of osteoporosis in postmenopausal women. Both proprietary names contain three syllables. The first syllable "Ires" in Iressa may sound similar to "Evis" in Evista, especially when a prescription is taken over a telephone. The last syllable "sa" in Iressa and the "sta" in Evista may also sound similar, depending on how well the practitioner enunciates when giving a

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RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Ronald Falcone, Ph.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 827-4590
Phone:	302-886-2715	**Phone:**	(301) 594-5779
Pages (including cover):	2	**Date:**	May 1, 2003
Re:	NDA 21-399 Iressa. Subpart H and Phase 4 commitments.		

✓ **Urgent** ☐ **For Review** ☐ **Please Comment** ✓ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Attached are the subpart H and phase 4 commitments that will be in the accelerated approval letter for Iressa. Please provide a written commitment to me via facsimile that AstraZeneca agrees to these subpart H and phase 4 commitments. Please call should you have any questions.

Thank you.

/S/

Amy Baird

****
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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

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Pages (including cover):	2	**Date:**	May 1, 2003
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✓ **Urgent** ☐ **For Review** ☐ **Please Comment** ✓ **Please Reply** ☐ **Please Recycle**

• Comments:

Attached are the subpart H and phase 4 commitments that will be in the accelerated approval letter for Iressa. Please provide a written commitment to me via facsimile that AstraZeneca agrees to these subpart H and phase 4 commitments. Please call should you have any questions.

Thank you,

/S/

Amy Baird

AstraZeneca

AstraZeneca
A Business Unit of Zeneca Inc.
1800 Concord Pike PO Box 15437
Wilmington, DE 19850-5437

Fax Cover Sheet

To: Amy BAIRD		**Fax number:** 301-827-4590	
Company:		**Phone number:**	
From:	Ron Falcone	**Fax number:** 301-885-5140	
		Phone number:	
Date/Time:		**Total pages:**	
Subject: Phase IV + Subpart H			

Comments: Hi Amy,

As discussed – pls let me know if you have any questions

Kind Regards

Ron

AstraZeneca

Dr. Richard Pazdur
Division Director
Division of Oncology Drug Products
Food and Drug Administration
HFD No. 150, Room No. 2055
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852-1448

Re: NDA21-399
IRESSA®, (gefitinib tablets) ZD1839
Subpart H and Phase IV commitment

Dear Dr. Pazdur:

Reference is made to the facsimile of May 1, 2003 in which Subpart H and Phase IV commitments were provided. In this regard, AstraZeneca hereby agrees to the Subpart H and Phase IV commitments as outlined in the aforementioned facsimile.

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Should you have any further questions, please do not hesitate to call me, or in my absence, please contact Rick Lampe, at 302-886-8546.

Sincerely,

Ronald C. Falcone

Ronald C. Falcone, Ph.D.
Director, Oncology
Regulatory Affairs Department
(302) 886-2715
886-2822 (fax)

US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
AstraZeneca UK Limited	
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(800) 456-3669	(302) 886-2822
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE:
Silk Road Business Park Macclesfield, Cheshire SK10 2NA, England	AstraZeneca Pharmaceuticals LP Ronald Falcone Ph.D Regulatory Affairs Director 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355 (302) 886-2715 (302) 886-2822

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-399

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*,	PROPRIETARY NAME *(trade name)* IF ANY
gefitinib	IRESSA

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
4-(3-Chloro-4-fluorophenylamino)-7-methoxy-6-(3-(4-Morpholinyl)propoxy)-quinazoline	ZD 1839

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	250 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment of patients with advanced non small cell lung cancer who have received a platinum and a taxane

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS: ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d) (1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e) (2) (i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d) (2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d) (3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d) (4))
☐	8. Clinical data section (e.g., 21 CFR 314.50 (d) (5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d) (5) (vi) (b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d) (6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f) (1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f) (2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k) (1))
☐	17. Field copy certification (21 CFR 314.50 (l) (3))
☐	18. Use Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense. U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Ronald C. Falcone	Ronald Falcone Ph.D Regulatory Affairs Director	

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1800 Concord Pike ,P.O. Box 8355 - Wilmington, DE 19803-8355	(302) 886-2715

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Ronald Falcone, Ph.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 827-4590
Phone:	302-886-2715	**Phone:**	(301) 594-5779
Pages (including cover):	1	**Date:**	April 21, 2003
Re:	NDA 21-399 Iressa. Industry Meeting scheduled for April 30, 2003 at 3:30pm.		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

- **Comments:**

The industry meeting scheduled for April 30, 2003 at 3:30pm to discuss the status of the Iressa NDA review has been cancelled. Please call should you have any questions.

Thank you,

Amy Baird

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Baird
4/21/03 04:37:37 PM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Ronald Falcone, Ph.D.	**From:**	Amy Baird, CSO
Fax:	302-886-2822	**Fax:**	(301) 827-4590
Phone:	302-886-2715	**Phone:**	(301) 594-5779
Pages (including cover):	1	**Date:**	April 10, 2003

Re: NDA 21-399 Iressa. Submission dated March 14, 2003, providing demographic information regarding the results from the INTACT trials (0017 and 0017) and the 2003 ASCO Abstract.

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ✔ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Please provide the following information. In your submission of March 14, 2003, your tables H1.3.5, H1.3.6, H1.3.19 for both Trial 0014 and 0017, the foot note says: "A hazard ratio > 1 indicates that group 2 lives longer than group 1 whereas a hazard ratio of < 1 indicates that group 1 lives longer than group 2." This means, for example, that in the adenocarcinoma + bronchoaveolar group placebo treated group lived longer than Iressa treated group. Is this interpretation correct? Please call should you have any questions.

Thank you,

Amy Baird

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amy Baird
4/10/03 09:33:56 AM
CSO