HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

19 February 2014

GIOTRIF 50 mg, film-coated tablet
B/28 (CIP: 34009 275 659 3 9)

GIOTRIF 40 mg, film-coated tablet
B/28 (CIP: 34009 275 658 7 8)

GIOTRIF 30 mg, film-coated tablet
B/28 (CIP: 34009 275 657 0 0)

GIOTRIF 20 mg, film-coated tablet
B/28 (CIP: 34009 275 656 4 9)

Applicant: BOEHRINGER INGELHEIM FRANCE

INN	Afatinib
ATC code (2013)	L01XE13 (protein kinase inhibitors)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Inclusion for hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s)."**

AB	**The actual benefit of GIOTRIF is substantial in the first-line therapy of locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation(s).**
IAB	**GIOTRIF provides no improvement in actual benefit (level V, non-existent) in the first-line therapy of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).**
Therapeutic use	**GIOTRIF is a first-line therapy for locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation(s). In the absence of any comparison, its role in relation to the other available tyrosine kinase inhibitors (gefitinib and erlotinib) has yet to be determined.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	25 September 2013 (centralised procedure) Previous temporary authorisation for use by a named patient
Prescribing and dispensing conditions/special status	List I Medicine for hospital prescription only. Prescription restricted to oncology specialists or doctors with cancer training. Medicinal product requiring special monitoring during treatment.
ATC Classification	2013 L Antineoplastic and immunomodulating agents L01 Antineoplastic agents L01X Other antineoplastic agents L01XE Protein kinase inhibitors L01XE13 afatinib

02 BACKGROUND

Assessment of the application for inclusion of GIOTRIF 20 mg, 30 mg, 40 mg and 50 mg film-coated tablet on the list of medicines refundable by National Insurance and on the list of medicines approved for hospital use.

Afatinib, the active substance in GIOTRIF, is a tyrosine kinase inhibitor (TKI). It is an irreversible ErbB family blocker.

03 THERAPEUTIC INDICATIONS

“GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) (see section 5.1 of the SPC).”

04 DOSAGE

“Treatment with GIOTRIF should be initiated and supervised by a physician experienced in the use of anticancer therapies.
EGFR mutation status should be established prior to initiation of GIOTRIF therapy (see section 4.4 of the SPC).
Posology
The recommended dose is 40 mg once daily.
This medicinal product should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking this medicinal product (see SPC).
GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 1 of the SPC).

Dose escalation
A dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate a 40 mg/day dose (i.e. absence of diarrhoea, skin rash, stomatitis, and other adverse reactions with CTCAE Grade > 1) in the first 3 weeks. The dose should not be escalated in any patients with a prior dose reduction.
The maximum daily dose is 50 mg.

Dose adjustment for adverse reactions
Symptomatic adverse reactions (e.g. severe/persistent diarrhoea or skin related adverse reactions) may be successfully managed by treatment interruption and dose reductions or treatment discontinuation of GIOTRIF as outlined in Table 1 of the SPC."

05 THERAPEUTIC NEED

The professional guidelines from the National Cancer Institute (INCa) published in September 2010 indicate that from first-line therapy onwards, the therapeutic strategy in patients with inoperable lung cancer must be determined by the presence or absence of an EGFR mutation in the tumour.
In those patients who have a tumour with no EGFR mutation, platinum-based chemotherapy is still the standard treatment.
In cases with a mutation, the recommended treatment is a tyrosine kinase inhibitor. EGFR mutations are present in about 10% of cases of non-small cell lung cancer; the majority of these genetic mutations express exon 19 deletions or exon 21 mutations.[1]
Two tyrosine kinase inhibitors are currently indicated in the first-line therapy of patients who have a tumour with EGFR gene activating mutations: gefitinib (IRESSA) and erlotinib (TARCEVA). To date, the benefit of tyrosine kinase inhibitors has been established by comparison with platinum-based chemotherapy mainly in terms of progression-free survival and with no demonstrated impact on overall survival.

[1] http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm360499.htm.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

GIOTRIF's clinically relevant comparators are medicines that can be used in the first-line therapy of locally advanced or metastatic forms of non-small cell lung cancer (NSCLC) in patients with EGFR activating mutations.

NAME (INN) *Company*	Same TC* Yes/No	Indication	Date of Opinion	AB	IAB (Wording)
IRESSA (gefitinib) *AstraZeneca*	Yes	IRESSA is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.	04/11/2009	Substantial	In the first-line therapy of locally advanced or metastatic NSCLC and in the presence of an EGFR-TK activating mutation, IRESSA provides a minor IAB (level IV) in comparison with carboplatin plus paclitaxel. In 2nd or 3rd-line therapy of locally advanced or metastatic NSCLC, the data available are limited: fewer than 5% of the patients included in both studies submitted had a tumour with EGFR mutation. Consequently, the committee considers that IRESSA does not provide any improvement in actual benefit (level V) in usual management.
TARCEVA (erlotinib) *Roche*	Yes	TARCEVA is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations.	06/12/2012	Substantial	In the first-line therapy of NSCLC with EGFR activating mutations, TARCEVA, like IRESSA, provides a minor improvement in actual benefit (level IV) in comparison with platinum-based chemotherapy.

* therapeutic category

06.2 Other health technologies

There are no non-medicinal treatment alternatives.

◗ Conclusion

TARCEVA and IRESSA are the clinically relevant comparators for GIOTRIF.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If no, why not	Population(s) MA population or restricted population
USA	YES (12/07/2013)	"GIOTRIF is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test."
Europe	In progress	

08 ANALYSIS OF AVAILABLE DATA

The dossier comprises:

- The LUX-LUNG 3 pivotal study, conducted on an international scale.
- The LUX-LUNG 6 study, conducted exclusively in an Asian population.

The results of these two studies are presented in this document.

- The LUX-LUNG 2 non-comparative phase II study (n=129), conducted in patients with NSCLC with an EGFR mutation who were treated with GIOTRIF as a first-line or second-line therapy. Given the heterogeneity of the population included, data from this study will not be taken into account.

08.1 Efficacy

8.1.1 LUX-LUNG 3 Study[2]

An open-label randomised study comparing GIOTRIF (afatinib) with platinum-based chemotherapy (pemetrexed/cisplatin) in treatment-naïve patients with locally advanced or metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC) with an EGFR tumour mutation.
Pemetrexed/cisplatin chemotherapy is the standard combination for NSCLC with non-squamous histology (INCa 2010).

Patients were randomised to one of the following treatment groups:

- Afatinib administered orally once daily at a dose of 40 mg;
- Pemetrexed at a dose of 500 mg/m² in combination with cisplatin 75 mg/m² administered every 3 weeks, with a maximum of six cycles of treatment.

Patients in the afatinib group were treated until disease progression, significant deviation from the protocol, patient refusal, or the occurrence of an adverse event judged to be unacceptable by the investigator.
The doses of afatinib could be increased to 50 mg/day after the first cycle (i.e. after the first 21 days of treatment) if there was no diarrhoea, rash or stomatitis attributable to treatment at any grade of severity or any other treatment-related adverse event graded ≥ 2.

Main inclusion criteria:

- adults (≥ 18 years) with stage IIIb or IV NSCLC with adenocarcinoma-type histology;
- EGFR status determined by a central laboratory using the Therascreen EGFR 29 mutation kit;
- measurable tumour according to RECIST criteria;[3]
- Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1;
- life expectancy of at least 3 months.

[2] Carried out between 17 August 2009 and 9 February 2012 (data collection end date for the first analysis).
[3] RECIST criteria: evaluation of tumour response in solid tumours as: complete response (disappearance of the target lesions), partial response (30% reduction in the target lesions in their longest diameter), disease progression (20% increase in the target lesions in their longest diameter) and stabilisation.

Main non-inclusion criteria:
- prior treatment with chemotherapy for NSCLC recurrence or metastatic disease;
- prior treatment with anti-EGFR TKI targeted therapy.

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the date of first documented disease progression or death from any cause. This was evaluated by an independent committee.

The secondary endpoints were:
- objective response rate, defined as the percentage of patients with a complete or partial response, calculated using the best response recorded between randomisation and the start of a subsequent line of treatment;
- overall survival, defined as the interval between the date of randomisation and the date of death from any cause;
- objective response duration, calculated in responders from the date when the complete/partial response criteria were first met until the date of disease progression or death from any cause;
- quality of life, evaluated using the EORTC QLQ-C30 questionnaire and its lung cancer-specific module QLQ-LC13, noting the percentage of patients with improvement in the following three pre-specified symptoms: cough (question 1 of LC13), dyspnoea (questions 3 to 5 of LC13, question 8 of C30) and pain (questions 9 and 19 of C30, questions 10 to 12 of LC13), and the time to deterioration of these symptoms;
- safety.

Results:
A total of 345 patients were randomised to one of the two treatment groups with a 2:1 ratio; there were 230 patients in the afatinib group and 115 in the combined pemetrexed/cisplatin chemotherapy group. Patients in Europe accounted for 21% of randomised patients.

Patients' demographic and clinical characteristics were comparable in both treatment groups:
- The mean age was 60.3 years (± 10.1), with 39% of patients aged over 65 in the afatinib group (versus 38% in the chemotherapy group).
- Two thirds were female (64% in the afatinib group versus 67% in the chemotherapy group).
- Two thirds of patients had never smoked (67% versus 70%) and 29% were former smokers (30% versus 28%).
- 61% of patients (60% versus 63%) had a performance status (PS) of 1.

In clinical terms, 89% of randomised patients had stage IV NSCLC (91% in the afatinib group versus 85% in the chemotherapy group) and 11% had stage IIIb NSCLC (9% versus 15%). The majority of randomised patients (99%; 100% versus 98%) had at least one metastasis in the bones (45%) and/or pleura (44%). Randomised patients reported breathing difficulties (62% in the afatinib group versus 60% in the chemotherapy group), cough (44% versus 43%), dyspnoea (18% versus 17%), musculoskeletal disorders (40% versus 34%) with back pain (13% versus 16%), vascular symptoms (38% versus 33%), gastrointestinal symptoms (37% versus 33%) and dietary issues (36% versus 28%).

As regards stratification factors, in each treatment group:
- 40% of patients had an L858R point mutation in exon 21, and 49% had an exon 19 deletion. The remaining 11% (N=37) with an EGFR mutation other than exon 21 L858R point mutation or exon 19 deletion could not be analysed separately due to their low numbers and the heterogeneity of the mutations;
- 72% of patients were Asian and 26% were Caucasian.

Table 1: Patient characteristics – randomised population

	GIOTRIF (afatinib)	CHEMOTHERAPY (pemetrexed/cisplatin)	Total
Randomised population [N(%)]	230 (100.0)	115 (100.0)	345 (100.0)
Sex [N(%)]			
- Male	83 (36.1)	38 (33.0)	121 (35.1)
- Female	147 (63.9)	77 (67.0)	224 (64.9)
Mean age [years] (± standard deviation)	60.5 (10.1)	59.9 (10.0)	60.3 (10.1)
- < 65 years	140 (60.9)	71 (61.7)	211 (61.2)
- ≥ 65 years	90 (39.1)	44 (38.3)	134 (38.8)
Ethnic origin [N(%)]			
- White	61 (26.5)	30 (26.1)	91 (26.4)
- Asian	166 (72.1)	83 (72.2)	249 (72.2)
- Other	3 (1.3)	2 (1.7)	5 (1.4)
Smoking status [N(%)]			
- Has never smoked	155 (67.4)	81 (70.4)	236 (68.4)
- Former smoker	70 (30.4)	32 (27.8)	102 (29.6)
- Smoker	5 (2.2)	2 (1.7)	7 (2.0)
Histology [N(%)]			
- Adenocarcinoma	227 (98.7)	111 (96.5)	338 (98.0)
- Predominantly adenocarcinoma	2 (0.9)	4 (3.5)	6 (1.7)
- Other	1 (0.4)	0 (0.0)	1 (0.3)
Performance status [N(%)]			
- 0	92 (40.0)	41 (35.7)	133 (38.6)
- 1	138 (60.0)	73 (63.5)	211 (61.2)
- [21]	0 (0.0)	1 (0.9)	1 (0.3)
Disease stage [N(%)]			
- IIIb	20 (8.7)	17 (14.8)	37 (10.7)
- IV	210 (91.3)	98 (85.2)	308 (89.3)
Number of metastatic sites [N(%)]			
- 0	7 (3.0)	3 (2.6)	10 (2.9)
- 1	60 (26.1)	33 (28.7)	93 (27.0)
- 2	58 (25.2)	31 (27.0)	89 (25.8)
- ≥ 3	105 (45.7)	48 (41.7)	153 (44.3)
Location of metastases [N(%)]			
- Bone	115 (50.0)	40 (34.8)	155 (44.9)
- Pleural effusion	102 (44.3)	49 (42.6)	151 (43.8)
- Liver	38 (16.5)	13 (11.3)	51 (14.8)
- Brain	27 (11.7)	15 (13.0)	42 (12.2)
- Other	163 (70.9)	79 (68.7)	242 (70.1)
EGFR mutation [N(%)]			
- L858R	91 (39.6)	47 (40.9)	138 (40.0)
- Exon 19 deletion	113 (49.1)	57 (49.6)	170 (49.3)
- Other	26 (11.3)	11 (9.6)	37 (10.7)

1. A performance status of 2 was a non-inclusion criterion; this patient's status deteriorated before starting treatment.

Primary efficacy endpoint: Progression-free survival evaluated by an independent committee.
Median progression-free survival was 11.1 months [9.6; 13.6] in the GIOTRIF group versus 6.9 months [5.4; 8.3] in the chemotherapy group, an absolute gain of 4.2 months (HR = 0.58, 95% CI [0.43; 0.78], p = 0.0004).

In patients with an exon 19 deletion or an L858R point mutation (accounting for 90% of EGFR mutations), median progression-free survival was 13.6 months [10.8; 13.8] in the GIOTRIF group versus 6.9 months [5.4; 8.3] in the comparator group (HR = 0.47, 95% CI [0.34; 0.65], p < 0.0001).

- Overall survival:

On the date that the primary efficacy endpoint was analysed (9 February 2012), median overall survival had not been reached in either of the two groups. On this date, no difference in survival was demonstrated between the two groups: 29.1% mortality rate in the GIOTRIF group versus 27.0% in the chemotherapy group.

No difference in overall survival was observed in an updated analysis in January 2013, with a median overall survival of 28 months in both groups (HR = 0.907, 95% CI [0.660; 1.246], p = 0.5457).

- Objective response:

The objective response rate was higher in the GIOTRIF group than in the chemotherapy group: 56% versus 23%, p < 0.0001. The median duration of objective response was 11.1 months in the GIOTRIF group versus 5.5 months in the chemotherapy group.

Table 2: Response duration and disease control evaluated by an independent committee (randomised population)

	GIOTRIF (afatinib)	CHEMOTHERAPY (pemetrexed/cisplatin)
Objective response N (%)	129 (56.1)	26 (22.6)
- week 6 (days 1 to 64) [1]	95 (41.3)	15 (13.0)
- week 12 (days 65 to 106) [1]	115 (50.0)	21 (18.3)
- week 18 (days 107 to 148) [1]	123 (53.5)	26 (22.6)
Median duration of objective response [month; 95% CI]	11.1 [8.5; 12.6]	5.5 [4.1; 8.3]
Disease control N (%)	207 (90.0)	93 (80.9)
Median duration of disease control [month, 95% CI]	13.6 [10.8; 13.8]	8.1 [6.7; 9.5]

[1] *Cumulative.*

- Subsequent lines of treatment:

The percentage of patients who received a subsequent line of treatment was 70% in the GIOTRIF group and 80% in the chemotherapy group. The subsequent treatments were distributed as follows:

- 62% of patients treated with afatinib subsequently received chemotherapy, which was platinum-based in two thirds of cases;
- 65% of patients treated with chemotherapy subsequently received a TKI.

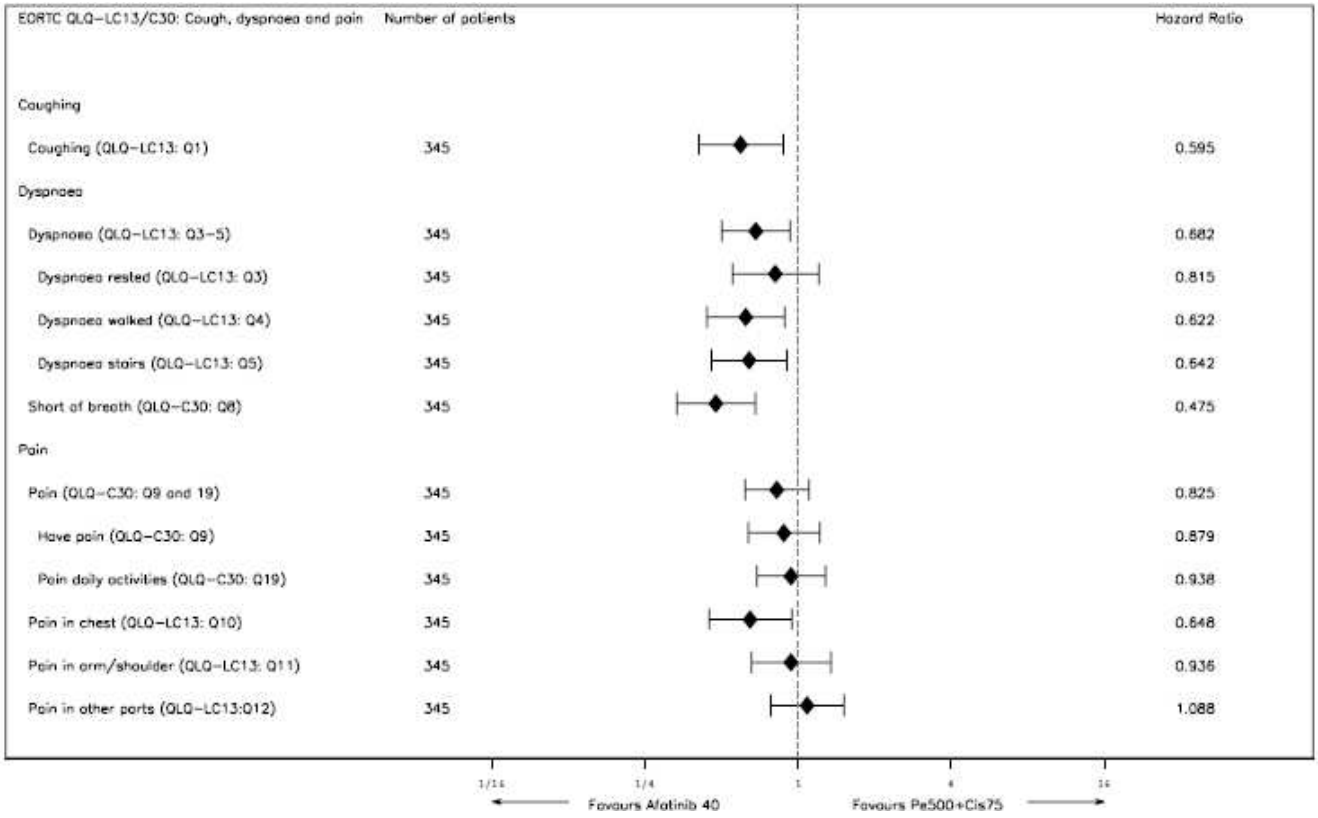
- Quality of life:

Quality of life was evaluated using the EORTC QLQ-C30 questionnaire and its lung cancer-specific module QLQ-LC13.

The time to deterioration was longer in the GIOTRIF group than in the pemetrexed/cisplatin group for cough (HR = 0.60 [0.41; 0.87], p = 0.007) and dyspnoea (HR = 0.68 [0.50; 0.93], p = 0.015) but no difference was observed for pain (improvement in pain: 59% versus 48%, p = 0.051).

The mean overall quality of life score from the QLQ-C30 questionnaire showed a greater improvement in the GIOTRIF treatment group than in the group treated with pemetrexed/cisplatin (a difference of 3.2 points [0.6; 5.8], p = 0.015).

Figure 1: Time to deterioration of dyspnoea and cough symptoms - randomised population



8.1.2 LUX-LUNG 6 Study

An open-label, 2:1 randomised study comparing GIOTRIF (afatinib) to platinum-based chemotherapy (gemcitabine/cisplatin[4]) in treatment-naive Asian patients (90% Chinese) with locally advanced or metastatic (stage IIIb or IV) non-small cell lung cancer (NSCLC) with an EGFR tumour mutation.

Patients were randomised to one of the following treatment groups:
- afatinib administered orally once daily at a dose of 40 mg;
- gemcitabine at a dose of 1000 mg/m² in combination with cisplatin 75 mg/m² administered every 3 weeks, with a maximum of six cycles of treatment.

The primary efficacy endpoint was progression-free survival, defined as the time from randomisation to the date of first documented disease progression or death from any cause. This was evaluated by an independent committee.

The main secondary endpoints were:
- objective response rate, defined as the percentage of patients with a complete or partial response, calculated using the best response recorded between randomisation and the start of a subsequent line of treatment;
- objective response duration, calculated in responders from the date when the complete/partial response criteria were first met until the date of disease progression or death from any cause;
- overall survival, defined as the interval between the date of randomisation and the date of death from any cause;
- quality of life evaluated using the EORTC QLQ-C30 questionnaire;
- safety.

Results:

[4] As pemetrexed is not available in China, gemcitabine/cisplatin chemotherapy is the local standard treatment for tumours with non-squamous histology.

Patients had a median age of 58 years. Two thirds were female (64% in the afatinib group versus 68% in the chemotherapy group). Three quarters of patients had never smoked (75% versus 81%) and 16% were former smokers (18% versus 11%). 76% of patients in the study had a performance status of 1.

Table 3: Patient characteristics – randomised population

	GIOTRIF (afatinib)	CHEMOTHERAPY (gemcitabine/cisplatin)	Total
Randomised population [N(%)]	242 (100.0)	122 (100.0)	364 (100.0)
Sex [N(%)]			
- Male	87 (36.0)	39 (32.0)	126 (34.6)
- Female	155 (64.0)	83 (68.0)	238 (65.4)
Median age [years] (min; max)	58.0 (29; 79)	58.0 (27; 76)	58.0 (27; 79)
- < 65 years	176 (72.7)	102 (83.6)	278 (76.4)
- ≥ 65 years	66 (27.3)	20 (16.4)	86 (23.6)
Smoking status [N(%)]			
- Has never smoked	181 (74.8)	99 (81.1)	280 (76.9)
- Former smoker	44 (18.2)	13 (10.7)	57 (15.7)
- Smoker	17 (7.0)	10 (8.2)	27 (7.4)
Histology [N(%)]			
- Adenocarcinoma	231 (95.5)	120 (98.4)	351 (96.4)
- Predominantly adenocarcinoma	7 (2.9)	2 (1.6)	9 (2.5)
- Other	4 (1.7)	0 (0.0)	4 (1.1)
Performance status [N(%)]			
- 0	48 (19.8)	41 (33.6)	89 (24.5)
- 1	194 (80.2)	81 (66.4)	275 (75.5)
Disease stage [N(%)]			
- IIIb	16 (6.6)	6 (4.9)	22 (6.0)
- IV	226 (93.4)	116 (95.1)	342 (94.0)
Number of metastatic sites [N(%)]			
- 0	5 (2.1)	1 (0.8)	6 (1.6)
- 1	72 (29.8)	52 (42.6)	124 (34.1)
- 2	91 (37.6)	36 (29.5)	127 (34.9)
- ≥ 3	74 (30.6)	33 (27.0)	107 (29.4)
EGFR mutation [N(%)]			
- L858R	92 (38.0)	46 (37.7)	138 (37.9)
- Exon 19 deletion	124 (51.2)	62 (50.8)	186 (51.1)
- Other	26 (10.7)	14 (11.5)	40 (11.0)

Results for the primary endpoint: progression-free survival
Median progression-free survival was 11.0 months in the GIOTRIF group versus 5.6 months in the chemotherapy group, an absolute gain of 5.4 months favouring GIOTRIF (HR = 0.28, 95% CI [0.20; 0.39], p < 0.0001).

Secondary endpoint results:
The objective response rate was 67% in the GIOTRIF group and 23% in the chemotherapy group, p < 0.0001.

Table 4: Objective response rate and disease control evaluated by an independent committee (randomised population)

N (%)	GIOTRIF (afatinib)	CHEMOTHERAPY (gemcitabine/cisplatin)
Patients randomised	242 (100.0)	122 (100.0)
Objective response	162 (66.9)	28 (23.0)
- Complete (CR)[1]	3 (1.2)	0 (0.0)
- Partial (PR)[1]	159 (65.7)	28 (23.0)
Stable disease (SD)[1]	52 (21.5)	65 (53.3)
No CR/No DP[2]	10 (4.1)	0 (0.0)
Disease control N (CR+PR+SD)[1]	224 (92.6)	93 (4.9)
Disease progression	9 (3.7)	6 (9.6)
- SD or No CR/No DP1 < 35 days[3]	0 (0.0)	2 (1.6)
Unable to evaluate	9 (3.7)	23 (18.9)

[1] Tumour evaluation using RECIST criteria version 1.1: CR = complete response, DP = disease progression, PR = partial response, SD = stable disease.

[2] Patients with stable disease in non-target lesions, in the absence of target lesions on randomisation.

[3] After randomisation.

- Overall survival:

Median overall survival, evaluated in an interim analysis, did not differ between the two groups: median overall survival was 22.24 months in the GIOTRIF group versus 22.11 months in the chemotherapy group (HR = 0.949, 95% CI [0.676; 1.330], p = 0.7593).

- Subsequent lines of treatment

The percentages of patients who received a subsequent line of treatment were comparable in both groups: 58% in the GIOTRIF group versus 61% in the gemcitabine/cisplatin group. Approximately half of patients in the GIOTRIF group (55%) subsequently received chemotherapy, primarily platinum-based. In the gemcitabine/cisplatin group, 48% of patients subsequently received a TKI.

The percentage of patients whose symptoms improved was higher in the GIOTRIF group than in the chemotherapy group for cough (76% versus 55%; OR = 2.52, p = 0.0003) and dyspnoea (71% versus 48%; OR = 2.67, p < 0.0001).
The overall quality of life score from the QLQ-C30 questionnaire also favoured the afatinib group over the comparator (-8.8 points, p < 0.0001).

08.2 Adverse affects

The treatment discontinuation rate due to adverse events was 14% in the GIOTRIF group versus 15.4% in the pemetrexed/cisplatin group.
Serious adverse events were observed in 28.8% of patients in the GIOTRIF group versus 22.5% of patients in the pemetrexed/cisplatin group.
Serious adverse events graded ≥ 3 were 60.6% (139/229) in the GIOTRIF group versus 56.7% (63/111) in the pemetrexed/cisplatin group.
In the GIOTRIF group, the most frequently reported adverse events were gastrointestinal: diarrhoea (96% of patients), stomatitis (74%) and nausea (25%), mucocutaneous: rash (63%), dry skin (30%) and acne (22%), paronychia (62%), or infectious: nasopharyngitis (14%) and upper respiratory tract infections (11%).
The most frequently reported grade 3 adverse events were diarrhoea (15% of patients), skin disorders (rash 14%, acne 2%), stomatitis (8%) and paronychia (12%).
In the pemetrexed/cisplatin group, the most frequently reported adverse events were gastrointestinal: nausea (68%), vomiting (47%) and constipation (35%), haematological: neutropenia (32%) and anaemia (28%), and general: fatigue (50%) and loss of appetite (55%).
The grade 3 adverse events in the chemotherapy group were neutropenia (16% of patients), fatigue (13%), anaemia (5%) and nausea (4%).

08.3 Summary & discussion

The evaluation of the therapeutic benefit of GIOTRIF (afatinib) as a first-line therapy for advanced non-small cell lung cancer with EGFR mutation is based primarily on an open-label, randomised pivotal study (LUX-LUNG 3) comparing GIOTRIF (afatinib) to a platinum-based chemotherapy (pemetrexed/cisplatin).
A total of 345 patients with a median age of 61 years were 2:1 randomised to receive GIOTRIF 40 mg orally once daily or pemetrexed/cisplatin chemotherapy administered intravenously for a maximum of six cycles. Their initial ECOG performance score was 0 (39%) or 1 (61%). 26% of patients were Caucasian and 72% were Asian.
Median progression-free survival (the primary efficacy endpoint) was 11.1 months in the GIOTRIF group versus 6.9 months in the pemetrexed/cisplatin group, an absolute gain of 4.2 months favouring GIOTRIF (HR = 0.58, 95% CI [0.43; 0.78], p = 0.0004).
Median overall survival was comparable in both groups (28 months in each group, HR = 0.907, 95% CI [0.660; 1.246], p = 0.5457, in a second interim analysis of this endpoint).
The objective response rate was higher in the GIOTRIF group than in the chemotherapy group: 56% versus 23%, p < 0.0001.
The median duration of objective response was 11.1 months in the GIOTRIF group versus 5.5 months in the chemotherapy group.
The time to deterioration was longer in the GIOTRIF group than in the pemetrexed/cisplatin group for cough (HR = 0.60 [0.41; 0.87], p = 0.007) and dyspnoea (HR = 0.68 [0.50; 0.93], p = 0.015) but no difference was observed for pain.

The results of a second study (LUX-LUNG 6) conducted in an exclusively Asian population were consistent with the pivotal study. An absolute gain in progression-free survival (the primary endpoint) of 5.4 months was noted for GIOTRIF, with combined gemcitabine/cisplatin as the comparator. However, there was no gain in overall survival.

The main adverse events reported in the GIOTRIF group were gastrointestinal (grade 3 diarrhoea: 15%, grade 3 stomatitis: 8%) and skin disorders (grade 3 rash: 14%, grade 3 paronychia: 12%). In the chemotherapy group, the main adverse events were neutropenia (grade 3: 16%) and fatigue (grade 3: 13%).
The Committee wishes to emphasise two points which pose a problem regarding the transferability of the data presented:

- In the pivotal study (LUX-LUNG 3), the chemotherapy was limited to six cycles of pemetrexed/cisplatin whereas the experimental group was treated until disease progression or death occurred. The possibility that better results might have been obtained in the chemotherapy group if these cycles had been followed by maintenance treatment with pemetrexed monotherapy, as approved in the Marketing Authorisation, cannot therefore be ruled out.
- In the LUX-LUNG 6 study, a gemcitabine/cisplatin combination was prescribed whereas this is not the standard treatment for adenocarcinoma in Europe.

08.4 Planned studies

Two other international phase III studies examining the treatment of non-small cell lung cancer (NSCLC) were set up in 2010:

• The phase IIb LUX-LUNG 7 study (1200.123, trial protocol [U11-3290-04]), a multicentre, randomised, open-label study comparing afatinib to gefitinib as first-line therapy in patients with advanced lung adenocarcinoma with common EGFR mutations.

The results of this study are expected in June 2015.

• The phase III LUX-LUNG 8 study (1200.125), a randomised, open-label study comparing afatinib to erlotinib in terms of progression-free survival and overall survival as a second-line therapy in patients with advanced squamous cell carcinoma of the lungs in whom first-line therapy with platinum-based chemotherapy has failed. The results of this study are expected in September 2015.

09 THERAPEUTIC USE

Surgery is the treatment of choice for the early stages of NSCLC. However, a large proportion of patients are diagnosed at an advanced stage of the disease (about 30% in the locally advanced stage and 40% in the metastatic stage) and the early stage is observed in only 25% to 30% of patients.

The professional guidelines of the National Cancer Institute (INCa) published in September 2010 indicate that from first-line therapy onwards, the therapeutic strategy in patients with inoperable lung cancer must be determined by the presence or absence of an EGFR mutation detected in the tumour.

In those patients who have a tumour with no EGFR mutation, platinum-based chemotherapy is still the standard treatment. In cases with a mutation, the recommended treatment is a tyrosine kinase inhibitor. Two tyrosine kinase inhibitors are currently indicated in the first-line therapy of patients who have a tumour with EGFR gene activating mutations: gefitinib (IRESSA) and erlotinib (TARCEVA). To date, the benefit of tyrosine kinase inhibitors has been established by comparison with platinum-based chemotherapy mainly in terms of progression-free survival and with no demonstrated impact on overall survival.

GIOTRIF is a first-line therapy for locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation(s). In the absence of any comparative study, its role in relation to the other available tyrosine kinase inhibitors (gefitinib and erlotinib) has yet to be determined.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Non-small cell lung cancer (NSCLC) is a life-threatening disease.
◗ The GIOTRIF medicinal products are intended as specific curative therapy for NSCLC.
◗ The efficacy/adverse effects ratio of GIOTRIF is high.

◗ Public health benefit:
In France, lung cancer is the number-one cause of cancer-related mortality in men, the number-three cause in women, and is a major public health burden. The burden of non-small cell lung cancer (NSCLC) (80% to 85% of lung cancers) which is locally advanced or metastatic is itself substantial. The burden of the population likely to benefit from GIOTRIF (tumour with an activating EGFR mutation, first-line therapy) can be considered as moderate.
Improving the management of cancer patients and their quality of life is a public health objective which is an established priority (French Public Health Law of 2004, Cancer Plan and the plan for improving the quality of life of patients with chronic diseases).
In view of the available clinical data and in comparison with cisplatin-based chemotherapy, a moderate additional impact on morbidity/mortality and quality of life is expected in patients treated with first-line GIOTRIF. It should be noted that there is no improvement in terms of overall survival.
In the absence of any clinical data comparing GIOTRIF with other tyrosine kinase inhibitors, the medicinal product GIOTRIF is not expected to have any additional impact on morbidity/mortality and quality of life in the current treatment strategy for these patients.
The transferability of the results of the studies to clinical practice in France is uncertain, due to the specific profile of the patients included. The majority of patients with an EGFR mutation included in the studies had adenocarcinoma and were Asian. This difference could have an impact in practical terms.
Consequently, we cannot assume that the medicinal product GIOTRIF will provide an additional response to the identified public health need.
As with the other oral chemotherapies, GIOTRIF has not been shown to have any impact on the organisation of healthcare (hospital admissions avoided, transfer of care to consultations).
In the current state of knowledge, these medicinal products are not expected to have an impact on public health in this indication.

◗ This is a first-line therapy.
◗ Alternative medicinal products exist.

Taking account of these points, the Committee considers that the actual benefit of GIOTRIF is substantial in the first-line therapy of locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation(s).

010.2 Improvement in actual benefit (IAB)

GIOTRIF provides no improvement in actual benefit (level V, non-existent) in the first-line therapy of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

010.3 Target population

The target population for GIOTRIF consists of patients with locally advanced or metastatic NSCLC whose tumour has EGFR activating mutations and who have not received prior treatment (first-line therapy).
The latest reports by the National Cancer Institute (INCa) show that the number of incident patients with lung cancer was equal to 39,495 new cases a year in France in 2012.[5]
About 85% of these are non-small cell cancers (KBP French population of lung cancers followed up in 2000),[6, 7] i.e. 33,570 new cases per year.
It is estimated that when the disease is first diagnosed:
- 65% (21,820 patients) have inoperable stage IIIb or IV;
- 35% (11,550 patients) have a localised stage eligible for initial surgical management or radiotherapy, but two out of five of these will experience recurrence (4620 patients) and become eligible for systemic treatment.

Thus, 26,440 patients are potentially eligible for first-line therapy of stage IIIb and IV lung cancer.
An EGFR activating mutation is found in about 10% of cases of NSCLC in France.[8]
Thus, the target population for first-line GIOTRIF can be estimated as about 2700 patients a year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

The packaging is not appropriate for the prescribing conditions. The Committee wishes to reiterate that, in accordance with its deliberations of 20 July 2005, standardisation of pack size to 30 days is recommended for treatments lasting 1 month.

◗ Proposed reimbursement rate: 100%

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the first-line therapy of locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

[5] Institut de veille sanitaire, Francim, Inserm CépiDc, Hôpitaux de Lyon, Institut national du cancer. Estimation nationale de l'incidence et de la mortalité par cancer entre 1980 et 2012. http://www.e-cancer.fr/publications/69-epidemiologie/696-estimation-nationale-de-lincidence-et-de-la-mortalite-par-cancer-en-france-entre-1980-et-2012-partie-1-tumeurs-solides.

[6] F. Blanchon F, Grivaux M, Collon T, Zureik M, Barbieux H, Benichou-Flurin M, et al. Epidémiologie du cancer bronchique primitif pris en charge dans les centres hospitaliers généraux français. Etude KBP-2000-CPHG du Collège des Pneumologues des Hôpitaux Généraux (CPHG). Rev Mal Respir 2002; 19: 727-34.

[7] INCa. Recommandations professionnelles. Cancer du poumon : Prise en charge thérapeutique du cancer du poumon non à petites cellules. September 2010.

[8] Institut National du Cancer (INCa). Mutations de l'EGFR dans le cancer du poumon: mise en évidence d'une cible moléculaire permettant un accès spécifique aux thérapies ciblées. February 2010 report. http://www.e-cancer.fr/publications/71-soins/554-mutations-de-legfr-dans-le-cancer-du-poumon-mise-en-evidence-dune-cible-moleculaire-permettant-un-acces-specifique-aux-therapies-ciblees.