Drug-Induced Disaster due to Iressa

Masato Sekiguchi

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What is IRESSA

- Is an anticancer drug for non-small-cell lung cancer.
- Has a novel mechanism of action (inhibition of EGFR).
  →"molecularly targeted drug"
- Has been extensively promoted as a "safe anticancer drug with few adverse reactions."

Approval of IRESSA

Approved with exceptional speed

1.25.2002 Application for importation approval
7.5.2002 Approved (global first)
↑
4.2004 Transfer of approval operations to the Pharmaceuticals and Medical Devices Agency

Phase II Approval [Does this reflect your intended meaning? Or do you mean "II. Approval Phases"?]

Guidelines for Methods of Clinical Evaluation for Anticancer Drugs (prior to 2005 revision)

Phase I Clinical Trials
Phase II Clinical Trials･･･Tumor-shrinkage effect (small-scale) ⟶ Approval
Phase III Clinical Trials･･･Survival benefit (large-scale) Post-approval

Approval Conditions for IRESSA

"Performance of a domestic randomized comparative clinical trial having a sufficient sample size, with the objective of further elucidating the efficacy and safety of this drug in the treatment of non-small cell lung cancer (unresectable or recurrent)"

Occurrence of suffering due to adverse reactions

Starting immediately after approval, there were multiple cases of adverse reactions of serious interstitial pneumonia and acute lung injury.

7.5.2002 Approval
7.15 First reported fatality
10.15 Urgent Safety Information Report
26 events 13 deaths

~~「Targeted attack of only cancer cells」~~

Deaths reported due to adverse reactions

2002 180 deaths (July – December)
2003 202 deaths
2004 175 deaths
Subtotal 557 deaths
2005 80 deaths
2006 51 deaths
⋮

As of March 2010, 810 deaths had been reported.

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Total number of treated patients is unknown

- 1.2005 AstraZeneca reported cumulatively approx. 86,800 patients treated Iressa as of Dec. 28, 2004.

3.2005 Revised to approx. 42,000 patients.

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Adverse reactions at the approval examination stage

Overview (Interstitial pneumonia cases)

- No. of adverse reaction cases reported up to preparation of the examination report before the approval
  - 3 in domestic clinical trials (3 in Japan)
  - 4 in overseas adverse reaction reports (4 overseas)
- Overlooked cases of adverse reactions
  - 196 cases up to approval
  - 10 of those cases were typical lung damage (10 typical cases)
- Additionally reported cases of adverse reactions (3 additional cases)

Overlooked adverse reactions (10 typical cases)

Patient No.	Patient	Adverse Reaction	Severity	Outcome
B3-54	51 y.o. F	Respiratory failure	Fatal	Fatal
B3-63	55 y.o. M	Respiratory failure	Life-threatening	Unresolved
B3-67	38 y.o. F	Pulmonary infiltration NOS	Life-threatening	Unknown
B3-79	68 y.o. F	Respiratory failure	Life-threatening	Recovered
B3-115	68 y.o. F	Dyspnea NOS	Fatal	Fatal
B3-132	54 y.o. M	Dyspnea NOS, pulmonary hemorrhage	Life-threatening	Unresolved
B3-140	63 y.o. M	Pulmonary infiltration NOS, respiratory failure	Fatal	Fatal
B3-152	39 y.o. F	Pulmonary infiltration NOS, allergic pulmonary alveolitis	Life-threatening	Unresolved
B3-164	62 y.o. F	Respiratory failure, lactic acidosis	Fatal	Fatal
B3-172	73 y.o. F	Pulmonary infiltration NOS	Fatal	Fatal

Not classified as "Interstitial pneumonia"; thus overlooked.

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Risk apparent from adverse reaction cases reported before the approval

- **High mortality rate**
  - **4 overseas cases + 3 additional cases: 4 deaths** 57%
  - **10 overlooked typical cases: 5 deaths** 50%
  - **2 Japanese EAP cases: 1 death** 50%
- **Risk trends for Japanese**
  - **All cases in clinical trials were Japanese (3/3)**
  - **3 domestic cases + 4 overseas cases + 3 additional cases: 5 Japanese cases (5/10)**
  - **All 5 Japanese cases were serious or fatal.**

These cases portended the rash of adverse reactions after marketing.

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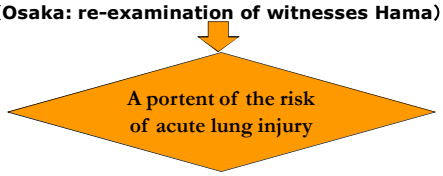
Handling of adverse reaction reports in the examination

- **Only the relevance was investigated, focusing on the 3 domestic cases.**
- **Only the existence of reports of 4 overseas cases was noted.**
- **Most cases were overlooked**

In The Second Section of Drug Examination Committee the risk of Interstitial Pneumonia was not even explained.

Insufficient consideration of adverse events

- **Adverse event-related deaths in clinical trials: 34/677 patients (5.0%)**
  Only 2 (0.3%) of those were treated as deaths due to adverse reactions.
- **Many cases of acute pulmonary damage due to IRESSA were overlooked.**
  (Osaka: re-examination of witnesses Hama)



Efficacy

Phase III clinical trials

1. INTACT 1
2. INTACT 2
3. ISEL
4. SWOG0023
5. V1532（Approval Conditions）
6. INTEREST
7. IPASS

Phase III clinical trials

- **INTACT 1, 2**
  Coadministration of IRESSA with existing anticancer drugs
  →The median survival time showed no significant difference between the IRESSA group and the placebo group.
- **ISEL**
  The median survival time showed no significant difference between the IRESSA group and the placebo group.
- **SWOG0023**
  Administration of gefitinib as maintenance therapy following chemoradiotherapy + docetaxel chemotherapy
  →The median survival time was significantly inferior in the IRESSA group (23 months) compared with the placebo group (35 months).

V1532

- Second-line or third-line patients
- Comparison of survival times with IRESSA and docetaxel
- **Domestic clinical trial carried out to satisfy the approval conditions**

Noninferiority of gefitinib to docetaxel with regard to the overall survival time was not proven.

Failure to prove a survival benefit

Phase III clinical trials

- Repeated failure in placebo-controlled comparative studies
- Reduced survival time shown in SWOG0023
- Failure of the trial (V1532) conducted to satisfy the domestic approval conditions
- Multiple cases of suffering due to adverse reactions

Dr. Nagahiro Saijo, witness

"Statistical utility of IRESSA has not been proven."

INTEREST

- Second-line or third-line patients
- Comparison of survival times with IRESSA and docetaxel
- Overseas clinical trial

Demonstration of noninferiority of gefitinib to docetaxel

? Failure of V1532 conducted in Japanese patients

? Docetaxel dosage larger than in V1532

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IPASS

- Patients with adenocarcinoma and no or only a slight history of smoking
- Comparison of IRESSA with doublet chemotherapy using carboplatin/paclitaxel
- Primary assessment endpoint was the progression-free survival time

Demonstration of superiority in the IRESSA group over doublet chemotherapy using carboplatin/paclitaxel

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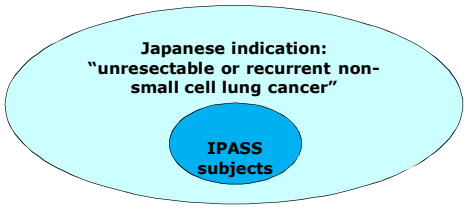
IPASS

The IPASS patient cohort does not cover the Japanese indication



In addition, the response rate in the EGFR mutation-negative group was 1.1%.

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欧米の状況

2003.5.5	FDAイレッサ承認
2004.12.17	ISEL初回解析
	FDA声明「回収するか、他に妥当な規制措置をとるかを決定する」
2005.1.4	アストラゼネカ
	EUへの承認申請を自ら取り下げ
2005.5.14	SWOG0023中間解析
2005.6.17	FDA、**新規患者への投与を原則禁止**

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Handling of IRESSA in the West

5.5.2003	FDA approval
12.17.2004	Initial analysis of ISEL
	FDA statement: "A decision will be made for recall or some other appropriate regulatory measure."
1.4.2005	**AstraZeneca itself withdraws its approval application to the EU**
5.14.2005	Interim analysis of SWOG0023
6.17.2005	FDA
	In principle, prohibition of administration to new patients

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Handling of IRESSA in the West

7.1.2009 Distribution approval granted in the EU on basis of IPASS & INTEREST

However, restricted to "adult patients with EGFR mutations and locally-advanced or metastasized non-small cell lung cancer"

Approval cannot be acquired in the case of an indication that is not focused on patients who have EGFR mutations (= the indication granted in Japan)

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Handling of IRESSA in Japan

1.25.2002 Approval application submitted to the Ministry of Health Labour and Welfare

7.5.2002 Approval ←without waiting for the INTACT results

8.19.2002 INTACT results reported

10.15.2002 Urgent Safety Information

12.25.2002 First Meeting to Discuss Gefitinib Safety Issues

12.26.2002 Revision of package insert→ Warning statement

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Handling of IRESSA in Japan

12.17.2004 Initial analysis of ISEL

1.2005 - Gefitinib Committee Meeting convened

Continued use of the drug was permitted under the condition that the package insert include a statement that, at the time of use, reference should be made to the Japan Clinical Guidelines for the Management of Lung Cancer. No changes were made in the approval content.

5.14.2005 Interim analysis of SWOG0023

7.25.2005 Revision of Clinical Guidelines for the Management of Lung Cancer

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Handling of IRESSA in Japan

2.1.2007 Initial analysis of V1532 announced
Safety Committee for Food and Drugs Safety Committee meeting held

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V1532

- Second-line or third-line patients
- Comparison of survival times with IRESSA and docetaxel
- **Domestic clinical trial carried out to satisfy the approval conditions**

Noninferiority of gefitinib to docetaxel with regard to the overall survival time was not proven.

Failure to prove a survival benefit

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Handling of IRESSA in Japan

2.1.2007 Initial analysis of V1532 announced
Safety Committee for Food and Drugs Safety Committee meeting held

"It was concluded that, in general, there is no basis for actively selecting gefitinib over docetaxel for treatment of patients with unresectable or recurrent non-small cell lung cancer who have already been treated with one or two chemotherapy regimens."

"In consideration of the fact that the status of manifestation of adverse reactions is as stated in the most recent package insert, etc.,…it is appropriate to continue to apply the current safety measures."

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Handling of IRESSA in Japan

What is meant by approval "conditions"?

- By when must they be satisfied?
  → In the 4 years and 7 months from approval until initial analysis
- What is the effect if the conditions are not met?
  →Even if there is failure to prove a survival benefit, no changes are made in the approved items.

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Promotional advertising

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In the clinical setting and status of promotional advertising

Characteristics of the defendant's promotional advertising

Content

- Emphasis on efficacy
- Emphasize that there are few adverse reactions
- No mention of interstitial pneumonia

Methods

- Directed at all concerned parties (doctors, patients, mass media)
- Use any and all media
- Pretence of providing scientific information (use specialists)
- Predating approval

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医師を対象とした宣伝

Medical Tribune Nov. 22, 2001

Interview with Dr. Nagahiro Saijo, National Cancer Center

- "If a survival benefit is found, then since ZD1839 is a drug that shows little toxicity, I think that it will probably be a very useful drug for the treatment of non-small cell lung cancer."
- "Since the toxicity of molecularly targeted drugs is not very strong, it can be surmised that reported patient deaths are probably due to administration of the drugs to patients in whom administration is not indicated ZD1839 also causes few adverse reactions, and for that reason I worry that it might also be used in the same manner."

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Medical Tribune Oct. 25, 2001

Interview with Dr. Kazuhiko Nakagawa and others

Fourth Department of Internal Medicine, Kinki University Faculty of Medicine

"With regard to adverse reactions, it is said that skin rash is very commonly seen. Are there any other adverse reactions observed that require caution?"

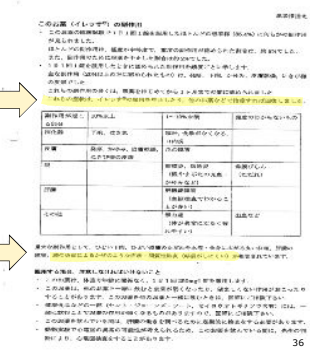
"Although their incidences are not very high, diarrhea and hepatic dysfunction can be raised as other adverse reactions. However, those reactions show very rapid improvement if drug administration is discontinued for a certain time, and for that reason I don't think they present much of a clinical problem."

* There was absolutely no mention of interstitial pneumonia.

Informed consent document for the patients

These symptoms recovered when IRESSA was discontinued or treatment using another drug, etc., was administered.

Cold-like symptoms due to pulmonary inflammation: Interstitial pneumonia (dyspnea) has been reported.



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Press release

"The important point is that these results indicate success in not causing the severe adverse reactions that are commonly seen in patients being treated for lung cancer. The main adverse reactions associated with administration of ZD1839 are mild to moderate skin reactions, such as rash, dry skin and itchiness, and diarrhea. Serious adverse reactions are rare, and are usually associated with progression of the disease."

* There is no mention of interstitial pneumonia.

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Intense media coverage predating approval

- 11.2.2001 "Targeted attack of cancer cells"
  With regard to adverse reactions, there have been some cases of rash and diarrhea, but compared with conventional drugs there is great improvement. (Asahi Shinbun newspaper)
- 5.25.2002 "Novel lung cancer drug, gefitinib, to be approved with exceptional speed."
  A drug that is said to act directly on receptors involved in cancer proliferation, to have no great effect on normal cells, and to cause few adverse reactions. (Tokyo Shimbun newspaper)
- 6.3.2002 "Hey, cancer! Don't overrate yourself!!"
  "Astounded." "Amazing." Comments made by specialists in regard to a novel cancer drug that was reported at a meeting of the American Society of Clinical Oncology last month. (Asahi Shinbun newspaper)

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Intense media coverage predating approval

- A search service was used to conduct a comprehensive search for past articles in the national newspapers (Asahi, Yomiuri, Mainichi, Sankei), local newspapers, specialist journals, and business magazines.
- 85 articles were found regarding IRESSA (gefitinib, ZD1839) written prior to its approval (before July 5, 2002).
- However, not even 1 mentioned interstitial pneumonia.
  This is because the defendant did not provide information regarding interstitial pneumonia.

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The fervent wish of a patient

Statement from Mr. Akio Chikazawa, a plaintiff:

"In mid-July of 2002, I found an Internet site that discussed IRESSA. Expressions like 'A novel drug that is like a dream,' 'An innovative lung cancer treatment that causes few adverse reactions and can be easily taken in your own home,' etc., grabbed my attention."

"…There were numerous quotes from many oncology specialists in articles in various magazines and newspapers, all offering only praise of IRESSA, such as 'Its response rate is several fold higher than that for any previous anticancer drugs,' etc., and no matter where I looked I found no troubling information. If such a fantastic anticancer drug were to become available, it would obviously be my wish to find a way to give it to my daughter."

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Instructions and Warnings

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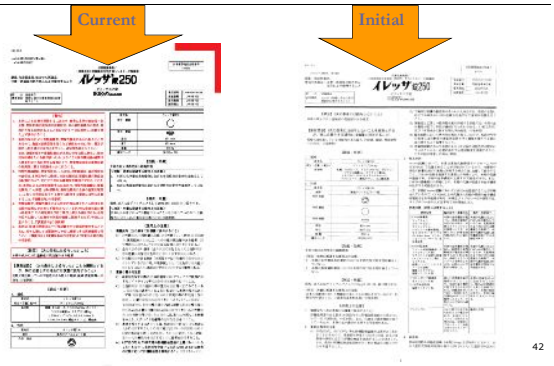
Comparison of IRESSA package inserts



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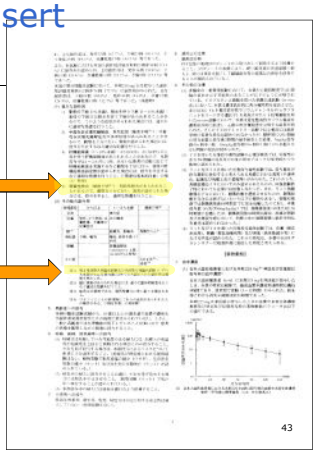
Initial package insert (reverse side)

Interstitial pneumonia (incidence unknown):
Interstitial pneumonia may manifest, and for that reason the patient should be carefully monitored. In the case of any abnormality, administration of the drug should be discontinued and appropriate measures should be taken.

Note 1)
Adverse reactions that occurred only in studies other than the Phase II International Collaborative Trial and the U.S.A. Phase II Clinical Trial (each of which administered the drug in a 250 mg/day group) were classified as "**incidence unknown**".



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Problems with the initial package insert

Content

There is absolutely no warning that interstitial pneumonia can be fatal.

Statement columns

No statement in the Warnings column.

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【警告】

1. 本剤による治療を開始するにあたり、患者に本剤の有効性・安全性、息切れ等の副作用の初期症状、非小細胞肺癌の治療法、致命的となる症例があること等について十分に説明し、同意を得た…ること。
2. 本剤の投与により急性肺障害、間質性肺炎があらわれることがあるので、胸部X線検査等を行うなど観察を十分に行い、異常が認められた場合には投与を中止し、適切な処置を行うこと。
また、急性肺障害や間質性肺炎が本剤の投与初期に発生し、致死的な転帰をたどる例が多いため、少な…たはそれに準ずる管理の下で、間…に関する観察を十分に行うこと。
3. 特発性肺線維症、間質性肺炎、じん肺症、放射線肺炎、薬剤性肺炎の合併は、本剤投与中に発現した急性肺障害、間質性肺炎発症後の転帰において、死亡につながる重要な危険因子である。このため、本剤による治療を開始するにあたり、特発性肺線維症、…ん肺症、放射線肺炎、薬剤性肺炎の合併の有無を確認し、これらの合併症を有する患者に使用する場合には特に注意すること。(「慎重投与」の項参照)
4. 急性肺障害、間質性肺炎による致死的な転帰をたどる例…の良悪にかかわらず報告されているが、特に全身状態の…び死亡率が上昇する傾向がある。本剤の投与に際…を慎重に観察するなど、十分に注意すること。(「慎重投与」の項参照)
5. 本剤は、肺癌化学療法に十分な経験をもつ医師が使用するとともに、投与に際しては緊急時に十分に措置できる医療機関で行うこと。(「慎重投与」、「重要な基本的注意」及び「重大な副作用」の項参照)

"fatal cases"
"occurrence of fatal results"
"will be fatal"
"fatal results"
"death rate"

Current statements in the Warnings column

- Manifestation of "life-threatening" interstitial pneumonia
- Necessary testing for initial symptoms and early diagnosis of interstitial pneumonia
- Restrictions on the medical care staff and medical facilities able to use the drug
- Hospitalization for a certain time period or equivalent management is necessary
- Idiopathic pulmonary fibrosis, etc., increase the risk of death
- Sufficient explanation regarding efficacy and safety, and informed consent
- Coadministration with other anticancer agents and radiotherapy is prohibited
- Administration to patients meeting clinical trial exclusion criteria is prohibited

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Conflict of Interest

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Defense witness in the Eastern Japan Lawsuit Nagahiro Saijo (National Cancer Center Hospital East, Vice Chairman)

- Clinical trials
  - V15-11 Trial 8.1998 – 5.2000 Efficacy and Safety Assessment Committee
  - V15-21 Trial 10.2000 – 5.2001 Efficacy and Safety Assessment Committee
  - V35-21 Trial 1.2001 – 10.2001 Efficacy and Safety Assessment Committee
  - V15-31 Trial 8.2002 – 4.2003 Efficacy and Safety Assessment Committee
  - V15-32 Trial 9.2003 – 10.2006 Post-production and distribution Clinical Trial Coordination Committee
  - IPASS Trial 4.2006 - Post-production and distribution Clinical Trial Coordination Committee
- Private
  - Acted as an interlocutor for articles provided by AstraZeneca
  - Member of editorial committee of a magazine (SIGNAL) issued by AstraZeneca
  - Attended numerous lectures sponsored by AstraZeneca, and received lecture fees, etc.

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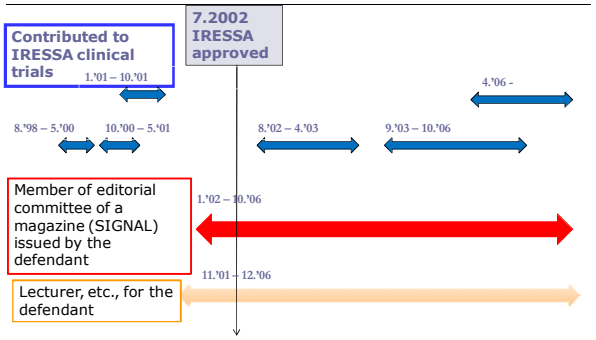
Defense witness in the Eastern Japan Lawsuit
Nagahiro Saijo (National Cancer Center Hospital East, Vice Chairman)



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Defense witness in the Western Japan Lawsuit
Masahiro Fukuoka (Kinki University Faculty of Medicine, Professor)

- From the development stage
  - Attended IRESSA-related seminars (guidance fee of 100,000 Yen per session)
- Clinical trials
  - Phase I clinical trial: Coordinating Investigator (contract research fee: in excess of 10 million Yen)
  - Phase II clinical trial: Coordinating Investigator (contract research fee: in excess of 10 million Yen)
- Donations to NPO, West Japan Thoracic Oncology Group (from Dec. 2000, Director; from May 2004, Chairman)
  - Donation of approx. 20 million Yen each year

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Handling of IRESSA in Japan

12.17.2004 Initial analysis of ISEL

1.2005 - Gefitinib Committee Meeting convened

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5.14.2005 Interim analysis of SWOG0023

7.25.2005 Revision of Clinical Guidelines for the Management of Lung Cancer

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Conflict of Interest

Members of the Guideline Planning Committee

①	N.Saijo	witness		clinical trials
②	M.Fukuoka	witness	WJTOG	clinical trials
③	S.Negoro		WJTOG	clinical trials
④	S.Kudo	witness		clinical trials
⑤	T.Tamura			clinical trials
⑥	H.Tada		WJTOG	clinical trials
⑦	T.Mitutomi	witness	WJTOG	clinical trials
⑧	H.Kato		WJTOG	
⑨	N.Yamamoto		WJTOG	
⑩	K.Hayakawa			

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Lawsuits regarding drug-induced suffering due to IRESSA

- Western Japan Lawsuit
  - Filed on July 15, 2004 (Osaka District Court)
  - Plaintiffs･･･3 families, 1 survival victim
  - **To be concluded on July 30, 2010**
- Eastern Japan Lawsuit
  - Filed on November 25, 2004 (Tokyo District Court)
  - Plaintiffs･･･3 families
  - **To be concluded on August 25, 2010**

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Lawsuits regarding drug-induced disaster due to IRESSA

1. The Japanese government and AstraZeneca should recognize their responsibility for the drug-induced suffering due to IRESSA and issue an apology to the victims and their families.
2. The Japanese government and AstraZeneca should pay compensation to the victims and their families for the drug-induced suffering due to IRESSA.
3. The re-examination to be started from July of this year should review the contents of the approval of IRESSA.
4. A relief system for deaths due to adverse reactions to anticancer drugs should be established, such as expanding the Relief System for Sufferers from Adverse Drug Reactions.
5. Verify the drug-induced suffering due to IRESSA and take initiatives to prevent recurrence of drug-induced suffering.

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