STA ERRATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

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CONTAINS IN CONFIDENCE DATA

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The manufacturer identified ten issues in relation to factual errors in the original ERG report. Only two were considered to be factual errors by the ERG resulting in changes being necessary to be made to the report. In addition the ERG identified three minor errors which also resulted in minor changes to the ERG report. The pages of the report affected are presented here. Text that remains unaltered is greyed out.

Table 7: PFS (assessed by local investigators) stratified by ethnicity in LUX-Lung 3

Endpoints	Asian patients		Non-Asian patients	
	Afatinib (n=166)	Pemetrexed/ cisplatin (n=83)	Afatinib (n=64)	Pemetrexed/ cisplatin (n=32)
Median PFS months (95% CI)	11.30 (10.02 to 13.70)	6.90 (5.49 to 8.21)	9.79 (6.77 to 13.70)	5.55 (4.01 to 9.46)
Hazard ratio vs chemotherapy (95% Confidence Interval) p-value (2-sided)	0.450 (0.327 to 0.619) p<0.0001		0.618 (0.359 to 1.064) p=0.0800	

PFS=Progression-free survival

Overall survival data presented in the MS[1] are not mature for either LUX-Lung 3[18,19] or LUX-Lung 6[20,21] as in neither trial, the planned number of events (deaths) to assess OS have not occurred. Most recent OS data for both trials are summarised in Table 8 below where it can be seen that hazard ratios in both trials are similar. Neither trial reports a significant difference in OS between afatinib and chemotherapy. However, it is noted in the MS that this may be explained by crossover, with most patients in LUX-Lung 3[18,19] and LUX-Lung 6[20,21] receiving chemotherapy following disease progression on afatinib ([redacted] and [redacted] respectively); for patients starting on chemotherapy, the majority of patients in LUX-Lung 3[18,19] and a large minority in LUX-Lung 6[20,21] received a TKI following progression on chemotherapy ([redacted] and [redacted] respectively).

Table 8: OS reported in LUX-Lung 3 (updated) and LUX-Lung 6

Endpoints	LUX-Lung 3[18]		LUX-Lung 6[20]	
	Afatinib (n=230)	Pemetrexed/ cisplatin (n=115)	Afatinib (n=242)	Gemcitabine/cisplatin (n=122)
Patients with event	116 (50.4%)	59 (51.3%)	104 (43.0%)	51 (41.8%)
Median OS months (95% CI)	[redacted]	[redacted]	[redacted]	22.24 (18.00 to NE)
Hazard ratio v chemotherapy (95% Confidence Interval) p-value (2-sided)	[redacted]		0.949 [redacted] 0.7593	

NE=not estimable; OS=overall survival

The manufacturer's subgroup analysis of OS in LUX-Lung 3[18,19] stratified by ethnicity is provided in Table 9. This exploratory analysis suggests that Asian patients may have improved OS compared with non-Asian patients.

Table 14 Progression-free survival from studies of patients with activating EGFR-mutations

Study	Treatments	Median PFS, hazard ratio (95% CI)	Median PFS (months)	Difference in median PFS (months)
LUX-Lung 3[18]	Afatinib	0.49 (0.37 to 0.65)	11.1	4.4
	Pemetrexed/cisplatin		6.7	
LUX-Lung 6[20]	Afatinib	0.26 (0.19 to 0.36)	13.7	8.1
	Gemcitabine/cisplatin		5.6	
EURTAC[28]	Erlotinib	0.37 (0.25 to 0.54)	9.7	4.5
	Chemotherapy*		5.2	
OPTIMAL[32]§	Erlotinib	0.16 (0.10 to 0.26)	13.1	8.5
	Gemcitabine/carboplatin		4.6	
First-SIGNAL[26]	Gefitinib	0.54 (0.27 to 1.1)	8.0	1.7
	Gemcitabine/cisplatin		6.3	
IPASS[12,13]	Gefitinib	0.48 (0.34 to 0.67)	NR†	NR†
	Paclitaxel/carboplatin		NR†	
NEJGSG002[36]	Gefitinib	0.32 (0.24 to 0.44)§	10.8	5.4
	Paclitaxel/carboplatin		5.4	
WJTOG34053405[31,37]	Gefitinib	0.49 (0.34 to 0.71)	9.2	2.9
	Docetaxel/cisplatin		6.3	

Where both central independent and local assessment are available for PFS, all values are those as assessed by local investigators; CI=confidence interval; NR=not reported; PFS=progression-free survival
* Chemotherapy was gemcitabine or docetaxel in combination with cisplatin or carboplatin
§ OPTIMAL[32] was only included in a sensitivity analysis conducted for the MTC
† The median PFS in months is not reported for EGFR-positive patients but for all patients of mixed EGFR status is reported to be 9.5 months vs 6.3 months, a difference of 3.2 months
§ Updated PFS results are reported here whereas original PFS results were presented in the MS. In both cases the hazard ratio was similar (0.30; 95% CI: 0.22 to 0.41) and median PFS in both arms was reported to be the same as the updated PFS

Table 15 Overall survival from studies of patients with activating EGFR mutations

Study	Treatments	Median OS, Hazard Ratio (95% CI)	Median OS (months)	Difference in median OS (months)
LUX-Lung 3[18]	Afatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed/cisplatin		[redacted]	
LUX-Lung 6[20]	Afatinib	0.95	[redacted]	Not estimable
	Gemcitabine/cisplatin	[redacted]	Not estimable	
EURTAC[28]	Erlotinib	1.04	19.3	0.2
	Chemotherapy†	(0.65 to 1.68)	19.5	
OPTIMAL[32]§	Erlotinib	1.06	Not reported	Not reported
	Gemcitabine/carboplatin	(95% CI not reported)	Not reported	
First-SIGNAL[26]	Gefitinib	1.04	27.2	1.8
	Gemcitabine/cisplatin	(0.49 to 2.18)	25.6	
IPASS[12,13]	Gefitinib	1.00	21.6	0.3
	Paclitaxel/carboplatin	(0.76 to 1.33)	21.9	
NEJGSG002[30,36]*	Gefitinib	0.88	27.7	1.1
	Paclitaxel/carboplatin	(0.63 to 1.24)	26.6	
WJTOG34053405[31,37]	Gefitinib	1.64	30.9	Not estimable
	Docetaxel/cisplatin	(0.75 to 3.58)	Not estimable	

CI=confidence interval; OS=overall survival
† Chemotherapy was gemcitabine or docetaxel in combination with cisplatin or carboplatin
§ OPTIMAL[32] was only included in a sensitivity analysis conducted for the MTC; OS data were not mature at the time of the original publication but have been presented at the 2010 ASCO Annual Meeting[77]
* OS data were not reported in the MS or used in the MTC conducted; updated OS data presented here

proportional hazards used in all of the MTCs appears to be violated in several, if not all, of the included studies.

High crossover rates in trials often mask real differences in OS. The ERG's exploratory subgroup analyses of survival outcomes for Asian vs non-Asian patients in LUX-Lung 3[18,19] showing Asians have improved OS compared with non-Asians may also suggest that crossover does not provide a simple explanation for the lack of OS gain in all trials.

The full range of results from all the different analyses are summarised in Table 21 which enables the reader to compare the different values for the hazard ratios generated by the analyses. The ERG reiterates that hazard ratios are only valid if proportional hazards can be assumed, an assumption the ERG disputes based on the Kaplan-Meier curves of the included studies. The ERG also cautions that the findings are derived from populations in which the majority of patients are Asian and are therefore not generalisable to England and Wales.

Table 21: Comparison of all hazard ratios generated by different analyses explored

Descriptive comparisons (original trial results)[c]	Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin Erlotinib vs chemotherapy Gefitinib vs gemcitabine/cisplatin	0.49 (0.37 to 0.65) 0.26 (0.19 to 0.36) 0.37 (0.25 to 0.54) 0.54 (0.27 to 1.10)	0.91 (0.66 to 1.25) 0.95 (0.68 to 1.33) 1.04 (0.65 to 1.68) 1.04 (0.49 to 2.18)
LUX-Lung 3 subgroup analysis requested by ERG	Afatinib vs pemetrexed/cisplatin: Asian subgroup Non-Asian subgroup	 0.45 (0.33 to 0.62) 0.62 (0.36 to 1.06)	 1.00 (0.68 to 1.46) 0.80 (0.46 to 1.40)
MTC in MS[a]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gem/cis	0.91 (0.53 to 1.50) 0.78 (0.47 to 1.20) 0.46 (0.32 to 0.66) 0.36 (0.25 to 0.52)	0.80 (0.56 to 1.14) 0.84 (0.55 to 1.30) 0.99 (0.78 to 1.27) 0.86 (0.67 to 1.10)
MTC minus EURTAC[b]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	Not estimable 0.70 (0.41 to 1.11) Not reported Not reported	Not estimable 0.91 (0.86 to 0.6)* Not reported Not reported
MTC with EGFR-positive population[b]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	0.69 (0.09 to 4.82) 0.50 (0.06 to 3.60) Not reported Not reported	0.94 (0.55 to 1.61) 0.86 (0.46 to 1.62) Not reported Not reported
MTC with EGFR-positive population minus EURTAC[b]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	Not estimable 0.48 (0.03 to 9.57) Not reported Not reported	Not estimable 0.91 (0.40 to 2.04) Not reported Not reported

For all MTC analyses, the random effects results are presented for PFS and fixed effects for OS
a central independently assessed PFS where available b local investigator assessed PFS where available c LUX-Lung 3[18] , LUX-Lung 6,[20] EURTAC[28] and First-SIGNAL[26] respectively
* The upper confidence interval appears to be reported incorrectly in the manufacturer's clarification response

started on 50 mg than those who started on 40 mg received a dose reduction or discontinued afatinib altogether as a result of an AE. This is largely why the subsequent LUX-Lung 3[18] and LUX-Lung 6[20] trials and also the licence for afatinib stipulate a starting dose of 40mg/day, with dose escalation only occurring if no AE are experienced during the first cycle.

The median number of courses of afatinib treatment in LUX-Lung 3[18] was 16 (336 days) and in LUX-lung 6[20] it was 19 (398 days). Serious AEs (SAEs) including fatalities and SAEs requiring hospitalisation were more common in the afatinib arm of both trials than the chemotherapy arms although the difference between arms was always less than 5%. The causes of death in the afatinib arm of LUX-Lung 3[18] were dyspnoea, sepsis, acute respiratory distress syndrome and unknown. In LUX-Lung 6[20] the cause was recorded as sudden death. The ERG also notes that the overall number of SAEs and SAEs requiring hospitalisation is greater in the afatinib arm of the LUX-Lung 3[18] trial than the afatinib arm of the LUX-Lung 6[20] trial. There also appeared to be a greater proportion of patients requiring a dose reduction or discontinuation of afatinib as a result of AEs in LUX-Lung 3[18] than LUX-Lung 6[20] (although the proportion of drug related AEs requiring discontinuation were similar across trials). These may be chance findings or may reflect differences in the patient populations (e.g. relating to the proportion of Asian patients).

In order to gain greater insight into whether AEs experienced by Asians may differ to non-Asian populations, during the clarification process the ERG requested the data for LUX-Lung 3[18] by Asian and non-Asian populations. These are summarised in Table 60. There did appear to be the following differences between Asian and non-Asian populations: AEs leading to dose reduction (higher in Asian patients), AEs leading to a permanent discontinuation (higher in non-Asian patients) and fatal SAEs (higher in non-Asian patients).

Specific AEs experienced by patients are also reported in the MS[1] although drug-related AEs are only presented for LUX-Lung 3.[18] Drug-related AEs for all studies are summarised in Table 61. The most common drug-related AEs reported by patients receiving afatinib were diarrhoea, rash/acne, stomatitis/mucositis, paronychia/nail effect, dry skin, decreased appetite, pruritus, ocular effect, epistaxis and rhinorrheoea. In those receiving chemotherapy, the most common drug-related AEs were nausea, vomiting, decreased appetite, fatigue, neutropenia, leukopenia and anaemia; in LUX-Lung 6[20] a decrease in both white blood cell and neutrophil count were also relatively common in the chemotherapy arm.

The MS does not report the most common type of SAEs experienced by patients. These are however reported in the EPAR (page 71) where it is noted that in a pooled analysis of LUX-

Table 61 Frequency of drug related adverse events (incidence >10% in any arm) reported in LUX-lung 2, LUX-Lung 3 and LUX-Lung 6

System organ/class/adverse events	LUX-Lung 3[18]				LUX-Lung 6[20]				LUX-Lung 2[23]	
	Afatinib (n=229)		Pemetrexed/cisplatin (n=111)		Afatinib (n=239)		Gemcitabine/cisplatin (n=113)		Afatinib 40mg (n=30)	Afatinib 50mg (n=99)
	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	All AEs
Diarrhoea	95.2	14.4	15.3	0	[redacted]	[redacted]	[redacted]	[redacted]	96.7	93.9
Rash/acne	89.1	16.2	6.3	0	[redacted]	[redacted]	[redacted]	[redacted]	90.0	93.9
Stomatitis/mucositis	72.1	8.3	15.3	0.9	[redacted]	[redacted]	[redacted]	[redacted]	50.0	89.9
Paronychia/nail effect	61.1	11.8	0	0	[redacted]	[redacted]	[redacted]	[redacted]	80.0	85.9
Dry skin	29.3	0.4	1.8	0	[redacted]	[redacted]	[redacted]	[redacted]	23.3	33.3
Decreased appetite	20.5	3.1	53.2	2.7	[redacted]	[redacted]	[redacted]	[redacted]	30.0	27.3
Fatigue	17.5	1.3	46.8	12.6	[redacted]	[redacted]	[redacted]	[redacted]	26.7	23.2
Vomiting	17.0	3.1	42.3	2.7	[redacted]	[redacted]	[redacted]	[redacted]	16.7	9.1
Nausea	17.9	0.9	65.8	3.6	[redacted]	[redacted]	[redacted]	[redacted]	16.7	12.1
Pruritus	18.8	0.4	0.9	0	[redacted]	[redacted]	[redacted]	[redacted]	46.7	59.6
Ocular effect	17.9	0.4	1.8	0	[redacted]	[redacted]	[redacted]	[redacted]	20.0	28.2
Lip effect	14.4	0	1.8	0	[redacted]	[redacted]	[redacted]	[redacted]	6.7	14.1
Epistaxis	13.1	0	0.9	0.9	[redacted]	[redacted]	[redacted]	[redacted]	30.0	25.3
Weight decreased	10.5	0	9.0	0	[redacted]	[redacted]	[redacted]	[redacted]	10.0	15.2
Alopecia	10.0	0	17.1	0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Anaemia	3.1	0.4	27.9	6.3	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Constipation	2.6	0	18.9	0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Leukopaenia	1.7	0.4	18.9	8.1	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Haemoglobin reduced	1.3	0	10.8	2.7	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Neutropenia	0.9	0.4	31.5	18.0	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
ALT increased	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
AST-increased	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Hypokalaemia	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Thrombocytopenia	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Platelet count reduced	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
White blood cell decreased	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Neutrophil count decreased	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR
Rhinorrheoea	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	26.7	31.3

All AEs are reported as a proportion (%) and taken from MS,[1] LUX-Lung 6 CTR[35] and LUX-Lung 2 published paper[23]
NR=not reported as AE > 10%