CONTEXT

IRESSA® is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK. The efficacy and good safety profile of IRESSA® have been demonstrated as part of a development programme including more than 4 300 patients in three prospective, randomised, phase III studies (IPASS, INTEREST and ISEL). On November 4, 2009, the Transparency Committee of French authority issued two requests to Astra Zeneca:

- To provide data on the practical conditions for the EGFR activating mutation testing
- To implement a study to include patients treated with IRESSA® in France in real life setting

In response to the second request, an observational study, known as Epidaure, which aims to describe the patient population treated with IRESSA® in France and the impact of treatment on morbidity/mortality, was proposed.

The analysis of the inclusion data took place in June 2014 and achieved the objectives of describing patients treated with IRESSA®, the physicians prescribing treatment with IRESSA® and the prescribing patterns for IRESSA® at initiation (dosage, concomitant medication, conditions for testing for the mutation of EGFR).

The analysis of the follow-up evaluated the impact of treatment on the health of the population concerned in terms of morbidity and mortality (clinical benefit, safety) and quality of life

METHODS

This is a prospective, observational, cohort follow-up pharmaco-epidemiological study, conducted in France in patients treated withIRESSA® from the beginning of 2011 to the end of the inclusion period. This study has been conducted in various centers among pulmonology, oncology and radiotherapy specialists.

300 patients were expected to be included. Investigators agreeing to participate in the study had to include, in an exhaustive manner, all eligible patients treated and followed up in their location of care. All of these patients correspond to the eligible population.

RESULTS

Representativeness of investigators

In total, 104 out of the 159 participating investigators, included at least one patient in the cohort. The participating investigators were representative for the sampling frame.

Sample sizes of patients included and followed up

361 patients fulfilling the study eligibility criteria were included between 27 January 2012 and 4 March 2013. Of these, 68% were prevalent patients (treatment with IRESSA® already in progress or discontinued at inclusion) and 32% were incident patients (initiated IRESSA® on the day of inclusion or within 15 days prior to inclusion). 340 patients (94.2%) had at least one follow-up visit, 38 (10.5%) were prematurely withdrawn from the study and 224 (62%) were deceased.

Representativeness of patients

Comparison between the included patients and excluded patients shows that there is no difference between the two groups in terms of age and sex, but excluded patients involve more patients for whom treatment is no longer ongoing..

Overview of the main data from the inclusion report at initiation of IRESSA®

At initiation of IRESSA®, the patient profile is comparable whether initiated as first line (80% of included patients) or as second-line or higher.

Smoking status confirms that the majority (59.2%) of patients were non-smokers or former smokers (28%). The patients included in the cohort are predominantly females (72.6%) with a mean age of 69.1 years (± 11.7), and Caucasian (93.6%) with a mean time since diagnosis corresponding to 7.2 months (± 18.6). Out of all patients, 96.3% presented an adenocarcinoma type tumour, and 85.9% had stage IIIb/IV disease at diagnosis.

The test for EGFR mutation was conducted for 98.3% of included patients, without any differences between the two groups. Out of these cases as a whole, 98.9% of patients had an EGFR mutation.

Prescribing patterns and conditions of use

The mean duration of exposure to treatment with IRESSA® was 11.8 months on average (± 8.9 months), median 9.2 months. 83.4% of patients discontinued treatment predominantly due to progression (82.2% of these patients) and toxicity (9.8% of these patients).

For 98.3% of all patients, IRESSA® is administered as monotherapy, without any difference in dosage (250 mg/day) whether at initiation or during follow-up. These patterns were observed irrespective of treatment line at initiation of IRESSA® (first-line or ≥ second-line).

The most frequently administered treatments after IRESSA® correspond to platinum-based treatments and/or treatment with Alimta (34% and 36%, respectively), if IRESSA® was prescribed as first-line treatment.

The median duration of patient follow-up was 17 months from inclusion in the study. The median duration of follow-up between initiation of IRESSA® and the last known date for the patient in the study was 20.8 months.

Impact of treatment with IRESSA®

Table 1: Summary of the results for the health impact of IRESSA® on patients receiving first metastatic (treatment) line (included patients and incident patients)

		All lines Total population* (N = 361)	First line, total population (N = 290)	First line, incident patients (N = 97)
RESPONSE TO TREATMENT				
ORR: Response to treatment with IRESSA® (complete or partial)	Yes	233 (66.8%)	191 (68.5%)	65 (71.4%)
	95% CI (Yes)	[60.3; 70.3]	[61.9; 72.9]	[60.9; 79.7]
	Not stated	12 -	11 -	6 -
PROGRESSION-FREE SURVIVAL				
No progression		73 (20.2%)	62 (21.4%)	24 (24.7%)
Total progression		288 (79.8%)	228 (78.6%)	73 (75.3%)
Median progression-free survival	**(months)**	11.1 [10.0; 11.9]	11.5 [10.0; 13.4]	10.5 [7.8; 12.2]
OVERALL SURVIVAL				
Death during the study	Yes	224 (62%)	171 (59%)	49 (50.5%)
	Sample size analysed	217*	165	46
Median overall survival	**(months)**	24.6 [21.4; 26.7]	25.7 [23.4; 27.9]	24.6 [20.8; 27.5]

* 217 out of 224 deaths are taken into account in the analysis of overall survival as 7 dates of death are missing

Sensitivity analysis among incident patients

An analysis was conducted on the sub-group of incident patients (n = 116) according to the line at initiation of IRESSA®). Prescribing patterns and conditions of exposure to IRESSA® are comparable to those of the total population of patients. Outcomes for the incident patients receiving first line differed, although not considerably, from those obtained for the overall population. It is likely that prevalent patients who had a better general status were included in the study and obtained slightly higher results for progression-free survival and overall survival than patients in the incident population.

Safety during exposure to IRESSA® *(incident patients and prevalent patients on treatment)*

The investigators reported 252 adverse reactions related to treatment with IRESSA® during the study for 114 (40.1%) of the 291 incident patients and prevalent patients on treatment. Twenty-two of these reactions were considered serious and occurred in 15 (5.3%) patients.

- Among all of the serious and non-serious ARs related to treatment, skin and subcutaneous tissue disorders (24.1%) and gastrointestinal disorders (19.6%) were the most common.
- Among all of the serious ARs related to treatment, hepatobiliary disorders are the most frequently reported reactions (2.7% of patients).

21 patients (7.2%) discontinued treatment due to an adverse reaction, corresponding to 38 adverse reactions in total.

Supportive treatment was prescribed to 40% of patients for the prevention of diarrhoea, to 54% for skin reactions, and to 15% for other symptoms at initiation of IRESSA®. During treatment with IRESSA®, these treatments were administered in identical, or, indeed, slightly higher proportions.

Mean tolerability assessed by patients at 3 months on a VAS of 0 to 10 was 8 on average. During the study period, this evaluation remained stable, between 7 and 9.

Changes in quality of life and symptoms *(incident patients)*

The patient population analysed for this endpoint showed good quality of life scores at baseline. Analysis of the changes in these scores evidenced a significant improvement in symptoms (LCS scale) and quality of life in general (FACT-L Total score) between initiation of treatment with IRESSA® and follow-up at 3 months.

The analysis of the changes in performance status (WHO) shows that 78% of patients presented a performance status of 0 or 1 at the time of inclusion. This performance status remains somewhat stable for all of the follow-up time-points for patients continuing treatment with IRESSA®.

Quality of life

Examining the FACT-L LCS score throughout follow-up, patient quality of life seems to improve at 3 months, and then stabilises. These results are in keeping with this type of treatment for which the expected response occurs fairly soon. However, as the patients show a very high performance status and few symptoms at initiation of treatment, the improvement is difficult to estimate and detect.

CONCLUSION

The Epidaure study provides additional data on the clinical development of IRESSA® by evaluating its use under actual practice conditions.

The results obtained for both inclusion and follow-up show that, in practice, the conditions for use of this treatment and the impact on patient health reflect the data generated by the clinical trials.

The study also made it possible to verify that practices remain consistent over time and that the characteristics of the beneficiary population remain stable.