NEW ZEALAND DATASHEET

1. PRODUCT NAME

GIOTRIF 20 mg film-coated tablets
GIOTRIF 30 mg film-coated tablets
GIOTRIF 40 mg film-coated tablets
GIOTRIF 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GIOTRIF 20 mg film-coated tablets
One film-coated tablet contains 20 mg afatinib (as dimaleate)
Excipient with known effect: One film-coated tablet contains 123.86 mg of lactose monohydrate

GIOTRIF 30 mg film-coated tablets
One film-coated tablet contains 30 mg afatinib (as dimaleate)
Excipient with known effect: One film-coated tablet contains 185.79 mg of lactose monohydrate

GIOTRIF 40 mg film-coated tablets
One film-coated tablet contains 40 mg afatinib (as dimaleate)
Excipient with known effect: One film-coated tablet contains 247.72 mg of lactose monohydrate

GIOTRIF 50 mg film-coated tablets
One film-coated tablet contains 50 mg afatinib (as dimaleate)
Excipient with known effect: One film-coated tablet contains 309.65 mg of lactose monohydrate

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

GIOTRIF 20 mg film-coated tablets
White to slightly yellowish, round, biconvex and bevel-edged film-coated tablet debossed with the code “T20” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF 30 mg film-coated tablets
Dark blue, round, biconvex and bevel-edged film-coated tablet debossed with the code “T30” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF 40 mg film-coated tablets
Light blue, round, biconvex and bevel-edged film-coated tablet debossed with the code “T40” on one side and the Boehringer Ingelheim company logo on the other.

GIOTRIF 50 mg film-coated tablets
Dark blue, oval and biconvex film-coated tablet debossed with the code “T50” on one side and the Boehringer Ingelheim company logo on the other.

Afatinib dimaleate is a white to brownish yellow powder. It is highly soluble in water and in aqueous buffer media up to pH 6 (> 50 mg/mL). Between pH 6 and 7, the solubility in these media decreases significantly but still exceeds 1 mg/mL. Above pH 7, solubility is reduced further to the low solubility of its free base (0.04 mg/mL at pH > 8). The highest

solubility in organic solvents is observed for DMSO (> 50 mg/mL). Solubility in methanol is between 10 and 25 mg/mL; in 1:1 mixtures of acetonitrile, methanol, and ethanol with water the solubility exceeds 50 mg/mL. Dissociation constants: pKa1 = 8.2 ± 0.1; pKa2 = 5.0 ± 0.1. Partition coefficient: log P = 4.7 (at pH ≥ 9); log D = 3.8 (at pH 7.4).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GIOTRIF is indicated as monotherapy for the treatment of patients with:

- Locally advanced or metastatic non-squamous non-small cell carcinoma of the lung, either as first line therapy or after failure of cytotoxic chemotherapy. Tumours must have Epidermal Growth Factor Receptor (EGFR) mutations.
- Locally advanced or metastatic non-small cell carcinoma of the lung of squamous histology progressing on or after platinum-based chemotherapy.

4.2 Dose and method of administration

Dose

The recommended dose of GIOTRIF is 40 mg orally once daily for first-line treatment or for patients not previously treated with an EGFR Tyrosine Kinase Inhibitor (EGFR TKI-naïve patients) and for patients with squamous NSCLC who have previously received first-line platinum-containing regimen.

GIOTRIF should be taken without food. Food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see sections 5.2 and 4.4). Tablets should be swallowed whole with water.

GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (see Table 1 below).

Dose escalation

A dose escalation to a maximum of 50 mg/day may be considered in patients who tolerate a 40 mg/day starting dose (i.e. absence of diarrhoea, skin rash, stomatitis and other drug related events of CTCAE Grade > 1) in the first cycle of treatment (for the definition of treatment cycle see Section 5 Pharmacological Properties). The dose should not be escalated in patients with a prior dose reduction.

The maximum daily dose in any setting is 50 mg.

Dose adjustment for adverse reactions

Symptomatic adverse drug reactions (e.g. severe/persistent diarrhoea or skin-related adverse reactions) may be successfully managed by treatment interruption and dose reductions of GIOTRIF as outlined in Table 1 (see sections 4.8 and 4.4).

Table 1: Dose Adjustment Information for Adverse Reactions

CTCAE[a] Drug Related Adverse Event	Recommended Dosing of GIOTRIF	
Grade 1 or Grade 2	No interruption[b]	No dose adjustment
Grade 2 (prolonged[c] or intolerable) or Grade ≥ 3	Interrupt until Grade 0/1[b]	Resume with dose reduction by 10 mg decrements[d]

[a] NCI Common Terminology Criteria for Adverse Events v 3.0
[b] In case of diarrhoea, antidiarrhoeal medicines (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until loose bowel movements cease.
[c] > 48 hours of diarrhoea and/or > 7 days of rash
[d] If patient cannot tolerate 20 mg/day, permanent discontinuation of GIOTRIF should be considered

Interstitial Lung Disease (ILD) should be considered if a patient develops acute or worsening of respiratory symptoms in which case GIOTRIF should be interrupted pending evaluation. If ILD is diagnosed, GIOTRIF should be discontinued and appropriate treatment instituted as necessary (see section 4.4).

Missed dose

If a dose of GIOTRIF is missed, it should be taken during the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped.

Patients with renal impairment

Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild, moderate or severe (eGFR 15-29 mL/min/1.73m^2) renal impairment. Monitor patients with severe renal impairment and adjust GIOTRIF dose if not tolerated. GIOTRIF treatment in patients with eGFR <15 mL/min/1.73m^2 or on dialysis is not recommended.

Patients with hepatic impairment

Exposure to afatinib is not significantly changed in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment (see section 5.2). Adjustments to the starting dose are not necessary in patients with mild or moderate hepatic impairment. GIOTRIF has not been studied in patients with severe (Child Pugh C) hepatic impairment. GIOTRIF treatment in this population is not recommended.

Age, Race, Gender

No dose adjustment is necessary based on patient age, race, or gender (see section 5.2).

Paediatric population

The safety and efficacy of GIOTRIF have not been studied in paediatric patients. Therefore, treatment of children or adolescents with GIOTRIF is not recommended.

Use of P-glycoprotein (P-gp) inhibitors

If P-gp inhibitors need to be taken, they should be administered simultaneously with or after GIOTRIF (see sections 5.2, 4.4 and 4.5).

Method of administration

GIOTRIF is for oral use. The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, GIOTRIF tablets can be dispersed in approximately 100 mL of non-carbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 minutes until the tablet is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 mL of water which should also be consumed. The dispersion can also be administered through a gastric tube.

4.3 Contraindications

GIOTRIF is contraindicated in patients with known hypersensitivity to afatinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported during treatment with GIOTRIF (see section 4.8). Diarrhoea may result in electrolyte abnormalities and/or dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Monitoring for serum electrolyte abnormalities may be required depending on the severity and duration of diarrhoea. Diarrhoea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurred within the first 6 weeks of treatment. Proactive management of diarrhoea including adequate hydration combined with antidiarrhoeal agents especially within the first six weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal agents (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Antidiarrhoeal agents should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with GIOTRIF (see section 4.2). Patients who become dehydrated may require administration of intravenous electrolytes and fluids.

Skin related adverse events

Rash/acne has been reported in patients treated with GIOTRIF (see section 4.8). In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and/or use of sun screen is advisable. Early intervention (e.g. emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment.

Patients with prolonged or severe skin reactions may also require temporary interruption of therapy, dose reduction (see section 4.2), additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis. GIOTRIF treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Female gender, lower body weight and underlying renal impairment

Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment (see section 5.2). This could result in a higher risk of developing EGFR-mediated adverse events such as diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors.

Interstitial Lung Disease (ILD)

There have been reports of ILD or ILD-like events (such as Lung infiltration, Pneumonitis, Acute Respiratory Distress Syndrome, Alveolitis allergic), including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. Drug-related ILD-like events were reported in 0.7% of patients treated with GIOTRIF across all clinical trials (including 0.5% of patients with CTCAE Grade ≥ 3 ILD-like adverse reactions) (see section 4.8). Patients with a history of ILD have not been studied. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. GIOTRIF should be interrupted pending investigation of these

symptoms. If ILD is diagnosed, GIOTRIF should be permanently discontinued and appropriate treatment instituted as necessary (see section 4.2).

Severe hepatic impairment
Hepatic failure, including fatalities, has been reported during treatment with GIOTRIF in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or co-morbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. GIOTRIF dose interruption may become necessary in patients who experience worsening of liver function (see section 4.2). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

Gastrointestinal perforations
Gastrointestinal perforation, including fatalities, has been reported during treatment with GIOTRIF in 0.2% of patients across all randomised controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking GIOTRIF, treatment should be permanently discontinued.

Keratitis
Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with GIOTRIF should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GIOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration (see section 4.8).

Left ventricular function
Left ventricular dysfunction has been associated with HER2 inhibition. GIOTRIF has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during GIOTRIF treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as GIOTRIF treatment interruption or discontinuation should be considered.

Pancreatitis
Adverse events of pancreatitis have been observed uncommonly in patients treated with GIOTRIF. Although a causal association was not established, patients who develop symptoms consistent with the diagnosis should be evaluated for pancreatitis.

P-glycoprotein (P-gp) interactions
Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (see sections 4.2 and 4.5).

Lactose monohydrate
GIOTRIF contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

P-glycoprotein (P-gp) interactions

Based on *in vitro* data, afatinib is a substrate of P-gp. Based on clinical data, concomitant administration of strong P-gp inhibitors or inducers may alter exposure to afatinib. Results of a drug interaction trial demonstrated that GIOTRIF can be safely combined with P-gp inhibitors (such as ritonavir) as long as the inhibitor is administered simultaneously with or after GIOTRIF. If administered prior to GIOTRIF, strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) may increase exposure to afatinib and should be used with caution (see sections 5.2, 4.4 and 4.2).

Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort) may decrease exposure to afatinib (see sections 5.2 and 4.4).

Interactions with breast cancer resistance protein (BCRP)

In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP. Afatinib may increase the bioavailability of orally administered BCRP substrates (including but not limited to rosuvastatin and sulfasalazine) and caution should be exercised when co-administrating GIOTRIF and BCRP substrates.

Food effect on afatinib

Co-administration of a high-fat meal with GIOTRIF resulted in a significant decrease of exposure to afatinib by about 50% in regard to Cmax and 39% in regard to $AUC_{0-\infty}$. GIOTRIF should be administered without food (see sections 5.2 and 4.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with GIOTRIF. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after the last dose.

Pregnancy (Category C)

Mechanistically, all EGFR targeting medicinal products have the potential to cause foetal harm. Animal studies with afatinib did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Studies in animals have shown no signs of teratogenicity up to and including maternally lethal dose levels. Adverse changes were restricted to toxic dose levels. However, systemic exposures achieved in animals were either in a similar range or below the levels observed in patients (see section 5.3).

There are no studies in pregnant women using GIOTRIF. It is unknown whether afatinib crosses the placenta in humans. The potential risk for humans is thus unknown. If GIOTRIF is used during pregnancy or if the patient becomes pregnant while receiving GIOTRIF, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding

Available pharmacokinetic data in animals have shown excretion of afatinib in milk (see section 5.3). Based on this, it is likely that afatinib is excreted in human milk. A risk to the breast-feeding child cannot be excluded. Mothers should be advised against breast-feeding while receiving this medicinal product.

Fertility

Fertility studies in humans have not been performed with GIOTRIF. Available nonclinical

toxicology data have shown effects on reproductive organs at higher doses. Therefore, an adverse effect of GIOTRIF therapy on human fertility cannot be excluded.

4.7 Effects on ability to drive and use machines

GIOTRIF has minor influence on the ability to drive and use machines. During treatment, ocular adverse reactions (conjunctivitis, dry eye, keratitis) have been reported in some patients (see section 4.8) which may affect patients ability to drive or use machines.

4.8 Undesirable Effects

Summary of the safety profile

The safety evaluation of GIOTRIF is based on the data from clinical trials and post marketing experience.

Controlled studies

In the pivotal LUX-Lung 3 (1200.32) trial a total of 229 EGFR TKI naïve patients were treated with GIOTRIF with a starting dose of 40 mg once daily. A total of 111 patients were treated with pemetrexed/cisplatin. The overall incidence of Adverse Drug Reactions (ADRs) in patients treated with GIOTRIF was similar to pemetrexed/cisplatin (100% vs. 96%). The incidence of diarrhoea (95% vs. 15%) and rash/acne (89% vs. 6%) ADRs were higher in the GIOTRIF-treated patients than in those patients treated with pemetrexed/cisplatin, respectively. Dose reductions due to adverse events occurred in 57% of GIOTRIF-treated patients. Overall dose reduction led to a lower frequency of common adverse events (e.g. after first dose reduction, frequency for diarrhoea regardless of causality decreased from 96% to 52%).

Elderly patients may be more likely to experience a higher grade of the more frequent EGFR TKI-associated events. Grade 3 AEs were observed in 67% in patients ≥70 years of age versus 47% in patients <70 years of age.

Discontinuation of therapy due to ADRs was lower in patients who received once daily GIOTRIF 40 mg compared with pemetrexed/cisplatin (8% vs. 12%). In patients treated with GIOTRIF, discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%, respectively.

In the LUX-Lung 6 (1200.34) trial a total of 239 EGFR TKI naïve patients were treated with GIOTRIF with a starting dose of 40 mg once daily. A total of 113 patients were treated with gemcitabine/cisplatin. The overall incidence of ADRs in patients treated with GIOTRIF was similar to gemcitabine/cisplatin (98.7% vs. 99.1%). The incidences of diarrhoea (88.7% vs. 10.6%) and rash/acne (81.2% vs. 8.8%) ADRs were higher in the GIOTRIF-treated patients than in patients treated with gemcitabine/cisplatin. Dose reductions due to adverse events occurred in 33.1% of GIOTRIF-treated patients and in 26.5% of gemcitabine/cisplatin-treated patients.

Discontinuations of study medication due to ADRs were less frequent in patients who received GIOTRIF compared with gemcitabine/cisplatin (6.3% vs. 39.8%). In patients treated with GIOTRIF, the incidences of discontinuations due to the ADRs diarrhoea and rash/acne were 0% and 2.5%, respectively.

In the pivotal LUX-Lung 8 (1200.125) trial a total of 392 patients with squamous NSCLC were treated with GIOTRIF with a starting dose of 40 mg once daily and a total of 395 patients were treated with 150 mg erlotinib once daily. After the first treatment cycle (28 days) the dose of GIOTRIF was escalated to 50 mg in 39 (10%) patients. The overall incidence of ADRs in patients treated with GIOTRIF or erlotinib was 93% vs. 81% respectively. The incidence of diarrhoea ADRs was higher in the GIOTRIF-treated patients compared to erlotinib (70% vs. 33%), while incidence of rash/acne was similar in both groups (67% vs. 67%). Dose

reductions due to adverse events occurred in 27% of GIOTRIF-treated patients. Treatment was discontinued due to ADRs in 11% of patients treated with GIOTRIF, and in 5% of erlotinib treated patients.

Description of selected adverse reactions

Very Common ADRs in GIOTRIF-treated patients occurring in at least 10% of patients in trial LUX-LUNG 3 are summarised by National Cancer Institute – Common Terminology Criteria (NCI-CTC) Grade in Table 2.

Table 2: Adverse Events Reported in ≥10% of GIOTRIF Treated Patients in LUX-Lung 3

	GIOTRIF N=229			**Pemetrexed/Cisplatin N=111**		
Adverse Event	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Gastrointestinal disorders						
Diarrhoea	96	15	0	23	2	0
Stomatitis[1]	71	8	0	15	1	0
Nausea	25	1	0	68	4	0
Vomiting	23	4	0	47	3	0
Constipation	13	0	0	35	0	0
Cheilitis	12	0	0	1	0	0
Skin and subcutaneous tissue disorders						
Rash[2]	71	14	0	11	0	0
Dermatitis acneiform[3]	35	3	0	0	0	0
Pruritus[4]	21	0	0	1	0	0
Dry skin[5]	31	0	0	2	0	0
Alopecia	13	0	0	18	0	0
Infections and infestations						
Paronychia[6]	58	11	0	0	0	0
Nasopharyngitis	14	0	0	8	0	0
Cystitis[7]	13	1	0	5	0	0
Upper respiratory tract infection	11	0	0	4	0	0
Metabolism and nutrition disorders						
Decreased appetite	29	4	0	55	4	0
Hypokalemia[8]	11	2	2	5	3	1
General disorders and administration site conditions						
Fatigue	19	2	0	36	10	0
Pyrexia[10]	12	0	0	6	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	17	0	0	2	1	0
Cough	15	0	0	19	1	0
Rhinorrhea[9]	11	0	0	6	0	0
Investigations						
Weight decreased	17	1	0	14	1	0
Alanine aminotransferase	11	2	0	4	0	0
Psychiatric disorders						
Insomnia	15	0	0	9	0	0

	GIOTRIF N=229			Pemetrexed/Cisplatin N=111		
Adverse Event	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Nervous system disorder						
Headache	14	0	0	17	0	0
Dizziness	11	0	0	11	0	0
Musculoskeletal and connective tissue disorders						
Back pain	14	0	0	12	2	0
Eye disorders						
Conjunctivitis[11]	11	0	0	3	0	0

[1]Includes stomatitis, aphthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration

[2]Includes group of rash preferred terms

[3]Includes acne, acne pustular, dermatitis acneiform

[4]Includes pruritus, pruritus generalized

[5]Includes dry skin, skin chapped

[6]Includes paronychia, nail infection, nail bed infection

[7]Includes cystitis, urinary tract infection

[8]Includes hypokalemia, blood potassium decreased

[9]Includes rhinorrhea, nasal inflammation

[10]Includes pyrexia, body temperature increased

[11]Includes conjunctivitis, conjunctival irritation, conjunctival hyperemia

All NSCLC-studies with daily dose of 40 mg or 50 mg GIOTRIF

The safety of GIOTRIF monotherapy at starting doses of 40 mg or 50 mg once daily was assessed in pooled analyses of NSCLC trials in patients with or enriched for EGFR mutations. The predominant type of histology in this patient population was adenocarcinoma of the lung. The types of ADRs were generally associated with the EGFR inhibitory mode of action of afatinib and the profile of ADRs was consistent with the LUX-Lung 3 trial. CTCAE Grade 1 or 2 ADRs occurred in 58.8% of patients treated with GIOTRIF 40 mg. CTCAE Grade 3 or 4 ADRs occurred in 38% of patients treated with GIOTRIF 40 mg. The majority of ADRs were of CTCAE Grade 1 or 2. ADRs were manageable as described in sections 4.2 and 4.4 which was reflected in the low treatment discontinuation rate of 7% due to ADRs.

A summary of common ADRs of diarrhoea and rash/acne in EGFR mutation positive or enriched population with NSCLC treated with GIOTRIF monotherapy is provided in Table 3.

Table 3: Pooled analyses of drug related diarrhoea and rash/acne in EGFR mutation positive or enriched NSCLC population receiving GIOTRIF monotherapy in clinical studies

	EGFR TKI-naïve (Starting dose 40 mg/day) N=497
CTCAE[a] Grade 3 rash/acne	14.3%
CTCAE[a] Grade 3 diarrhoea	9.9%
Discontinuation due to rash/acne (all Grades)	1.2%
Discontinuation due to diarrhoea (all Grades)	0.6%

[a] NCI Common Terminology Criteria for Adverse Events v 3.0

One patient (0.2%) receiving a 40 mg starting dose experienced Grade 4 rash/acne.

The safety of GIOTRIF monotherapy in patients with squamous cell carcinoma of the lung receiving 40 mg starting dose was assessed in trial LUX-Lung 8. The most frequent ADRs were associated with the EGFR inhibitory mode of action of GIOTRIF and were consistent with trial LUX-Lung 3 in patients with adenocarcinoma of the lung. The majority of patients with ADRs (65%) had Grade 1 or 2 events. The ADR of CTCAE grade 3 / 4 diarrhoea occurred in 9.9% / 0.5% of patients. The rate of drug-related CTCAE grade 3 rash was 5.9%. ADRs led to discontinuation of treatment for 11% of patients. Discontinuation of treatment due to ADRs diarrhea and rash/acne regardless of severity grade occurred in 3.8% and 2.0% of patients.

Tabulated list of adverse reactions

The ADRs pooled from all NSCLC trials with daily GIOTRIF doses as monotherapy (N=2135) and post-marketing experience are shown below by system organ class. The frequency categories used are defined as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000).

Body System	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Infections and infestations	Paronychia	Cystitis		
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hypokalemia		
Nervous system disorders		Dysgeusia		
Eye disorders		Conjunctivitis Dry eye	Keratitis	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Rhinorrhea	Interstitial lung disease	
Gastrointestinal disorders	Diarrhea Stomatitis Nausea Vomiting	Dyspepsia Cheilitis	Pancreatitis Gastrointestinal perforation	
Hepatobiliary disorders		ALT increased AST increased		
Skin and subcutaneous tissue disorders	Rash Dermatitis acneiform Pruritus Dry skin	Nail disorders Palmar-plantar erythrodysesthesia syndrome		Stevens-Johnson syndrome* Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders		Muscle spasms		
Renal and urinary disorders		Renal impairment /renal failure		
General disorders and administration site conditions		Pyrexia		
Investigations		Weight decreased		

* derived from post-marketing experience

Liver function test abnormalities

Liver function test abnormalities (including elevated alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were observed in patients receiving GIOTRIF 40 mg. These elevations were mainly transient and did not lead to discontinuation of treatment. Grade 2 (>2.5 to 5.0 times ULN [upper limit of normal]) ALT elevations occurred in 7.9% and 3.6% of patients treated with GIOTRIF or chemotherapy, respectively. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in 3.5% and 1.8% of patients treated with GIOTRIF or chemotherapy, respectively (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose, please contact the National Poisons Centre on 0800 764766.

Symptoms
The highest dose of GIOTRIF studied in a limited number of patients in Phase I clinical trials was 160 mg once daily for 3 days and 100 mg once daily for 2 weeks. The adverse reactions observed at this dose were primarily dermatological (rash/acne) and gastrointestinal events (especially diarrhoea). Overdose in 2 healthy adolescents involving the ingestion of 360 mg each of GIOTRIF (as part of a mixed drug ingestion) was associated with adverse drug reactions of nausea, vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). Both subjects recovered from these adverse events.

Treatment
There is no specific antidote for overdose with GIOTRIF. In cases of suspected overdose, GIOTRIF should be withheld and supportive care instituted.

If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents – protein kinase inhibitors, ATC code: L01XE13.

Mechanism of action
Afatinib is an irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (epidermal growth factor receptor, ErbB1), HER2 (human epidermal growth factor receptor 2, ErbB2), ErbB3 and ErbB4.

Pharmacodynamic effects
Aberrant ErbB signalling triggered by, for instance, EGFR mutations and/or amplification, HER2 amplification or mutation and/or ErbB ligand or receptor overexpression contributes to the malignant phenotype in subsets of patients across multiple cancer types.

In nonclinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. Anti-tumour activity of afatinib was demonstrated in HER2 overexpressing models. Various ErbB pathway aberrations (e.g. EGFR overexpression or mutation) were also the most likely underlying cause for the activity of afatinib in lung cancer models. NSCLC models with either L858R or Del 19 EGFR mutations are particularly sensitive to afatinib treatment.

In NSCLC, the acquisition of a secondary T790M mutation is a major mechanism of acquired resistance to afatinib and gene dosage of the T790M-containing allele correlates with the degree of resistance in vitro. The T790M mutation is found in approximately 50% of patients' tumours upon disease progression on afatinib, for which T790M targeted EGFR TKIs may be considered as a next line treatment option.

Cardiac Electrophysiology
GIOTRIF at doses of 50 mg daily did not result in significant prolongation of the QTcF

interval after single and multiple administrations in patients with relapsed or refractory solid tumours. There were no cardiac safety findings of clinical concern. This suggests that GIOTRIF does not have a relevant effect on the QTcF interval.

Clinical efficacy and safety

GIOTRIF in EGFR mutation positive patients naïve to EGFR TKI treatment

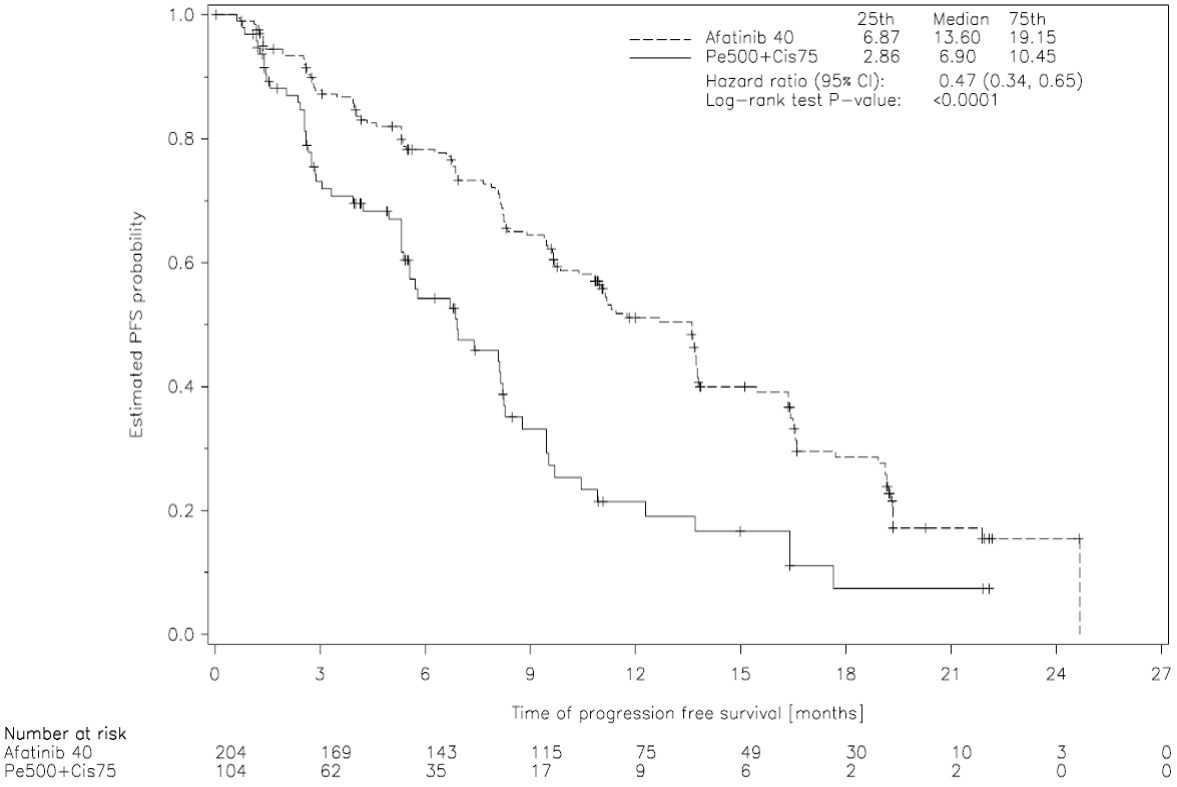
LUX-Lung 3 (1200.32)

In the first-line setting, the efficacy and safety of GIOTRIF in patients with EGFR mutation-positive locally advanced or metastatic NSCLC (stage IIIB or IV) were assessed in a global, randomised, multicentre, open-label trial (LUX-Lung 3). Patients naïve to prior systemic treatment for their advanced or metastatic disease were screened for the presence of 29 different EGFR mutations using a polymerase chain reaction (PCR)-based method (TheraScreen®: EGFR29 Mutation Kit, Qiagen Manchester Ltd). Patients (N=345) were randomised (2:1) to receive GIOTRIF 40 mg orally once daily (N=230) or up to 6 cycles pemetrexed/cisplatin (N=115). Randomisation was stratified according to EGFR mutation status (L858R; Del 19; other) and race (Asian; non-Asian). Dose escalation of GIOTRIF to 50 mg was allowed after the first treatment cycle (21 days) if patients had no or limited drug-related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug-related events above Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), were compliant, and had no prior dose reduction.

In the overall trial population, the primary endpoint of progression free survival (PFS – independent review, 221 events) showed a statistically significant improvement in PFS for patients treated with GIOTRIF compared with patients treated with chemotherapy (median PFS: 11.1 vs. 6.9 months HR 0.58, 95% CI 0.43-0.78; p=0.0004). The percentages of patients being alive and progression-free (PFS rate) at 12 months were 46.5% in patients treated with GIOTRIF and 22% in patients treated with chemotherapy for the overall trial population.

In the pre-defined sub-group of common mutations (L858R, Del 19) for GIOTRIF (N=204) and chemotherapy (N=104) the median PFS was 13.6 months vs. 6.9 months respectively (HR 0.47; 95% CI 0.34-0.65; p<0.0001). The PFS rate at 12 months was 51.1% in patients treated with GIOTRIF and 21.4% in patients treated with chemotherapy and the median OS was 30.3 months vs. 26.2 months (HR 0.82; 95% CI 0.59-1.14; p=0.2244). The Kaplan-Meier curves for the primary PFS analysis in common mutations are shown in Figure 1.

Figure 1: Kaplan-Meier Curves for PFS by independent review by treatment group in LUX-Lung 3 for sub-group of common mutations (L858R, Del 19)



Of the 26 GIOTRIF-treated patients, eight achieved a partial response (N=4) or prolonged disease control of longer than 6 months (N=4): 4 patients with mutations of the category L858R+T790M (1 PR, PFS 11.0 months; 3 SD, 9.6+, 8.3, and 6.7 months); and 1 patient in each with a mutation of the categories L861Q (1 SD, 8.3 months); G719X (1 PR, 10.8 months); S768I+L858R (1 PR, 13.8+ months); and S768I (1 PR, 19.2+ months). The PFS was shorter than 6 months in all patients with the following mutation categories: T790M alone (N=2), deletion 19 and T790M (N=3), G719X and T790M (N=1), exon 20 insertion (n=6). There were 11 chemotherapy-treated patients in the "other" uncommon EGFR mutation subgroup; of these, four (36%) achieved a partial response.

Efficacy results of trial LUX-Lung 3 are summarised in Table 4 below.

Table 4: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3) based on the primary PFS analysis as of 9 February 2012 (Independent review)

	GIOTRIF (N=230)	**Pemetrexed / Cisplatin** (N=115)	**Hazard Ratio (HR) / Odds Ratio (OR) (95% CI) p-value[4]**
PFS, Overall Study Population Months (median) 1-year PFS Rate 18-month PFS Rate	**11.1** 46.5% 26.4%	**6.9** 22.0% 8.6%	HR 0.58 (0.43-0.78) 0.0004
PFS, Patients with L858R or Del 19 Mutations[1] Months (median) 1-year PFS Rate 18-month PFS Rate	**13.6** 51.1% 28.6%	**6.9** 21.4% 7.4%	HR 0.47 (0.34-0.65) <0.0001
Objective Response Rate (CR+PR)[2]	**56.1%**	**22.6%**	OR 4.66 (2.77-7.83) <0.0001
Disease Control Rate (CR+PR+SD)[2]	**90.0%**	**80.9%**	OR 2.14 (1.13-4.04) 0.0189
Response Duration Months (median)	**11.1**	**5.5**	-
Overall Survival (OS), Overall Trial Population Months (median)[3]	**28.2**	**28.2**	HR 0.88 (0.66, 1.17) 0.39

[1] N=308 (GIOTRIF: 204, pemetrexed/cisplatin: 104)
[2] CR=complete response; PR=partial response; SD=stable disease
[3] OS analysis as of December 2013
[4] p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

The effect on PFS was consistent across major subgroups, including gender, age, race, ECOG status, and mutation type (L858R, Del 19). There was no difference in overall survival (OS) based on immature OS data with 28% deaths at the time of primary analysis (PFS). In the predefined sub-group of common EGFR mutations (L858R, Del 19) for GIOTRIF (N=203) and chemotherapy (N=104) the median OS was 31.6 months vs. 28.2 months (HR=0.78, 95% CI (0.58, 1.06), p=0.1090. In the pre-defined EGFR mutation subgroups, the median OS with first-line GIOTRIF vs. chemotherapy was 33.3 months vs. 21.1 months (HR = 0.54, (95% CI 0.36-0.79), p=0.0015) in patients with Del19 (n=169) and 27.6 months vs. 40.3 months (HR = 1.30, (95% CI: 0.80-2.11), p=0.2919) in patients with L858R (n=138).

The PFS benefit of GIOTRIF was accompanied by improvement in disease-related symptoms, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-LC13). In the overall trial population, GIOTRIF significantly delayed the time to deterioration for the pre-specified symptoms of cough (HR 0.60; p=0.0072; median time not reached for GIOTRIF vs. 8.0 months for chemotherapy) and dyspnea (HR 0.68; p=0.0145; median time of 10.3 vs. 2.9 months). Significantly more patients treated with GIOTRIF compared with chemotherapy had improvements for dyspnoea (64% vs. 50%; p=0.0103) and individual items of pain ('Have pain': 56.0% vs. 40.0%; p=0.0095; 'Pain in chest': 51.0% vs. 37.0%; p=0.0184; 'Pain in arm or shoulder': 41.0% vs. 26.0%; p=0.0103). For cough, numerically more patients improved on GIOTRIF (67% vs. 60%; p=0.2444).

LUX-Lung 6 (1200.34)

The efficacy and safety of GIOTRIF in Asian patients with EGFR mutation-positive locally advanced or metastatic adenocarcinoma of the lung (stage IIIB/IV) was assessed in a randomised, multicenter, open-label trial (LUX-Lung 6). Similar to LUX-Lung 3, patients naïve to prior systemic treatment for their advanced or metastatic disease were screened for the presence of 29 different EGFR mutations using a PCR based method (TheraScreen®: EGFR29 Mutation Kit, Qiagen Manchester Ltd). Patients (N=364) were randomised (2:1) to receive GIOTRIF 40 mg orally once daily (N=242) or up to 6 cycles gemcitabine/cisplatin (N=122). Randomisation was stratified according to EGFR mutation status (L858R; Del 19; other). Dose escalation of GIOTRIF to 50 mg was allowed after the first treatment cycle (21 days) if patients had no or limited drug-related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug related events above CTCAE Grade 1), were compliant, and had no prior dose reduction. Among randomised patients, 65% were female; the median age was 58 years and all patients were Asian. Patients with common (L858R or Del 19) EGFR mutations accounted for 89% of the study population.

The primary endpoint of PFS (central independent review, 221 events) showed a statistically significant improvement in PFS for patients treated with GIOTRIF compared with patients treated with chemotherapy (median PFS: 11.0 vs. 5.6 months). When comparing the prespecified subgroup of common (L858R or Del 19) EGFR mutations, the difference in median PFS remained constant (11.0 vs. 5.6 months). The percentages of patients being alive and progression-free (PFS rate) at 12 months were 46.7% in patients treated with GIOTRIF and 2.1% in patients treated with chemotherapy for the overall trial population, and 56.4% vs. 4.4% in the subgroup of common mutations.

The Kaplan-Meier curves of the primary PFS analysis are shown in Figure 2, and efficacy results are summarised in Table 5. At the time of primary PFS analysis, a total of 57 (15.7%) patients treated with GIOTRIF were known to be alive and progression-free and thus censored in Figure 2.

Figure 2: Kaplan-Meier curves for PFS by independent review by treatment group in LUX-Lung 6 Trial (Primary Analysis, Overall Population)

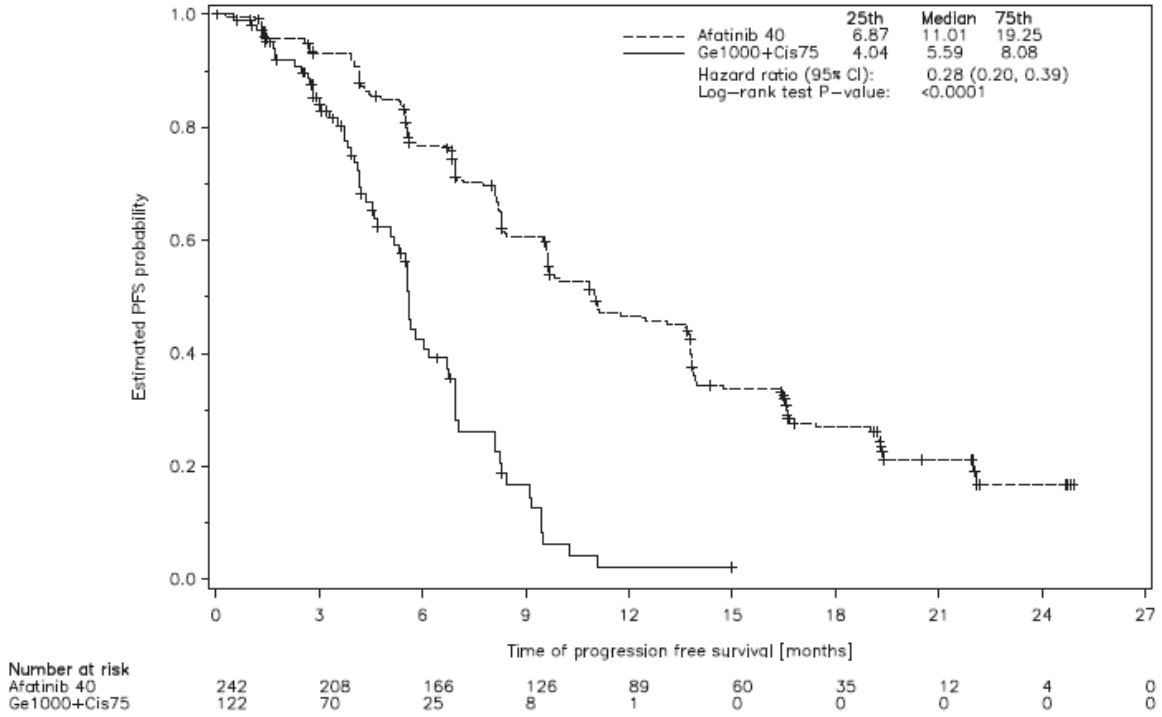


Table 5: Efficacy results for GIOTRIF vs. gemcitabine/cisplatin (LUX-Lung 6 Trial) based on the primary PFS analysis as of 29 October 2012 (Independent review)

	GIOTRIF (N=242)	**Gemcitabine/ Cisplatin** (N=122)	**Hazard Ratio/ Odds Ratio (95%CI) p-value[4]**
PFS, Overall Trial Population			
Months (median)	**11.0**	**5.6**	HR 0.28 (0.20-0.39)
1-year PFS Rate	46.7%	2.1%	<0.0001
18-months PFS Rate	26.8%	0.0%	

	GIOTRIF (N=242)	Gemcitabine/ Cisplatin (N=122)	Hazard Ratio/ Odds Ratio (95%CI) p-value[4]
PFS, Patients with L858R or Del 19 Mutations [1]			
Months (median)	**11.0**	**5.6**	HR 0.25 (0.18-0.35)
1-year PFS Rate	56.4%	4.4%	< 0.0001
18-months PFS Rate	26.8%	0.0%	
Objective Response Rate (CR+PR)[2]	**66.9%**	**23.0%**	OR 7.28 (4.36-12.18) < 0.0001
Disease Control Rate (CR+PR+SD)[2]	**92.6%**	**76.2%**	OR 3.84 (2.04-7.24) <0.0001
Response Duration			
Months (median)	**9.7**	**4.3**	-
Overall Survival (OS), Overall Trial Population			
Months (median) [3]	**23.1**	**23.5**	HR 0.93 (0.72, 1.22) 0.6137

[1] N=324 (GIOTRIF: 216, gemcitabine/cisplatin: 108)
[2] CR=complete response; PR=partial response; SD=stable disease
[3] Main OS analysis as of 27 December 2013 (when 246 patients had died)
[4] p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

The analysis of PFS based on investigator review yielded similar results (HR=0.26, CI= 95% 0.19–0.36; p<0.0001; median PFS: 13.7 vs. 5.6 months) as the analysis based on the independent review. The effect on PFS was consistent across major subgroups, including gender, age, race, ECOG status, and mutation type (L858R, Del 19) in both the independent and investigator reviews. Based on investigator review, ORR was 74.4% vs. 31.1% and DCR was 93.0% vs. 75.4% in GIOTRIF-treated patients compared with chemotherapy-treated

patients. In the pre-defined subgroup of common EGFR mutations (Del 19, L858R) for GIOTRIF (N=216) and chemotherapy (N=108) the median OS was 23.6 months vs. 23.5 months (HR=0.83, 95% CI (0.62-1.09), p=0.1756). In the pre-defined EGFR mutation subgroups, the median OS with first-line GIOTRIF vs chemotherapy was 31.4 months vs 18.4 months (HR=0.64, (95% CI 0.44-0.94), p=0.0229) in patients with Del 19 (n=186) and 19.6 months vs 24.3 months (HR=1.22, (95% CI: 0.81-1.83), p=0.3432) in patients with L858R (n=138).

The PFS benefit of GIOTRIF was accompanied by improvement in disease-related symptoms, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-LC13). GIOTRIF statistically significantly delayed the time to deterioration for the pre-specified symptoms of cough (HR 0.453; 95% CI 0.299, 0.685; p = 0.0001), dyspnoea (HR 0.536; 95% CI 0.395, 0.727; p <0.0001), and pain (HR 0.703; 95% CI 0.514, 0.961; p = 0.0265) compared with chemotherapy. Significantly more patients treated with GIOTRIF compared with chemotherapy had improvements for cough (75.9% of patients vs. 55.4%; p=0.0003), dyspnoea (70.9% vs. 47.5%; p <0.0001), and pain (64.3% vs. 46.5%; p=0.0029).

Mean scores over time for health-related quality of life (HRQoL) were measured using the EORTC QLQ-C30. Mean scores over time for overall quality of life, global health status and physical, role, cognitive, social and emotional functioning were significantly favouring GIOTRIF over chemotherapy.

LUX-Lung 2 (1200.22)

LUX-Lung 2 was an open label single arm Phase II trial which investigated the efficacy and safety of GIOTRIF in 129 EGFR TKI-naïve patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations. Patients were enrolled in the first-line (N=61) or second-line setting (N=68) (i.e. after failure of one prior chemotherapy regimen). Patients were centrally screened for EGFR mutations. Patients received either 40 mg (N=30) or 50 mg (N=99) of GIOTRIF once daily.

The primary endpoint was ORR. Secondary endpoints included PFS, DCR and OS.

In 61 patients treated in the first-line setting, confirmed ORR was 65.6% and DCR was 86.9% according to independent review. The median PFS was 12.0 months by independent review and 15.6 months by investigator assessment. Median OS was not reached in the first-line population. Efficacy was similarly high in the group of patients who had received prior chemotherapy (N=68; ORR 57.4%; PFS by independent review 8 months and by investigator assessment 10.5 months; DCR 77.9%). Median OS in the second line patients was 23.3 months (95% CI 18.5-38).

LUX-Lung 7 (1200.123)

LUX-Lung 7 is a randomised, global, open label Phase IIb trial investigating the efficacy and safety of GIOTRIF in patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations in the first-line setting. Patients were screened for the presence of activating EGFR mutations (Del 19 and/or L858R) using the TheraScreen® EGFR RGQ PCR Kit, Qiagen Manchester Ltd). Patients (N=319) were randomised (1:1) to receive GIOTRIF 40 mg orally once daily (N=160) or gefitinib 250 mg orally once daily (N=159). Randomisation was stratified according to EGFR mutation status (Del 19; L858R) and presence of brain metastases (yes; no).

Among the patients randomised, 62% were female, the median age was 63 years, 16% of patients had brain metastases, the baseline ECOG performance status was 0 (31%) or 1 (69%), 57% were Asian and 43% were non-Asian. Patients had a tumour sample with an EGFR mutation categorised as either exon 19 deletion (58%) or exon 21 L858R substitutions (42%).

The co-primary endpoints are PFS by independent review, time to treatment failure (TTF) and OS. Secondary endpoints include ORR and DCR. The risk of progression was significantly reduced for afatinib versus gefitinib (see Table 6) and ORR was 70% for afatinib and 56% for gefitinib. Primary analysis of OS will be conducted after the number of required events has occurred as per protocol.

Table 6: Efficacy results of GIOTRIF vs. gefitinib (LUX-Lung 7 Trial) based on primary analysis as of August 2015

	GIOTRIF (N=160)	**Gefitinib** (N=159)	**Hazard Ratio/ Odds Ratio (95%CI) p-value[2]**
Median PFS (months), Overall Trial Population	11.0	10.9	HR 0.73 (0.57-0.95) 0.0165
18-months PFS rate	27%	15%	
24-months PFS rate	18%	8%	
Time to Treatment Failure (months)	13.7	11.5	HR 0.73 (0.58-0.92) 0.0073
18-months TTF rate	35%	27%	
24-months TTF rate	25%	13%	
Median OS (months)[1], Overall Trial Population	27.9	25.0	HR 0.87 (0.65, 1.15) 0.33

[1] OS analysis immature as of August 2015
[2] p-value for PFS/ TTF/OS based on stratified log-rank test

The PFS hazard ratio for patients with DEL 19 mutations and L858R mutations was 0.76 (95% CI [0.55, 1.06]; p=0.1071), and 0.71 (95% CI [0.47, 1.06]; p=0.0856) respectively for afatinib vs gefitinib.

Analysis of GIOTRIF's efficacy in EGFR TKI naïve patients with tumours harbouring uncommon EGFR Mutations (LUX-Lung 2, -3, and -6)

In three clinical trials of GIOTRIF with prospective tumour genotyping (Phase 3 trials LUX-Lung 3 and – 6, and single arm Phase 2 trial LUX-Lung 2), an analysis was conducted of data from a total of 75 TKI-naive patients with advanced (stage IIIb–IV) lung adenocarcinomas harbouring uncommon EGFR mutations, which were defined as all mutations other than Del 19 and L858R mutations. Patients were treated with GIOTRIF 40 mg (all three trials) or 50 mg (LUX-Lung 2) orally once daily.

In patients with tumours harbouring either G719X (N=18), L861Q (N=16), or S768I substitution mutation (N=8), the confirmed ORR was 72.2%, 56.3%, 75.0%, respectively, and the median duration of response was 13.2 months, 12.9 months and 26.3 months, respectively.

In patients with tumours harbouring exon 20 insertions (N=23) the confirmed ORR was 8.7% and the median duration of response was 7.1 months. In patients with tumours harbouring de-novo T790M mutations (N=14) the confirmed ORR was 14.3% and the median duration of response was 8.3 months.

GIOTRIF in patients with NSCLC of squamous histology

LUX-Lung 8 (1200.125)

The efficacy and safety of GIOTRIF as second-line treatment for patients with advanced NSCLC of squamous histology was investigated in a randomised open-label global Phase III trial LUX-Lung 8. Patients who received at least 4 cycles of platinum-based therapy in the first line setting were subsequently randomised 1:1 to daily GIOTRIF 40 mg or erlotinib 150 mg until progression. Dose escalation of GIOTRIF to 50 mg was allowed after first cycle (28 days) on treatment in case of no or limited drug related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug related events above CTCAE Grade 1), compliant dosing and no prior dose reduction. Randomisation was stratified by race (Eastern Asian vs non Eastern Asian). The primary endpoint was PFS (analysed when at least 372 events were reported by independent review); OS was the key secondary endpoint (analysed at first 632 deaths). Other secondary endpoints included ORR, DCR, change in tumour size and HRQOL.

Among 795 patients randomised, the majority were males (83.8%), white (72.8%), current or former smokers (91.6%) with baseline performance status ECOG 1 (66.8%).

Second-line GIOTRIF significantly improved PFS and OS of patients with squamous NSCLC compared to erlotinib. In the primary PFS analysis median PFS was 2.43 months in the GIOTRIF group and 1.94 months on erlotinib (HR=0.82, 95% CI (0.676, 0.998), p=0.0427). The final PFS analysis including all randomised patients confirmed earlier results (Table 7). The primary analysis of OS demonstrated significant reduction in the risk of death for patients treated with GIOTRIF compared with erlotinib (HR=0.81 95% CI (0.69, 0.95), p=0.0077) with significantly higher proportions of GIOTRIF-treated patients alive at the landmark points throughout the period of observation such as 12 and 18 months post randomisation.

The rates of objective tumour response and stabilisation of disease were higher with GIOTRIF. The median duration of response was 7.29 months on GIOTRIF and 3.71 months on erlotinib.

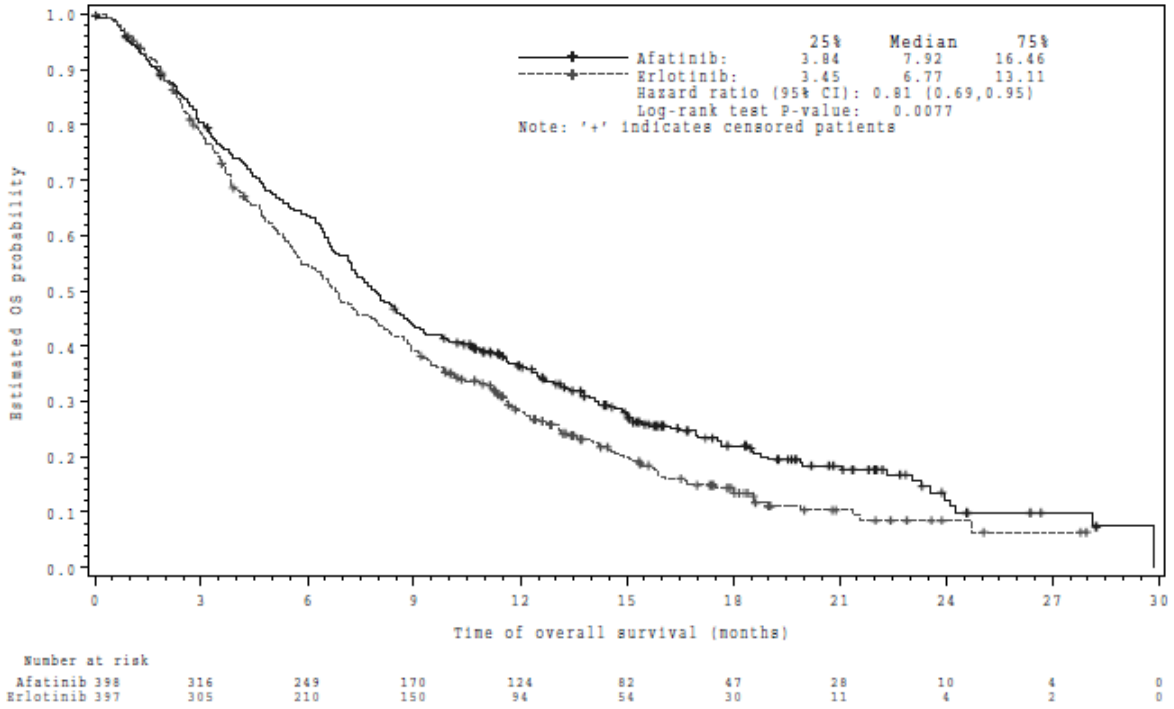
Table 7 Efficacy results for GIOTRIF vs erlotinib in LUX-Lung 8, based on primary analysis of OS, including all randomised patients

	GIOTRIF (N=398)	**Erlotinib (n=397)**	**Hazard Ratio/ Odds Ratio (95%CI) p-value[1]**
PFS **Months (median)**	2.63	1.94	HR 0.81 (0.69, 0.96) 0.0103
OS **Months (median)**	7.92	6.77	HR 0.81 (0.69, 0.95) 0.0077
Alive at 12 months **Alive at 18 months**	36.4% 22.0%	28.2% 14.4%	
Objective Response Rate (CR+PR)*	**5.5%**	**2.8%**	OR 2.06 (0.98, 4.32) 0.0551
Disease Control Rate (CR+PR+SD)*	**50.5%**	**39.5%**	OR 1.56 (1.18, 2.06) 0.0020

*CR=complete response; PR=partial response; SD=stable disease

[1] p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

Figure 3: Kaplan-Meier Curve for OS by treatment group in LUX Lung 8



The analyses of patient reported outcomes, based on the QLQ-C30 and QLQ-LC13 questionnaires favoured GIOTRIF. Significantly more patients in the GIOTRIF group reported improvement in the global health status/quality of life compared to erlotinib (35.7% vs 28.3%, p=0.0406). Higher proportion of GIOTRIF patients had improvement in cough (43.4% vs 35.2%, p=0.0294) and dyspnoea (51.3% vs 44.1%, p=0.0605), while no difference was observed for pain (40.2% vs 39.2%, p=0.7752). GIOTRIF significantly delayed the time to deterioration of dyspnoea (HR 0.79, p=0.0078). Mean scores over time for cough, dyspnoea, and pain as well as for physical, role, cognitive, and emotional functioning were significantly better for GIOTRIF than for erlotinib.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of GIOTRIF, maximum concentrations (C_{max}) of afatinib are observed approximately 2 to 5 hours post-dose. Mean C_{max} and $AUC_{0-\infty}$ values increased slightly more than proportional in the dose range from 20 mg to 50 mg GIOTRIF. Systemic exposure to afatinib is decreased by 50% (C_{max}) and 39% ($AUC_{0-\infty}$), when administered with a high-fat meal compared with administration in the fasted state. Based on population pharmacokinetic data derived from clinical trials in various tumour types, an average decrease of 26% in $AUC_{\tau,ss}$ was observed when food was consumed within 3 hours before or 1 hour after taking GIOTRIF. Therefore, food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see sections 4.2 and 4.4). After administration of GIOTRIF, the mean relative bioavailability was 92% (adjusted gMean ratio of $AUC_{0-\infty}$) when compared to an oral solution. The absolute bioavailability of afatinib has not been determined.

Distribution

In vitro binding of afatinib to human plasma proteins is approximately 95%.

Biotransformation

Enzyme-catalysed reactions play a minor role in the metabolism of afatinib *in vivo*. Covalent adducts to proteins are the major circulating metabolites of afatinib. Approximately 2% of the afatinib dose was metabolised by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Elimination

Following administration of an oral solution of 15 mg afatinib, 85.4% of the dose was recovered in the faeces and 4.3% in urine. The parent compound afatinib accounted for 88% of the recovered dose. The apparent terminal half-life is 37 hours. Steady state plasma concentrations of afatinib are achieved within 8 days of multiple dosing of afatinib resulting in an accumulation of 2.77-fold (AUC) and 2.11-fold (C_{max}).

Special populations

Renal impairment

Less than 5% of a single dose of afatinib is excreted via the kidneys. Exposure to afatinib in subjects with renal impairment was compared to healthy volunteers following a single dose of 40 mg GIOTRIF. Subjects with moderate renal impairment (estimated glomerular filtration rate [eGFR] of 30 to 59 mL/min/1.73m^2 according to MDRD formula) had an exposure of 101% (C_{max}) and 122% (AUC_{0-tz}) in comparison to their healthy controls. Subjects with severe renal impairment (eGFR of 15 to 29 mL/min/1.73m^2 according to MDRD formula) had an exposure of 122% (C_{max}) and 150% (AUC_{0-tz}) in comparison to their healthy controls. Based on this trial and population pharmacokinetic analysis of data derived from clinical trials in various tumour types it is concluded, that adjustments to the starting dose in patients with mild (eGFR 60-89 mL/min/1.73m^2), moderate (eGFR 30-59 mL/min/1.73m^2), or severe (eGFR 15-29 mL/min/1.73m^2) renal impairment are not necessary but patients with severe impairment should be monitored (see "Population pharmacokinetic analysis in special populations" below and section 4.2). GIOTRIF has not been studied in patients with eGFR <15 mL/min/1.73m^2 or on dialysis.

Hepatic impairment

Afatinib is eliminated mainly by biliary/faecal excretion. Subjects with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had similar exposure in comparison to healthy volunteers following a single dose of 50 mg GIOTRIF. This is consistent with population pharmacokinetic data derived from clinical trials in various tumour types (see Population pharmacokinetic analysis in special populations below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see section 4.2). The pharmacokinetics of afatinib had not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see section 4.4).

Pharmacokinetic analysis in target populations

A population pharmacokinetic analysis was performed in 927 cancer patients (764 with NSCLC) receiving GIOTRIF monotherapy. No starting dose adjustment is considered necessary for any of the following covariates tested.

Age

No significant impact of age (range: 28-87 years) on the pharmacokinetics of afatinib could be observed.

Body weight

Plasma exposure ($AUC_{\tau,ss}$) was increased by 26% for a 42 kg patient (2.5th percentile) and decreased by 22% for a 95 kg patient (97.5th percentile) relative to a patient weighing 62 kg (median body weight of patients in the overall patient population).

Gender

Female patients had a 15% higher plasma exposure ($AUC_{\tau,ss}$, body weight corrected) than

male patients.

Race
There was no statistically significant difference in afatinib pharmacokinetics between Asian and Caucasian patients. Also no obvious difference in pharmacokinetics for American Indian/Alaska native or Black patients could be detected based on the limited data available in these populations (6 and 9 out of 927 patients included in the analysis, respectively).

Renal impairment
Exposure to GIOTRIF moderately increased with lowering the creatinine clearance (CrCL), i.e. for a patient with a CrCL of 60 or 30 mL/min exposure ($AUC_{T,ss}$) to afatinib increased by 13% and 42%, respectively, and decreased by 6% and 20% for a patient with CrCL of 90 or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median CrCL of patients in the overall patient population analysed).

Hepatic impairment
Patients with mild and moderate hepatic impairment as identified by abnormal liver tests did not correlate with any significant change in afatinib exposure.

Other patient characteristics/intrinsic factors
Other patient characteristics/intrinsic factors found with a significant impact on afatinib exposure were: ECOG performance score, lactate dehydrogenase levels, alkaline phosphatase levels and total protein. The individual effect sizes of these covariates were considered not clinically relevant.

Smoking history, alcohol consumption, or presence of liver metastases had no significant impact on the pharmacokinetics of afatinib.

Pharmacokinetic Drug Interactions

Drug transporters:

P-glycoprotein (P-gp)

Effect of P-gp inhibitors and inducers on afatinib: Two trials were conducted to assess the effect of ritonavir, a potent inhibitor of P-gp, on the pharmacokinetics of afatinib. In one trial, the relative bioavailability of afatinib was investigated when ritonavir (200 mg b.i.d. for 3 days) was given either simultaneously or 6 hours after a single dose of 40 mg GIOTRIF. The relative bioavailability of afatinib was 119% ($AUC_{0-\infty}$) and 104% (C_{max}) when administered simultaneously with ritonavir and 111% ($AUC_{0-\infty}$) and 105% (C_{max}) when ritonavir was administered 6 hours after GIOTRIF. In a second trial, when ritonavir (200 mg b.i.d. for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% ($AUC_{0-\infty}$) and 39% (C_{max}) (see sections 4.4, 4.5 and 4.2).

Pre-treatment with rifampicin (600 mg q.d. for 7 days), a potent inducer of P-gp, decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) after administration of a single dose of 40 mg GIOTRIF (see sections 4.4 and 4.5).

Effect of afatinib on P-gp Substrates: Based on *in vitro* data, afatinib is a moderate inhibitor of P-gp. However, based on clinical data it is considered unlikely that GIOTRIF treatment will result in changes of the plasma concentrations of other P-gp substrates.

Breast cancer resistance protein (BCRP)
In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP.

Drug Uptake Transport Systems

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of OATB1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and OCT3 transporters are considered unlikely.

Drug Metabolising Enzymes:
Cytochrome P450 (CYP) enzymes

Effect of CYP enzymes inducers and inhibitors on afatinib: In vitro data indicated that drug-drug interactions with afatinib due to inhibition or induction of CYP enzymes by concomitant medicines are considered unlikely. In humans it was found that enzyme-catalysed metabolic reactions play a negligible role in the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolised by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Effect of afatinib on CYP enzymes: Afatinib is neither an inhibitor or an inducer of CYP enzymes. Therefore, GIOTRIF is unlikely to affect the metabolism of other medicines that are dependent on CYP enzymes.

UDP-glucuronosyltransferase 1A1 (UGT1A1)

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of UGT1A1 are considered unlikely.

5.3 Preclinical safety data

Oral administration of single doses to mice and rats indicated a low acute toxic potential of afatinib. In oral repeated-dose studies for up to 26 weeks in rats or 52 weeks in minipigs the main effects were identified in the skin (dermal changes, epithelial atrophy and folliculitis in rats), the gastrointestinal tract (diarrhoea, erosions in the stomach, epithelial atrophy in rats and minipigs) and the kidneys (papillary necrosis in rats). Depending on the finding, these changes occurred at exposures below, in the range of or above clinically relevant levels. Additionally, in various organs pharmacodynamically mediated atrophy of epithelia was observed in both species.

Reproduction toxicity
Based on the mechanism of action, all EGFR targeting medicinal products including GIOTRIF have the potential to cause foetal harm. The embryo-foetal development studies performed on afatinib revealed no indication of teratogenicity. The respective total systemic exposure (AUC) was either slightly above (2.2 times in rats) or below (0.3 times in rabbits) compared with levels in patients.

Radiolabelled afatinib administered orally to rats on Day 11 of lactation was excreted in the breast milk of the dams.

A fertility study in male and female rats up to the maximum tolerated dose revealed no significant impact on fertility. The total systemic exposure (AUC_{0-24}) in male and female rats was in the range or less than that observed in patients (1.3 times and 0.51 times, respectively). A study in rats up to the maximum tolerated doses revealed no significant impact on pre-/postnatal development. The highest total systemic exposure (AUC_{0-24}) in female rats was less than that observed in patients (0.23 times).

Phototoxicity
An *in vitro* mouse 3T3 cell phototoxicity test with afatinib was performed. It was concluded that GIOTRIF may have phototoxicity potential.

Carcinogenicity
Carcinogenicity studies have not been conducted with afatinib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
lactose monohydrate
microcrystalline cellulose
colloidal silicon dioxide
crospovidone
magnesium stearate.

Film coating
GIOTRIF 20 mg film-coated tablets
hypromellose
macrogol 400
titanium dioxide
purified talc
polysorbate 80

GIOTRIF 30, 40 and 50 mg film-coated tablets
hypromellose
macrogol 400
titanium dioxide
purified talc
polysorbate 80
Indigo carmine aluminium lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

PVC/PVDC perforated unit dose blister. Each blister is packed together with a desiccant sachet in a laminated aluminium pouch and contains 7 x 1 film-coated tablets. Pack sizes of 7 x 1, 14 x 1 or 28 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P.O. Box 76-216
Manukau City
Auckland
NEW ZEALAND

Telephone 0800 802 461

9. DATE OF FIRST APPROVAL

6 November 2014

10. DATE OF REVISION OF THE TEXT

18 January 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2	Editorial revisions
5.2	Editorial revisions
8	Sponsor facsimile removed