

**7.02 AFATINIB DIMALEATE, tablets, 50 mg, 40 mg, 30 mg, 20 mg, GIOTRIF<sup>®</sup>, Boehringer Ingelheim.**

**1 Purpose of Application**

1.1 The re-submission requested a Section 85, Authority Required listing for afatinib under a special pricing arrangement (SPA). The listing was for the use of afatinib as a first or subsequent line of treatment in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) characterised by exon 19 deletion mutations of the epidermal growth factor receptor (EGFR) gene.

**2 Requested listing**

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty (effective price for Max. Qty) | Proprietary Manufacturer | Name and                         |
|--|----------|-----------|---|--------------------------|----------------------------------|
| AFATINIB DIMALEATE                                   |          |           |   |                          |                                  |
| Tablet 20 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               | Giotrif <sup>®</sup>     | Boehringer Ingelheim Pty Limited |
| Tablet 30 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               |                          |                                  |
| Tablet 40 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               |                          |                                  |
| Tablet 50 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               |                          |                                  |

|                                    |  |
|------------------------------------|--|
| <b>Category / Program</b>          | GENERAL – General Schedule (Code GE)   |
| <b>Prescriber type:</b>            | <input checked="" type="checkbox"/> Medical Practitioners  |
| <b>Severity:</b>                   | Stage IIIB (locally advanced) or Stage IV (metastatic)   |
| <b>Condition:</b>                  | Non-small cell lung cancer (NSCLC)   |
| <b>PBS Indication:</b>             | Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC   |
| <b>Treatment phase:</b>            | Initial treatment  |
| <b>Restriction Level / Method:</b> | Authority required   |
| <b>Clinical criteria:</b>          | <p>The treatment must be as monotherapy</p> <p>AND</p> <p>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC</p> <p>AND</p> <p>Patient must not have received previous PBS-subsidised treatment with another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI); OR Patient must have developed intolerance to another EGFR TKI of a severity necessitating permanent treatment withdrawal</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less.</p> |

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|                               |   |
|-------------------------------|---|
| <b>Population criteria:</b>   | Patient must have evidence of exon 19 deletion mutation(s) of the epidermal growth factor receptor (EGFR) gene, which are known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs), in tumour material. |
| <b>Administrative Advice:</b> | <i>Special Pricing Arrangements apply.</i>  |

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Dispensed Price for Max. Qty (effective price for Max. Qty) | Proprietary Name and Manufacturer            |
|--|----------|-----------|---|--|
| AFATINIB DIMALEATE                                   |          |           |   |  |
| Tablet 20 mg   | 28       | 3         | \$ [REDACTED]   | Giotrif®<br>Boehringer Ingelheim Pty Limited |
| Tablet 30 mg   | 28       | 3         | (\$ [REDACTED])   |  |
| Tablet 40 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               |  |
| Tablet 50 mg   | 28       | 3         | \$ [REDACTED] (\$ [REDACTED])                               |  |

|                                    |   |
|------------------------------------|---|
| <b>Severity:</b>                   | Stage IIIB (locally advanced) or Stage IV (metastatic)  |
| <b>Condition:</b>                  | Non-small cell lung cancer (NSCLC)  |
| <b>PBS Indication:</b>             | Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC  |
| <b>Treatment phase:</b>            | Continuing treatment  |
| <b>Restriction Level / Method:</b> | Authority required  |
| <b>Clinical criteria:</b>          | The treatment must be as monotherapy<br><br>AND<br><br>Patient must have previously been issued with an authority prescription for this drug<br><br>AND<br><br>Patient must not have progressive disease. |
| <b>Administrative Advice:</b>      | <i>Special Pricing Arrangements apply.</i>  |

- 2.2 This re-submission proposed a narrower population than previously recommended: patients only with exon 19 deletions. Afatinib was recommended for use in the broader EGFR activating mutation population and erlotinib and gefitinib were listed in the PBS on that basis. The re-submission claimed that afatinib was associated with improved clinical outcomes in this population subgroup, compared with gefitinib and erlotinib, and requested that the Australian effective prices for afatinib remained confidential by way of a SPA. The requested effective prices would remain the same as those approved by the Pharmaceutical Benefits Pricing Authority (PBPA) in December 2013.
- 2.3 The requested listing restricted eligibility to NSCLC patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 while the LUX Lung 3 and 6 trials exclusively enrolled patients with a performance status of 0-1.
- 2.4 Listing was sought on the basis that afatinib is cost-effective in comparison with erlotinib and gefitinib.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### 3 Background

- 3.1 TGA status at time of PBAC consideration: Afatinib was registered by the TGA on 7 November 2013, as monotherapy for patients with advanced or metastatic non-squamous NSCLC, either as a first line therapy or after failure of cytotoxic chemotherapy. Tumours must have EGFR exon 19 deletions or L858R substitution mutations.
- 3.2 This is the third submission to list afatinib in the PBS for the treatment of NSCLC patients with positive EGFR gene mutations, although it is the first submission to specify the exon 19 deletion mutation subgroup as the proposed PBS population.
- 3.3 At its July 2013 meeting, the PBAC considered the original submission for an Authority required listing of afatinib as first-line treatment of locally advanced or metastatic NSCLC in patients with EGFR gene mutation(s).
- 3.4 Subsequent to the meeting, after a price negotiation, the sponsor offered to reduce its price to an effective price of \$ [REDACTED] for the 40 mg strength of afatinib under the proposed restriction to patients with NSCLC who are EGFR mutation positive. The prices of the other strengths were calculated according to standard PBPA methodology.
- 3.5 The PBAC therefore recommended the PBS listing of afatinib on a cost-minimisation basis with erlotinib. The equi-effective doses were afatinib 40 mg to erlotinib 150 mg, based on the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration.
- 3.6 The PBPA accepted a SPA for afatinib in December 2013. However, SPAs for gefitinib and erlotinib were removed at the request of the respective sponsors on 1 April 2014. The removal of the SPA from the cost-minimised comparators meant that afatinib was no longer eligible for the SPA. The Department advised the sponsor of afatinib of this change and also advised that the listed price must reflect the effective prices as approved by the PBPA in December 2013.
- 3.7 In July 2014, the PBAC considered a minor re-submission from the sponsor requesting a SPA for afatinib to enable the PBS listing to proceed. No change to the approved restriction was requested.
- 3.8 The PBAC considered the evidence provided in the minor re-submission and in the pre-PBAC response. The PBAC advised the Department that it did not accept that afatinib has unique characteristics compared to other available therapies for the treatment of patients with advanced or metastatic non-squamous NSCLC. Afatinib did not meet the criteria for a SPA. Therefore, the PBAC rejected the minor re-submission.
- 3.9 The current re-submission claimed that the inability to obtain a SPA has prevented the sponsor from progressing the PBS listing of afatinib. An SPA is therefore sought in a subgroup (EGFR exon 19 deletion mutation) of the population previously approved (all activating EGFR mutations) on the basis of improved clinical outcomes in this subgroup.

#### **4 Clinical place for the proposed therapy**

- 4.1 The re-submission proposed that afatinib replace erlotinib or gefitinib, as a first-line or later-line therapy, for the treatment of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified NSCLC in patients with evidence of EGFR exon 19 deletions. The PBAC previously recommended afatinib for the treatment of locally advanced or metastatic non-squamous or not otherwise specified NSCLC in patients with evidence of any activating EGFR mutations.
- 4.2 Restricting afatinib to patients with exon 19 deletion mutations is not consistent with previous recommendations by the PBAC, MSAC and US guidelines (October 2012 EGFR/TKI stakeholder meeting and Paragraph 2.3: Consolidated July 2013 PBAC Minutes) which note that the definition of the biomarker should not be restricted to specific activating EGFR mutations (i.e. L858R or exon 19 deletions). The Pre-Sub-Committee Response (PSCR) acknowledged that the proposed population is a subgroup of the PBAC-recommended population, stating that it has been proposed to “present a solution to the SPA issue that is preventing the listing of afatinib”.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

#### **5 Comparator**

- 5.1 Erlotinib and gefitinib are each appropriate comparators.
- 5.2 Gefitinib and erlotinib were both PBS-listed on a cost-minimisation basis in January 2014 for the initial and continuing treatment, as monotherapy, of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified NSCLC in patients with evidence that the tumour harbours an activating mutation(s) of the EGFR gene known to confer sensitivity to treatment with an EGFR tyrosine kinase.

#### **6 Consideration of the evidence**

##### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

##### ***Consumer comments***

- 6.2 The PBAC noted that no consumer comments were received for this item.

##### ***Clinical trials***

- 6.3 For the comparison of afatinib and gefitinib, the re-submission provided an indirect comparison between afatinib (two open-label randomised controlled trials (RCTs): LUX Lung 3 and LUX Lung 6) and gefitinib (three open-label RCTs: IPASS, NEJ002 and WJTOG3405). The indirect comparison was based on a population subgroup from the trials with tumours characterised by an EGFR exon 19 deletion, as well as a

“common reference” of doublet chemotherapy. The afatinib LUX Lung and gefitinib NEJ002 trials required that patient NSCLC tumours had evidence of any activating mutation as an inclusion criterion. The WJTOG3405 trial required that patients had a common activating mutation (exon 19 deletion or L858R). The IPASS trial did not require any evidence of an EGFR mutation.

- 6.4 For the comparison of afatinib and erlotinib, the re-submission indirectly compared LUX Lung 3 and LUX Lung 6 (afatinib) with EURTAC, OPTIMAL and ENSURE (erlotinib) in the EGFR exon 19 deletion subgroup, using a “common reference” of doublet chemotherapy. All three erlotinib trials required that patients have NSCLC with a common activating mutation (exon 19 deletion or L858R).
- 6.5 The trials included for this indirect comparison were considered in detail by the July 2013 PBAC meeting (except for LUX Lung 6, which was presented in the pre-subcommittee response), albeit for the broader population of any EGFR activating mutation. At that time, the PBAC had concerns regarding the exchangeability of the trials as a consequence of the different doublet chemotherapy regimens and differences in baseline characteristics (Afatinib Public Summary Document (PSD)). These concerns remain for the current re-submission.
- 6.6 A head-to-head RCT, comparing afatinib with gefitinib, in the treatment of NSCLC patients who have EGFR positive mutations (LUX Lung 7) is currently ongoing. The estimated final data collection for the primary outcomes (progression-free survival (PFS), time to treatment failure (TTF) and overall survival (OS)) is August 2015. The results from LUX Lung 7 would provide a more robust estimate of the comparative effectiveness of afatinib versus gefitinib than the indirect comparisons that have been provided. The PSCR noted that the results of LUX-Lung 7 are expected in December 2015 and that the data can be made available to the PBAC on a confidential basis if requested. The ESC noted that, although providing a more rigorous comparison between afatinib and gefitinib, it would not also address the comparison between afatinib and erlotinib, which would be necessary to complete an assessment of the claim that afatinib is unique.
- 6.7 Details of the trials presented in the re-submission are provided in the table below.

**Table 1: Trials and associated reports presented in the re-submission**

| Trial ID/First Author                         | Protocol title/ Publication title  | Publication citation  |
|---|--|---|
| <b>Trials of afatinib versus chemotherapy</b> |  |   |
| LUX Lung 3                                    | Clinical Study Report: LUX Lung 3. A randomised, open-label, phase III study of BIBW 2992 <sup>s</sup> versus chemotherapy as first-line treatment for patients with Stage IIIb or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation.<br>Yang JC-H, Schuler MH, Yamamoto N et al. LUX Lung 3: A randomised, open-label phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harbouring EGFR-activating mutations.<br>Yang JC, Hirsch V, Schuler M et al. Symptom control and quality of life in LUX Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. | July 2012<br><br><i>Annals of Oncology</i> 2012; 23(Suppl. 9) ix410<br>Abstract 1252P.<br><br><i>Journal of Clinical Oncology</i> 2013; 31(27):3342-50. |

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|   | <p>Yang JC-H, Wu Y-L, Schuler M, Sebastian M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation positive lung adenocarcinoma (LUX Lung 3 and LUX Lung 6): analysis of overall survival data from two randomised, phase 3 trials.</p> <p>Yang JCH, Sequist L, O'Byrne K, et al. Epidermal growth factor receptor (EGFR) – mediated adverse events (AEs) in patients with EGFR mutation positive (EGFR M+) non-small-cell lung cancer treated with afatinib.</p> <p>Sequist LV, Schuler M, Yamamoto N et al. LUX Lung 3 Symptom control and health related quality of life results from a randomised phase III study in first-line patients with advanced NSCLC harbouring EGFR mutations.</p> <p>Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations.</p>   | <p><i>The Lancet Oncology</i> 2015 Published online January 12 DOI 10.1016.</p> <p><i>European Journal of Cancer</i> 2013; 49: Abstract S190.</p> <p><i>Annals of Oncology</i> 2012; 23(Suppl. 9) ix402 Abstract 1229PD.</p> <p><i>Journal of Clinical Oncology</i> 2013; 20;31(27):3327-34</p> |
| LUX Lung 6  | <p>Clinical Trial Report 1200.34 LUX Lung 6: A randomised, open-label, phase III study of BIBW 2992<sup>s</sup> versus chemotherapy as first line treatment for patients with Stage IIIb or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation.</p> <p>Wu YL, Zhou C, Hu CP, et al.: Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (Lux Lung 6): An open-label, randomised phase 3 trial.</p> <p>Geater S, Zhou C, Hu CP, et al. LUX Lung 6: Patient reported outcomes (PROs) from a randomised open-label, phase III study in first-line advanced NSCLC patients (pts) harboring epidermal growth factor receptor (EGFR) mutations</p> <p>Wu YL, Zhou C, Hu CP, et al. LUX Lung 6: a randomised, open-label phase III study of afatinib (A) vs gemcitabine/cisplatin (GC) as first line treatment for Asian patients (pts) with EGFR mutation positive (EGFR M+) advanced adenocarcinoma of the lung</p> <p>Yang JC-H, Wu Y-L, Schuler M, Sebastian M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation positive lung adenocarcinoma (LUX Lung 3 and LUX Lung 6): analysis of overall survival data from two randomised, phase 3 trials.</p> | <p>April 2013</p> <p><i>The Lancet Oncology</i> 2014; (15):213-222.</p> <p><i>Journal of Clinical Oncology</i> 2013; 31(15) Suppl.1: Abstract 8061</p> <p><i>ERS Annual Congress</i>, 2013; (42): 46s</p> <p><i>The Lancet Oncology</i> 2015; Published online January 12 DOI 10.1016</p>       |
| <b>Trials of gefitinib (comparator) versus chemotherapy</b> |   |   |
| IPASS   | <p>Mok TS, Wu YL, Thongprasert S et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma.</p> <p>Fukuoka M, Wu YL, Thongprasert S et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non - small-cell lung cancer in Asia (IPASS).</p> <p>Satouchi M, Ichinose Y, Nishiwaki Y et al. Final analysis of overall survival (OS) in the IPASS, an international multicenter phase III study on gefitinib and carboplatin/paclitaxel for treatment-naïve NSCLC patients. [Japanese].</p>  | <p><i>New England Journal of Medicine</i> 2009; (361):947-957.</p> <p><i>Journal of Clinical Oncology</i> 2011; (29):2866-2874.</p> <p><i>Japanese Journal of Lung Cancer</i> 2012; (52):153-160.</p>   |

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|   | <p>Thongprasert S, Duffield E, Saijo N et al. Health-related quality-of-life in a randomized phase III first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients from Asia with advanced NSCLC (IPASS).</p> <p>Goto K, Ichinose Y, Ohe Y, et al. Epidermal growth factor receptor mutation status in circulating free DNA in serum: from IPASS, a phase III study of gefitinib or carboplatin/paclitaxel in non-small-cell lung cancer.</p> <p>Wu YL, Chu DT, Han B, et al. Phase III, randomised, open-label first line study in Asia of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer; evaluation of patients recruited from mainland China.</p> | <p><i>Journal of Thoracic Oncology</i> 2011; (6):1872-1880.</p> <p><i>Thoracic Oncology</i> 2012; 7(1):115-21.</p> <p><i>Asia-Pacific Journal of Clinical Oncology</i> 2012; 8(3) 232-43.</p> |
| NEJ002  | <p>Maemondo M, Inoue A, Kobayashi K et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR.</p> <p>Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002).</p> <p>Oizumi S, Kobayashi K, Inoue A, et al. Quality of life with gefitinib in patients with EGFR-mutated non-small-cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial.</p>  | <p><i>New England Journal of Medicine</i> 2010; (362):2380-2388.</p> <p><i>Annals of Oncology</i> 2013; (24):54-59.</p> <p><i>Oncologist</i> 2012; 17(6):863-870.</p>                         |
| WJTOG3405   | <p>Mitsudomi T, Morita S, Yatabe Y et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial.</p> <p>Yoshioka H, Mitsudomi T, Morita S, et al.: Final overall survival results of WJTOG 3405, a randomized phase 3 trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer (NSCLC) harboring mutations of the epidermal growth factor receptor (EGFR).</p>   | <p><i>The Lancet Oncology</i> 2010; (11):121-128.</p> <p><i>Journal of Clinical Oncology</i> 2014 ASCO Annual Meeting Abstract 8117.</p>  |
| <b>Trials of erlotinib (comparator) versus chemotherapy</b> |   |   |
| EURTAC  | <p>Rosell R, Carcereny E, Gervais R et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial.</p>  | <p><i>The Lancet Oncology</i> 2012; (13):239-246.</p>   |
| OPTIMAL   | <p>Zhou C, Wu YL, Chen G et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study.</p>   | <p><i>The Lancet Oncology</i> 2011; (12):735-742.</p>   |

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|        | <p>Zhou C, Wu YL, Chen G et al. Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomized, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC).</p> <p>Zhou C, Wu Y, Liu X, Wang C, et al. Preliminary overall survival results from OPTIMAL, a phase III trial of erlotinib versus carboplatin plus gemcitabine as first-line treatment for Chinese patients with EGFR M+ advanced NSCLC.</p> <p>Chen G, Feng J, Zhou C, et al. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC).</p> | <p>ASCO Annual Meeting 2011; Abstract 7520.</p> <p>ASCO Annual Meeting 2012; Poster 7520.</p> <p><i>Annals of Oncology</i> 2013; (24):1615-1622.</p>   |
| ENSURE | <p>Wu Y-L, Liam C-K, Zhou C et al.: First line erlotinib versus cisplatin/gemcitabine (GP) in patients with advanced, EGFR mutation positive non-small-cell lung cancer (NSCLC): interim analyses from the phase 3, open-label ENSURE study.</p> <p>Wu Y, Zhou C, Wu G, et al.: Quality of life (QOL) analysis from ENSURE, a phase 3, open-label study of first-line erlotinib versus gemcitabine/cisplatin (GP) in Asian patients with epidermal growth factor receptor (EGFR) mutation-positive (MUT+) non-small-cell lung cancer (NSCLC).</p>  | <p><i>Journal of Thoracic Oncology</i> 2013; (8), Suppl. 2: S603-4.</p> <p><i>Journal of Thoracic Oncology</i> 4<sup>th</sup> European Lung Cancer Conference, ELCC14 Geneva, Switzerland 2014; Abstract number S37.</p> |

<sup>§</sup>Refers to afatinib.

EGFR = Epidermal growth factor receptor; NSCLC = Non-small cell lung cancer

- 6.8 The key features of the randomised trials included in the indirect comparison are summarised in the table below.

**Table 2: Key features of the trials included for the indirect comparisons**

| <b>Trials</b>   | <b>N</b>                       | <b>Design/analysis<br/>Trial duration<sup>μ</sup></b>   | <b>Risk of bias<sup>€</sup></b> | <b>Patient population</b>                               | <b>Outcome(s)</b> | <b>Use in<br/>modelled<br/>evaluation</b> |
|---|--------------------------------|---|---------------------------------|---|-------------------|---|
| <b>Afatinib vs chemotherapy</b>   |                                |   |                                 |   |                   |   |
| LUX Lung 3  | 345                            | R, OL<br>49 months  | High                            | Any activating EGFR<br>mutation                         | OS, PFS           | Not used                                  |
| LUX Lung 6  | 364                            | R, OL<br>43 months  | High                            | Any activating EGFR<br>mutation                         | OS, PFS           | Not used                                  |
| <b>Erlotinib vs chemotherapy</b>  |                                |   |                                 |   |                   |   |
| EURTAC  | 154                            | R, OL   | High                            | Exon 19 deletion or<br>L858R mutation                   | OS, PFS           | Not used                                  |
| OPTIMAL   | 165                            | R, OL   | High                            | Exon 19 deletion or<br>L858R mutation                   | OS PFS            | Not used                                  |
| ENSURE  | 217                            | R, OL   | High                            | Exon 19 deletion or<br>L858R mutation                   | PFS               | Not used                                  |
| <b>Gefitinib vs chemotherapy</b>  |                                |   |                                 |   |                   |   |
| IPASS   | 1217                           | R, OL   | High                            | Unselected (no EGFR<br>mutation status<br>required)     | OS, PFS           | Not used                                  |
| NEJ002  | 228                            | R, OL   | High                            | Any activating EGFR<br>mutation and absence<br>of T790M | OS, PFS           | Not used                                  |
| WJTOG3405   | 172                            | R, OL   | High                            | Exon 19 deletion or<br>L858R mutation                   | OS, PFS           | Not used                                  |
| <b>Afatinib versus erlotinib</b>  |                                |   |                                 |   |                   |   |
| <u>Meta-analysis</u><br>Pooled<br>afatinib trials<br>1) vs pooled<br>erlotinib trials<br>for PFS, and<br>2) vs<br>EURTAC for<br>OS <sup>β</sup> | PFS:553 <sup>∞</sup><br>OS:471 | <u>Indirect<br/>comparison</u> , non-<br>randomised. <i>Post<br/>hoc</i> subgroup<br>analysis | High                            | Exon 19 deletion<br>mutation                            | OS, PFS           | Used**                                    |
| <b>Afatinib versus gefitinib</b>  |                                |   |                                 |   |                   |   |
| <u>Meta-analysis</u><br>Pooled<br>afatinib trials<br>vs pooled<br>gefitinib trials<br>for PFS &<br>OS.  | PFS/OS:61<br>3 <sup>∞</sup>    | <u>Indirect<br/>comparison</u> , non-<br>randomised. <i>Post<br/>hoc</i> subgroup<br>analysis | High                            | Exon 19 deletion<br>mutation                            | OS, PFS           | Used**                                    |

OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised

<sup>μ</sup>Trial durations were not provided for the erlotinib and gefitinib trials.

<sup>€</sup>Risk of confounding of OS due to treatment switching from chemotherapy arm to a TKI upon progression for all the trials and risk of bias for PFS (investigator based) for the erlotinib and gefitinib trials. The risk of bias is much more of a concern in the indirect comparisons between the TKIs arising from lack of exchangeability and subgroup related limitations.

\*\*Hazard ratios for both PFS and OS from indirect comparisons are applied to the observed and extrapolated survival curves of afatinib in the exon 19 deletion subgroup to estimate the corresponding curves of erlotinib or gefitinib.

<sup>∞</sup>Sample sizes for the exon 19 deletion subgroup exclude those for the erlotinib ENSURE and gefitinib WJTOG3405 trials which were not reported.

<sup>β</sup> OS for exon 19 deletion subgroup was only available from EURTAC.

Source: compiled during the evaluation

- 6.9 There was a high risk of bias in the indirect comparisons of afatinib with erlotinib or gefitinib, for the proposed population. In addition to the PBAC's outstanding concerns with regard to the exchangeability of the trials included in the indirect comparison, there were a number of concerns regarding the proposed population subgroup used:
- The proposed population for afatinib - patients with evidence of EGFR exon 19 deletions - is a subgroup of the patients included in the trials. In most of the erlotinib and gefitinib trials, this population subgroup was not pre-specified.
  - There were limited baseline data available for these subgroups, by treatment arm, in the erlotinib and gefitinib trials. In the afatinib trials, which employed stratified randomisation by mutation subgroup, an imbalance in baseline characteristics across treatment arms was apparent for the mutation subgroups. Although mutation subgroup was a stratification factor during randomisation in EURTAC, baseline characteristics for specific mutation subgroups were not available. The lack of baseline data for the EGFR mutation subgroups limited the ability to assess prognostic balance within the mutation subgroups and further compounded the uncertainties relating to exchangeability of the patient groups included in the indirect comparison.
  - For the EGFR mutation subgroups, limited data were available regarding the proportion of patients who switched from the assigned treatment arms upon disease progression. For the ITT populations included in the trials that were indirectly compared, there were different rates of treatment switching from the chemotherapy arm to subsequent treatment with a tyrosine kinase inhibitor (TKI), upon progression, which are likely to have confounded the OS results.
  - Across the trials, the primary analysis of progression free survival (PFS) varied as to whether the assessment was investigator-based (non-blinded) or conducted independently and centrally (blinded).
- 6.10 On the basis of the data available, there were serious concerns regarding the exchangeability of the trial populations and therefore their use in an indirect comparison was inappropriate. The review by Sebastien et al (2014) concluded that the chemotherapy regimens used in each trial and the characteristics of patients across the trials were not comparable.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Comparative effectiveness**

- 6.11 In the PBAC consideration of afatinib in July 2013, afatinib, erlotinib and gefitinib were considered to be non-inferior to each other in NSCLC patients with EGFR activating mutations. In the current re-submission, PBS listing was proposed for an exon 19 deletion mutation subgroup. The re-submission claimed that afatinib was associated with improved clinical outcomes compared to erlotinib or gefitinib.
- 6.12 Two additional important issues arose for PBAC consideration:
- Whether the mutation subgroup predicted treatment effect variation in the TKI versus chemotherapy trials;
  - Whether the mutation subgroup predicted treatment effect variation in terms of the effectiveness of afatinib relative to other TKIs such as erlotinib or gefitinib.
- Therefore, where data permitted, data were extracted for the L858R subgroup from the trial reports/publications and additional tests for interaction were conducted

between mutation subgroup status and TKI treatment effect. L858R is the substitution mutation that also occurs commonly in NSCLC.

- 6.13 Indirect comparisons between afatinib and gefitinib/erlotinib: Table 3 summarises the results of the indirect comparisons in the exon 19 deletion mutation subgroup, as presented in the re-submission. Additional statistical analyses were conducted during the evaluation for the L858R mutation subgroup.

**Table 3: Indirect comparisons of PFS and OS between afatinib and gefitinib or erlotinib**

| Indirect comparisons                     | Mutation subgroup<br>HR (95% CI) |                   |
|--|----------------------------------|-------------------|
|  | Exon 19 deletion mutations       | L858R mutations   |
| <b>Progression-free survival (PFS)</b>   |                                  |                   |
| <b>Afatinib vs gefitinib</b>             |                                  |                   |
| LUX Lung 3 vs pooled gefitinib           |                                  | 1.74 (0.94, 3.22) |
| LUX Lung 6 vs pooled gefitinib           |                                  | 0.76 (0.40, 1.45) |
| Pooled afatinib vs pooled gefitinib      |                                  | 1.17 (0.36, 3.74) |
| <b>Afatinib vs erlotinib</b>             |                                  |                   |
| LUX Lung 3 vs pooled erlotinib           |                                  | 1.78 (0.86, 3.70) |
| LUX Lung 6 vs pooled erlotinib           |                                  | 0.78 (0.37, 1.66) |
| Pooled afatinib vs pooled erlotinib      |                                  | 1.20 (0.35, 4.09) |
| <b>Overall survival (OS)</b>             |                                  |                   |
| <b>Afatinib vs gefitinib</b>             |                                  |                   |
| LUX Lung 3 vs pooled gefitinib           |                                  | 1.28 (0.67, 2.44) |
| LUX Lung 6 vs pooled gefitinib           |                                  | 1.20 (0.66, 2.17) |
| Pooled afatinib vs pooled gefitinib      |                                  | 1.23 (0.71, 2.12) |
| <b>Afatinib vs erlotinib<sup>∞</sup></b> |                                  |                   |
| LUX Lung 3 vs erlotinib (EURTAC)         |                                  | 1.30 (0.61, 2.75) |
| LUX Lung 6 vs erlotinib (EURTAC)         |                                  | 1.22 (0.60, 2.46) |
| Pooled afatinib vs erlotinib (EURTAC)    |                                  | 1.25 (0.66, 2.42) |
| Pooled afatinib vs pooled erlotinib      | NA                               | NA                |

Italicised estimates were calculated during the evaluation.

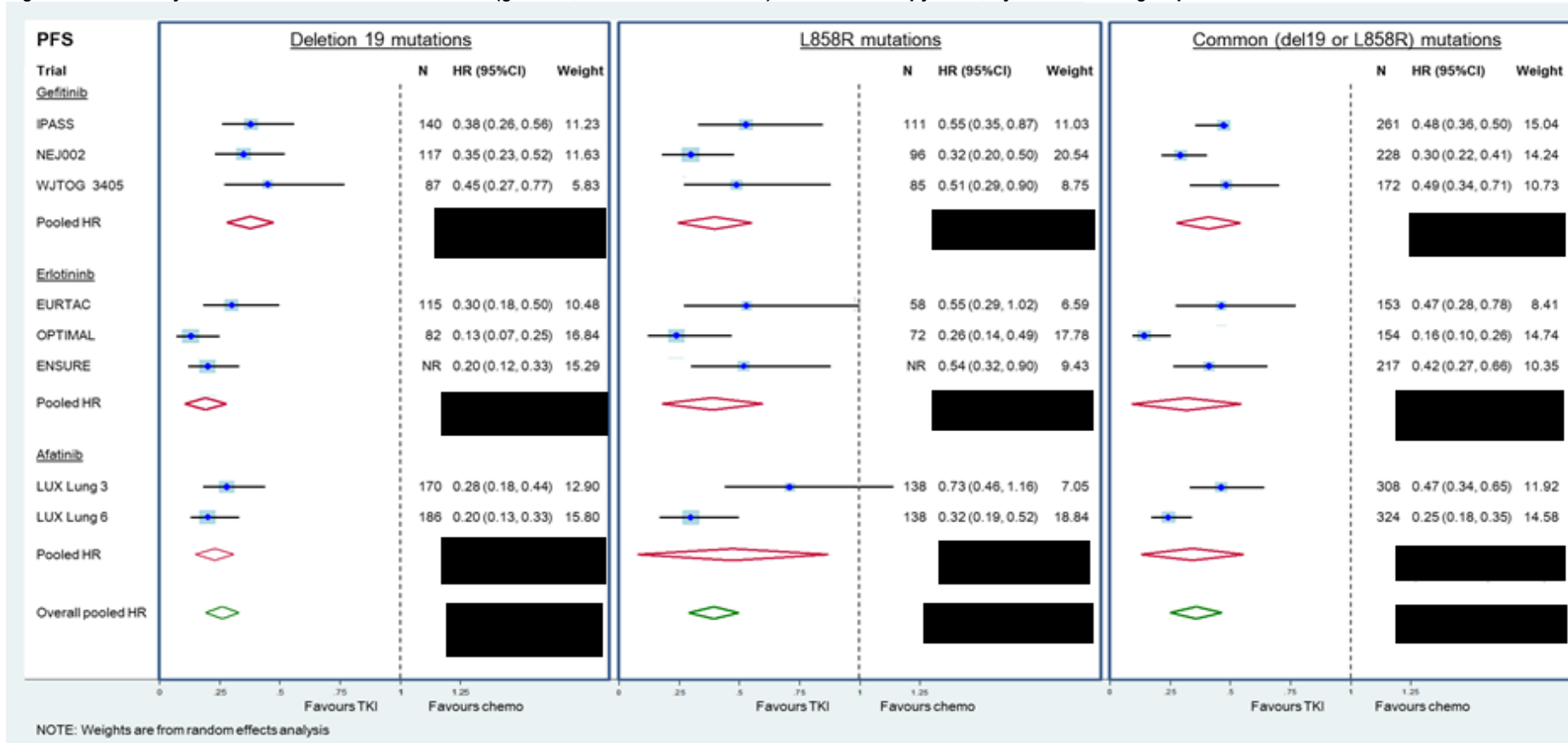
<sup>∞</sup>Only the EURTAC trial provided OS data for the exon 19 deletion subgroup. All erlotinib trials provided OS data for the total “common mutations” (exon 19 deletion or L858R subgroup) population.

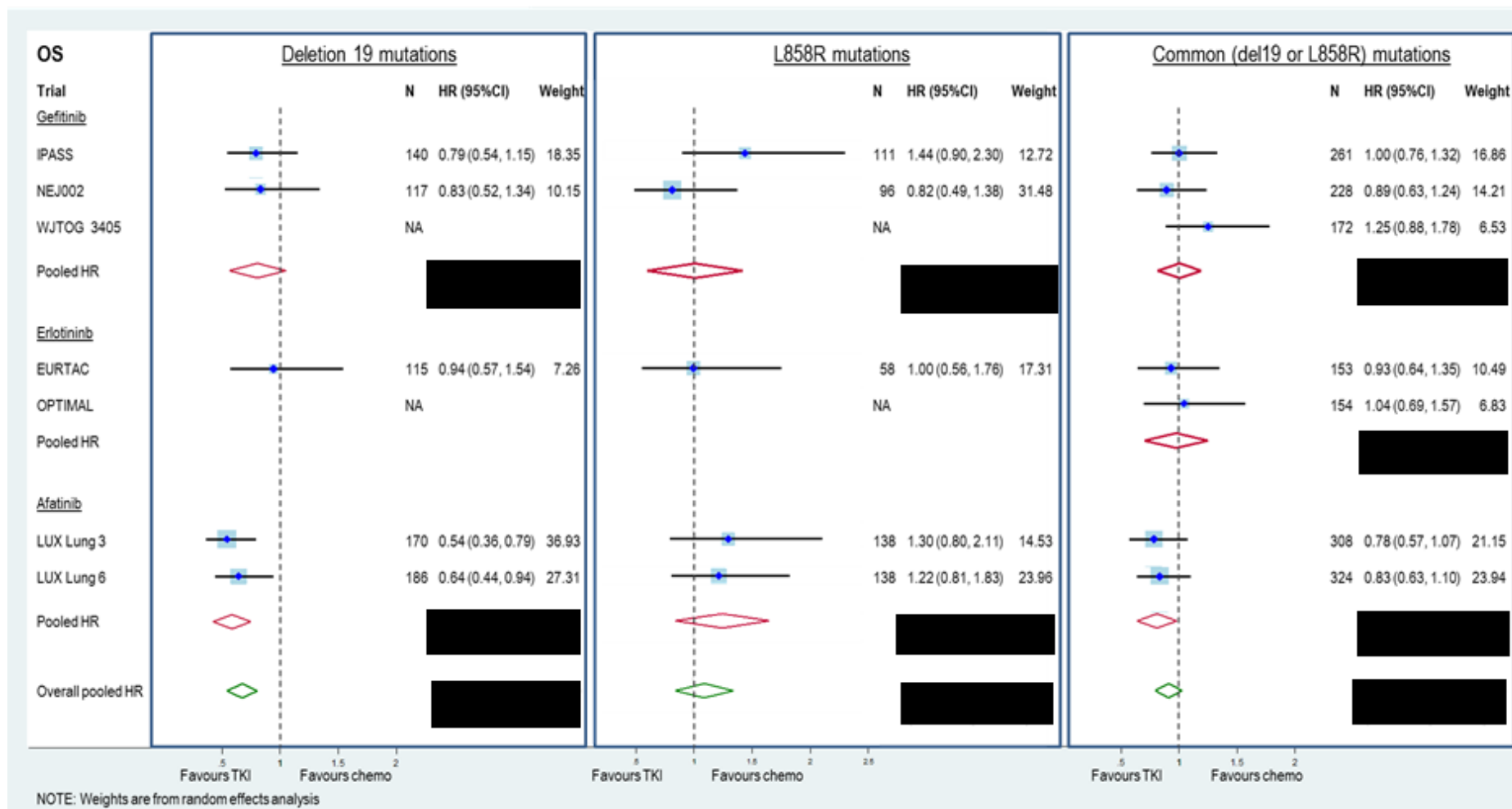
NA = not available; PFS = progression-free survival; OS = overall survival; CI = confidence interval; HR = Hazard ratio

- 6.14 The majority of the results for the indirect comparisons were not statistically significant, with wide confidence intervals around the point estimates indicating a high degree of uncertainty in the HRs estimated for both PFS and OS, especially in the L858R mutation subgroup. Pooled results of PFS from the afatinib LUX Lung trials should be interpreted with caution given the heterogeneity in the comparative treatment effects for afatinib versus chemotherapy across these studies (afatinib performed comparatively better in the LUX Lung 6 trial, see Table 3).
- 6.15 As discussed above, the interpretation of the results of the indirect comparisons should consider the lack of trial exchangeability, due to varying eligibility criteria and PFS measurement, the lack of stratified randomisation by mutation subtype or pre-specification of subgroup analyses, the imbalances between treatment arms for the small mutation subgroups in some of the trials (where baseline data were available), the unknown rate of treatment switching after disease progression, and that fact that the published literature on NSCLC has not supported PFS as a surrogate for quality of life or OS, the two most important clinical outcomes for patients with advanced cancer.

- 6.16 **Meta-analyses of the TKI versus chemotherapy trials:** Figure 1 summarises the results of meta-analyses performed during the evaluation for each mutation subgroup.

Figure 1 Meta-analyses of PFS and OS<sup>s</sup> across the TKI (gefitinib, erlotinib and afatinib) vs chemotherapy trials, by mutation subgroup





Green: Overall pooled; Red: Pooled within drug

There is potential confounding of OS in the individual trials due to treatment switching post-progression from chemotherapy to subsequent tyrosine kinase inhibitor in the ITT population and in each

mutation subgroup and these rates differ between the individual trials: Gefitinib-IPASS: 52%, NEJ002: 99%, WJTOG: 60%. Erlotinib-EURTAC: 76%, OPTIMAL: Not reported. Afatinib-LUX Lung3:65%, LUX Lung6:48%. Rates of treatment switching from chemotherapy to TKI, by mutation subgroup, were not available for the majority of the gefitinib and erlotinib trials.

NA=Not available; TKI=Tyrosine kinase inhibitor.

Sources: Compiled during the evaluation based on afatinib CSRs and gefitinib and erlotinib trial publications.

- 6.17 There was a statistically significant benefit in PFS in patients receiving TKIs, compared to those receiving chemotherapy, in all of the trials. A larger PFS benefit was apparent in the exon 19 deletion subgroup than the L858R mutation subgroup. For the exon 19 deletion mutation subgroup, there were overlapping 95% confidence intervals across the TKI trials. The clinical relevance of any observed differences in PFS across the trials was unclear.
- 6.18 In the exon deletion 19 subgroup, there was a statistically significant OS benefit associated with afatinib versus chemotherapy whereas a trend was observed with gefitinib (only two studies provided data) and no benefit was observed with erlotinib (only one study provided OS data). The mutation subgroups were larger in the afatinib studies than in the other TKI studies and so were more likely to have statistical power to find an effect. In the L858R subgroup, there was a trend favouring chemotherapy over afatinib, with no difference relative to erlotinib and mixed results in comparison to gefitinib.
- 6.19 Interpretation of the meta-analysis results should consider the following:
- The majority of gefitinib trials did not stratify patients by mutation status and in trials which employed stratification at randomisation (such as the LUX Lung trials), imbalances were apparent for the L858R subgroup. There were limited baseline data for specific mutation subgroups (by treatment arm) for the majority of the erlotinib and gefitinib trials;
  - None of the tests for interaction between (a) treatment effect on PFS or OS and (b) being in one or other of the exon 19 deletion or L858R subgroups was significant for any of the pooled afatinib vs pooled gefitinib or pooled afatinib vs pooled erlotinib indirect comparisons;
  - Analyses for the L858R mutation subgroup were not adequately powered; and
  - OS results are likely to be confounded by subsequent treatments post-progression and ITT data suggested different rates of treatment switching from chemotherapy to TKI across the trials (LUX Lung 3 and 6: 65% and 48%, respectively) compared to the erlotinib (EURTAC, 76%) and gefitinib trials (NEJ002 and IPASS, 99% and 52%).
  - The ESC also noted that no biological rationale was suggested for why the type of EGFR mutation might predict treatment effect variation, and why any such prediction might be confined to afatinib alone. A plausible explanation would help draw a conclusion that any such prediction is real, and not just a chance finding.
- The ESC agreed that, given the aforementioned limitations of the data and analyses, the potential trend towards greater survival benefit for afatinib versus gefitinib and versus erlotinib required further exploration and confirmatory studies that are better designed to clearly assess any superiority of afatinib over its alternatives in the exon 19 deletion subgroup (e.g. LUX Lung 7 for the comparison with gefitinib).
- 6.20 The ESC noted findings from a recently published paper (Karachaliou, N. et al, 2015)<sup>a</sup> suggesting that exon 19 deletion and L858R EGFR mutations may represent distinct subgroups in terms of predicting overall survival in patients with advanced NSCLC. This paper presented a post hoc analysis of 97 (56%) of the 173

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<sup>a</sup> Karachaliou, N., Mayo-de las Casas, C., Queralt, C., et al (2015). Association of EGFR L858R Mutation in Circulating Free DNA With Survival in the EURTAC Trial. *JAMA Oncol.* 2015;1(2):149-157. doi:10.1001/jamaoncol.2014.257. Published online February 26, 2015

randomised patients (the subset defined as those with available baseline blood samples) from the EURTAC trial (comparing erlotinib to platinum-based chemotherapy). It reported that there was a difference in overall survival between the two types of mutation, irrespective of whether they received erlotinib or chemotherapy: based on the tissue EGFR results, a median 24.9 [95%CI, 18.8-36.2] months for the exon 19 deletion subgroup versus a median 17.7 [95%CI, 10.0-23.5] months for the L858R subgroup;  $P < 0.006$ . A difference was also reported for the 49 patients who received erlotinib (based on the tissue EGFR results, a median 30.4 [95%CI, 19.8-55.7] months for the exon 19 deletion subgroup versus a median 17.7 [95%CI, 6.3-26.8] months for the L858R subgroup;  $P = 0.02$ ), but not for the 48 patients who received chemotherapy (based on the tissue EGFR results, a median 18.9 [95%CI, 10.4-36.2] months for the exon 19 deletion subgroup versus a median 17.5 [95%CI, 8.2-23.5] months for the L858R subgroup; no P-value for the difference provided). The ESC noted that these results did not align readily with the ITT-based hazard ratios of the treatment effect on overall survival of erlotinib over chemotherapy from this trial reported in Figure 1 below (HR of 0.94 [95%CI, 0.57-1.54] for the exon 19 deletion versus HR of 1.00 [95%CI, 0.56-1.76] for the L858R subgroup). The ESC therefore considered that the publication provided weak supporting evidence that the exon 19 deletion may predict better outcomes related to treatment with erlotinib, with the consequence that any such prediction in treatment effect variation is unlikely to be unique to afatinib.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Comparative harms**

- 6.21 No formal statistical indirect comparison of relative TKI safety was presented in the re-submission. A comparison of single arm data from each of the trials indicated that patients treated with afatinib had a higher risk of Grade 3/4 adverse events (AEs) (diarrhoea, rash/acne, stomatitis and nail effect/paronychia) compared with erlotinib or gefitinib.
- 6.22 An independent search of the literature during the evaluation identified a recent systematic review by Takeda et al (2015), in which a pooled analysis of severe AEs (Grade  $\geq 3$ ) of gefitinib, erlotinib, or afatinib in NSCLC patients with EGFR mutations was reported. Takeda et al (2015) reported that, compared to erlotinib and gefitinib, afatinib was associated with a significantly increased risk of Grade  $\geq 3$  rash and diarrhoea and a decreased risk of hepatotoxicity. The overall frequency of AEs leading to treatment withdrawal was statistically significantly more frequent with afatinib than with erlotinib (7.2% vs. 4.1%,  $p=0.04$ ), and more frequent with gefitinib than with erlotinib (7.6% vs. 4.1%,  $p=0.03$ ).

### **Benefits/harms**

- 6.23 A summary of the comparative benefits and harms for afatinib versus either erlotinib or gefitinib for the exon 19 deletion subgroup is presented in the table below.

**Table 4: Summary of comparative benefits and harms for afatinib and erlotinib or gefitinib for the exon 19 deletion subgroup**

| <b>Benefits*</b> (the indirect comparisons of PFS or OS, between afatinib and either erlotinib or gefitinib for the exon 19 deletion subgroups, rather than the ITT populations of the trials, were considered insufficient to support any conclusion of improved clinical outcomes with afatinib and not with erlotinib or with gefitinib) |                    |                    |                    |                          |           |                       |
|---|--------------------|--------------------|--------------------|--------------------------|-----------|-----------------------|
| <b>Harms</b>  |                    |                    |                    |                          |           |                       |
|   | afatinib           | gefitinib          | RR (95% CI)        | Event rate/100 patients* |           | RD (95% CI)           |
|   |                    |                    |                    | afatinib                 | gefitinib |                       |
| <b>Grade≥3 rash</b>   |                    |                    |                    |                          |           |                       |
| Pooled trials   | 74/498<br>(14.89%) | 16/457<br>(3.5%)   | 4.24 (2.65, 6.81)  | 15                       | 4         | 0.11 (0.08, 0.15)     |
| <b>Grade≥3 diarrhoea</b>  |                    |                    |                    |                          |           |                       |
| Pooled trials   | 48/498<br>(9.64%)  | 5/457<br>(1.09%)   | 8.81 (4.20, 18.48) | 10                       | 1         | 0.09 (0.06, 0.11)     |
| <b>Grade≥3 hepatotoxicity</b>   |                    |                    |                    |                          |           |                       |
| Pooled trials   | 4/498<br>(0.80%)   | 80/457<br>(17.51%) | 0.05 (0.02, 0.09)  | 1                        | 18        | -0.17 (-0.20, -0.13)  |
|   | afatinib           | erlotinib          | RR (95% CI)        | Event rate/100 patients* |           | RD (95% CI)           |
|   |                    |                    |                    | afatinib                 | erlotinib |                       |
| <b>Grade≥3 rash</b>   |                    |                    |                    |                          |           |                       |
| Pooled trials   | 74/498<br>(14.89%) | 45/513<br>(8.77%)  | 1.70 (1.20, 2.40)  | 15                       | 9         | 0.06 (0.02, 0.10)     |
| <b>Grade≥3 diarrhoea</b>  |                    |                    |                    |                          |           |                       |
| Pooled trials   | 48/498<br>(9.64%)  | 14/513<br>(2.73%)  | 3.53 (2.06, 6.06)  | 10                       | 3         | 0.07 (0.04, 0.10)     |
| <b>Grade≥3 hepatotoxicity</b>   |                    |                    |                    |                          |           |                       |
| Pooled trials   | 4/498<br>(0.80%)   | 16/513<br>(3.12%)  | 0.26 (0.09, 0.70)  | 1                        | 3         | -0.02 (-0.04, -0.006) |

Source: Compiled during the evaluation and Takeda et al (2015)

- 6.24 The ESC agreed that the available evidence for afatinib compared with gefitinib and with erlotinib was not sufficiently strong to clearly support a case for unique characteristics (or therapeutic superiority) of afatinib compared with gefitinib and with erlotinib, including in patients with exon 19 deletion mutations.
- 6.25 On the basis of indirect analyses presented in the re-submission, the comparison of afatinib with gefitinib (both drugs administered until progression) in NSCLC patients with exon 19 deletion mutations (drug exposure in mutation subgroup was not reported) resulted in:
- approximately 11 additional patients experiencing a Grade≥3 rash for every 100 patients treated
  - approximately 9 additional patients experiencing a Grade≥3 diarrhoea for every 100 patients treated
  - approximately 17 fewer patients experiencing a Grade≥3 hepatotoxicity for every 100 patients treated.
- 6.26 On the basis of indirect analyses presented in the re-submission, the comparison of afatinib with erlotinib (both drugs administered until progression) in NSCLC patients with exon 19 deletion mutations (drug exposure in mutation subgroup was not reported) resulted in:
- approximately 6 additional patients experiencing a Grade≥3 rash for every 100 patients treated

- approximately 7 additional patients experiencing a Grade $\geq$ 3 diarrhoea for every 100 patients treated
- approximately 2 fewer patients experiencing a Grade $\geq$ 3 hepatotoxicity for every 100 patients treated.

### **Clinical claim**

- 6.27 The re-submission described afatinib as having “improved clinical outcomes compared with the other EGFR TKIs (gefitinib and erlotinib) in patients with exon 19 deletion EGFR mutations”. In terms of safety, the re-submission claimed that the differences in the adverse event profiles of the EGFR TKIs means that it would be desirable to have a choice of TKIs in terms of managing the risks to individual patients. The re-submission indicated that the unique benefits of afatinib justified the use of a SPA.

The description in the re-submission that afatinib was associated with improved clinical outcomes compared with gefitinib and with erlotinib was not adequately supported, in terms of comparative effectiveness, by the evidence/analyses presented. The evidence was based on indirect comparisons of subgroups from non-exchangeable trials and subgroups, and the results were not statistically significant across the two mutation subgroups, with wide confidence intervals around the point estimates.

- 6.28 The safety data from the trials suggested that there are likely differences in the adverse event profiles of these EGFR TKIs. Indirect safety analyses indicated that afatinib was associated with an increased risk of Grade  $\geq$ 3 rash and diarrhoea and a decreased risk of hepatotoxicity versus erlotinib and versus gefitinib.
- 6.29 In its Pre-PBAC Response, the sponsor stated that the clinical evidence presented demonstrates that there are important differences in efficacy and safety between afatinib, gefitinib, and erlotinib in the proposed patient population, irrespective of whether these differences reached statistical significance in the indirect comparison.
- 6.30 The PBAC considered that the claim of improved clinical outcomes (or “uniqueness”) of afatinib compared with gefitinib and with erlotinib in patients with exon 19 deletion EGFR mutations was not adequately supported by the data.
- 6.31 The PBAC considered that the claim of similar comparative safety was reasonable.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### **Economic analysis**

- 6.32 The re-submission presented a modelled economic evaluation (cost-utility analysis) based on point estimates of the PFS and OS hazard ratios for afatinib, compared with erlotinib or gefitinib, in the subgroup of NSCLC patients with exon 19 deletion EGFR mutations. The modelled cost-effectiveness of afatinib compared with erlotinib or gefitinib relied on the point estimates of hazard ratios for PFS and OS obtained from indirect comparisons of non-exchangeable trials. The majority of the results were not statistically significant and there were wide confidence intervals around the point estimates. The use of this approach cannot confidently estimate

the quantified differences in efficacy and safety that were proposed. The PSCR noted that the lack of statistically significant results could be expected given the small number of patients in the trials; however, it further stated that there is a “a clear trend towards improved overall survival with afatinib” and in terms of PFS, that “the results of the indirect comparison versus gefitinib showed a statistically significant difference while the comparison versus erlotinib indicates that afatinib may be equally effective”. The PSCR argued that these differences are clinically important; however, the ESC considered that no evidence was presented to support this claim.

- 6.33 Further, the ESC agreed that the available clinical evidence did not support the assertion of improved clinical outcomes in the exon 19 deletion subgroup with afatinib over erlotinib and over gefitinib and thus did not support a cost-effectiveness analysis rather than a cost-minimisation analysis as the appropriate form of economic evaluation. The Pre-PBAC Response accepted that the usual approach to the economic evaluation would be a cost-minimisation analysis, but argued that a cost-analysis was presented to highlight the differences in efficacy and safety between afatinib, gefitinib and erlotinib. The Pre-PBAC Response also reiterated that the sponsor was not seeking a higher price for afatinib.
- 6.34 Three health states were considered for stage IIIb/IV NSCLC patients entering the model: progression-free, progressive disease and death. All patients entered the model in the progression-free health state.
- 6.35 The model structure remained unchanged from the original July 2013 submission. The requested population, comparator and all model inputs have been changed compared with the original submission of afatinib. No economic evaluation was presented in the July 2014 minor re-submission.
- 6.36 Progression-free and overall survival curves for afatinib were derived from the pooled LUX Lung trials and extrapolated from the last time point of follow-up in the trials (49 months) to the modelled time horizon of five years. It may be more appropriate to extrapolate from the median duration of follow-up (as recommended by the PBAC Guidelines). As patient data at the last follow-up time were scant, this approach meant that the extrapolation was unreliable. The re-submission selected a Weibull distribution to extrapolate both PFS and OS curves. A Weibull distribution was not the model that best fit the trial PFS data. However, the impact of alternative models to extrapolate OS and PFS were not examined in the re-submission and the model did not allow such an analysis during the evaluation. Therefore the impact of the extrapolated survival gains on the results of the economic evaluation remained an area of uncertainty and the selected extrapolation method remained unjustified.
- 6.37 Progression-free and overall survival curves for erlotinib and gefitinib were generated by applying HR of afatinib versus either erlotinib or gefitinib from the indirect comparisons to the survival curves of afatinib. Both erlotinib and gefitinib survival curves were estimated in this way throughout the modelled time horizon of five years. As noted earlier, the HRs from the indirect comparisons are uncertain. Furthermore, the re-submission did not provide a justification for the assumed constant proportional hazard throughout the modelled time horizon.

**Table 5: Summary of model structure and rationale**

|                                  |   |
|----------------------------------|---|
| Time horizon                     | 5 years in the model base case versus maximum of 49 months in the LUX Lung 3 trial  |
| Outcomes                         | PFLYG, LYG and QALYs  |
| Methods used to generate results | Markov model (half-cycle applied). Cohort expected value analysis   |
| Cycle length                     | 1 month   |
| Transition probabilities         | Pooled PFS and OS from LUX Lung 3 and LUX Lung 6 clinical trials for afatinib transition probabilities.<br>Erlotinib and gefitinib transition probabilities were determined from the application of the hazard ratios from the indirect comparisons (Table 3) to the pooled afatinib survival curves. |
| Discount rate                    | 5% for costs and outcomes   |
| Software package                 | Excel 2010  |

PFLYG = progression-free life-year gained; LYG = life-year gained; QALY = quality-adjusted life year; PFS = progression-free survival; OS = overall survival.

Source: compiled during the evaluation

- 6.38 The PBAC has previously considered that, for patients with any activating EGFR mutation, afatinib 40 mg is equi-effective to erlotinib 150 mg or gefitinib 250 mg. For the costs of erlotinib and afatinib, the re-submission did not use the listed or proposed DPMQ based on these doses. As different strengths are available, the re-submission weighted the DPMQ by PBS item statistics (for erlotinib), or by use in the LUX Lung trials (for afatinib). This resulted in the modelled cost per cycle for afatinib and erlotinib being less than that for gefitinib, which was inconsistent with the previous PBAC decisions. The model was moderately sensitive to the costs calculated on the basis of these recommended strengths.
- 6.39 The model in the re-submission assumed that all patients who progressed while on treatment received subsequent treatments. This was inconsistent with the Lux Lung 3 and 6 trials, where 28.0% and 41.6% of patients, respectively, discontinued treatment following the failure of first-line afatinib (Table 15.2.3.2:2, p650 of the Lux Lung 3 CSR and Table 15.2.3.2:2, p568 of the Lux Lung 6 CSR). These observations were consistent with a sample of Medicare Australia data which indicated that 45% of patients who were currently receiving first-line treatment would receive second-line therapy (PBAC gefitinib PSD, November 2012). Due to the structure of the model, it was not possible to assess the sensitivity of the economic evaluation to this assumption during the evaluation.
- 6.40 Consistent with guidelines and its clinical management algorithms, the re-submission modelled two possible treatment sequences after each first-line TKI:
- second-line platinum doublet chemotherapy, followed by third-line monotherapy, followed by best supportive care (BSC); and
  - second-line monotherapy, followed by BSC.
- 6.41 The cost of treatment in the progressive disease health state was weighted according to the estimated time in each post-progression line of treatment, i.e. platinum doublet chemotherapy, monotherapy or best supportive care. Treatment durations on post-progression platinum doublet chemotherapy and monotherapy were assumed to be the same across the three first-line TKIs based on studies that were unlikely to be applicable to the proposed PBS population. Therefore, the shorter the progressive disease state, the greater the relative proportion of time that would be spent on active treatment. The weighted costs for each treatment sequence in the progressive disease health state, for the erlotinib arm, were much higher (\$█████/cycle and \$█████/cycle) than those for the afatinib (\$█████/cycle and \$█████/cycle) or gefitinib

(\$■■■■/cycle and \$■■■■/cycle) arms, due to a shorter time spent in the progressive disease health state (7.8 months (erlotinib) vs 16.6 months (afatinib) vs 16.9 months (gefitinib)). Therefore, the cost of the erlotinib arm was overestimated. A sensitivity analysis that assumed an equal proportion of time spent on each post progression treatment (and therefore, the same costs and utilities per cycle for erlotinib and afatinib) substantially increased the ICER. The PSCR acknowledges that the treatment durations for each subsequent therapy did not exactly match the corresponding line of therapy, but considered that the estimated time on treatment would be unlikely to differ significantly. The ESC noted that this aspect of the model contributed significantly to the cost of erlotinib arm and therefore minimised the incremental cost between afatinib and erlotinib.

6.42 The key drivers of the model are summarised below.

**Table 6: Key drivers of the model**

| Description   | Method/Value   | Impact  |
|---|--|---|
| Relative treatment effect of afatinib versus erlotinib or gefitinib | Point estimates of the HRs were obtained from indirect comparisons of trials that lacked exchangeability. Most of the findings were not statistically significant. The HR point estimates were applied to the PFS and OS curves of afatinib to derive the corresponding curves for erlotinib and gefitinib throughout the modelled time horizon. The re-submission did not provide a justification for the implied constant proportional hazard.   | High, favours afatinib  |
| Cost of progressive disease state for erlotinib arm                 | Cost of treatment in the PD health state was weighted on the estimated time in each post-progression line of treatment. Treatment durations (in months) on post-progression platinum doublet chemotherapy and monotherapy were assumed to be the same across these three first-line TKIs. In comparison to afatinib, the longer PFS and shorter OS observed for erlotinib meant a shorter progressive disease state, and therefore a relatively greater proportion of time that would be spent on active treatment | High, favours afatinib  |
| Costs of afatinib and erlotinib                                     | As different strengths exist, the re-submission weighted the DPMQ by PBS item statistics (for erlotinib), or by use in the LUX Lung trials (for afatinib). This resulted in the modelled cost per cycle for afatinib and erlotinib being lower than that for gefitinib.  | <b>Compared with erlotinib:</b><br>Moderate, favours erlotinib<br><b>Compared with gefitinib:</b><br>Moderate, favours afatinib |

HR = hazard ratio; PFS = progression-free survival; OS = overall survival; TKI = tyrosine kinase inhibitor; PD = progressive disease; DPMQ = dispensed price for maximum quantity

Source: compiled during the evaluation

6.43 The results of the economic evaluation are summarised below. The re-submission presents a weighted comparator (70% erlotinib, 30% gefitinib) in the model, based on the ratio of first-line erlotinib to gefitinib use observed in Ipsos oncology monitor data from Q3 2014 for patients with EGFR mutation positive NSCLC.

Table 7: Results of the stepped economic evaluation

|  | Afatinib                           | Erlotinib     | Increment      | Gefitinib     | Increment     | Weighted <sup>a</sup> | Increment     |
|--|------------------------------------|---------------|----------------|---------------|---------------|-----------------------|---------------|
| <b>Step 1: trial-based costs and outcomes</b>                              |                                    |               |                |               |               |                       |               |
| Costs  | \$ [redacted]                      | \$ [redacted] | -\$ [redacted] | \$ [redacted] | \$ [redacted] | \$ [redacted]         | \$ [redacted] |
| PFLY   | [redacted]                         | [redacted]    | - [redacted]   | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/<br/>PFLY gained</b>                                   | <b>Less costly, less effective</b> |               |                |               |               | \$ [redacted]         | \$ [redacted] |
| LY   | [redacted]                         | [redacted]    | [redacted]     | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/ LY<br/>gained</b>                                     | <b>Dominant</b>                    |               |                |               |               | \$ [redacted]         | \$ [redacted] |
| <b>Step 2: modelling post-progression therapies and disease monitoring</b> |                                    |               |                |               |               |                       |               |
| Costs  | \$ [redacted]                      | \$ [redacted] | \$ [redacted]  | \$ [redacted] | \$ [redacted] | \$ [redacted]         | \$ [redacted] |
| PFLY   | [redacted]                         | [redacted]    | - [redacted]   | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/<br/>PFLY gained</b>                                   | <b>Dominated</b>                   |               |                |               |               | \$ [redacted]         | \$ [redacted] |
| LY   | [redacted]                         | [redacted]    | [redacted]     | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/ LY<br/>gained</b>                                     | \$ [redacted]                      |               |                | \$ [redacted] |               | \$ [redacted]         | \$ [redacted] |
| <b>Step 3: extrapolation to 5-year time horizon</b>                        |                                    |               |                |               |               |                       |               |
| Costs  | \$ [redacted]                      | \$ [redacted] | \$ [redacted]  | \$ [redacted] | \$ [redacted] | \$ [redacted]         | \$ [redacted] |
| PFLY   | [redacted]                         | [redacted]    | - [redacted]   | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/<br/>PFLY gained</b>                                   | <b>Dominated</b>                   |               |                |               |               | \$ [redacted]         | \$ [redacted] |
| LY   | [redacted]                         | [redacted]    | [redacted]     | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/ LY<br/>gained</b>                                     | \$ [redacted]                      |               |                | \$ [redacted] |               | \$ [redacted]         | \$ [redacted] |
| <b>Step 4: transformation of outcomes into QALYs</b>                       |                                    |               |                |               |               |                       |               |
| Costs  | \$ [redacted]                      | \$ [redacted] | \$ [redacted]  | \$ [redacted] | \$ [redacted] | \$ [redacted]         | \$ [redacted] |
| QALY   | [redacted]                         | [redacted]    | [redacted]     | [redacted]    | [redacted]    | [redacted]            | [redacted]    |
| <b>Incremental cost/<br/>QALY gained</b>                                   | \$ [redacted]                      |               |                | \$ [redacted] |               | \$ [redacted]         | \$ [redacted] |

PFLY = progression-free life year; LY = life year; QALY = quality-adjusted life year

<sup>a</sup> The analysis was weighted 70% erlotinib: 30% gefitinib.

6.44 In the comparison of afatinib with erlotinib, the afatinib arm was associated with fewer progression-free life years (PFLYs), and so fewer progression-free QALYs, as afatinib was modelled to have inferior PFS, but with net life-year and QALY gains resulting from the superior OS modelled. This was not plausible, as it was assumed that benefits of afatinib would continue after treatment was stopped. As neither of the HRs (PFS, OS) of afatinib compared to erlotinib reached statistical significance, the direction and magnitude of the effect is highly uncertain. The PSCR agreed that this result is not clinically plausible, stating that the “aim of the economic evaluation was only to quantify any observed differences, irrespective of statistical significance or methodological correctness, to enable the PBAC to determine afatinib has unique characteristics compared to gefitinib and erlotinib and hence meets the criteria for a SPA”.

6.45 The PBAC has previously concluded that the two comparators in the model – erlotinib and gefitinib – are non-inferior to each other and they were PBS listed on a cost-minimisation basis for NSCLC patients with any activating mutations. However, erlotinib and gefitinib were not considered to be equi-effective in this afatinib model, due to the point estimates of treatment effect of afatinib (based on the indirect comparison of subgroups within trials) differing according to the comparator. The

PSCR) argued that the subgroup analysis of the afatinib data indicated improved survival for patients with exon 19 deletion mutations compared to the complete common EGFR mutation population and that there may be differences in the comparative efficacy and safety when assessed separately by patients with exon 19 deletion mutations.

- 6.46 Sensitivity analyses were presented in the re-submission. The results indicated that the model was most sensitive to the hazard ratios obtained from the indirect comparison and these were, in turn, uncertain.
- 6.47 During the evaluation, additional sensitivity analyses were performed and the key results are summarised below.

**Table 8: Results of sensitivity analyses conducted during the evaluation**

| Parameters tested   | ICER                 |                      |                                  |
|---|----------------------|----------------------|----------------------------------|
|   | Erlotinib comparison | Gefitinib comparison | Weighted comparison <sup>^</sup> |
| <b>Base case</b>  | \$ [REDACTED]        | \$ [REDACTED]        | \$ [REDACTED]                    |
| <b>Key univariate analyses</b>  |                      |                      |                                  |
| #1 Weighting of time spent in each treatment post-progression for erlotinib is assumed to be the same as for afatinib | \$ [REDACTED]        | \$ [REDACTED]        | \$ [REDACTED]                    |
| #2 Cost of afatinib based on 40 mg DPMQ   | \$ [REDACTED]        | \$ [REDACTED]        | \$ [REDACTED]                    |
| #3 Cost of erlotinib based on 150 mg DPMQ   | Dominant             | \$ [REDACTED]        | \$ [REDACTED]                    |
| <b>Multivariate analyses</b>  |                      |                      |                                  |
| #4 HR (PFS) = 0.95 (afatinib vs. gefitinib), all other HRs = 1*   | Dominated            | Dominant             | \$ [REDACTED]                    |
| #5 #2 and #3  | Dominant             | \$ [REDACTED]        | \$ [REDACTED]                    |
| #6 #1 and #2 and #3   | \$ [REDACTED]        | \$ [REDACTED]        | \$ [REDACTED]                    |
| #7 #2 and #3 and #4   | Dominated            | \$ [REDACTED]        | \$ [REDACTED]                    |

\* based on the results of the indirect comparison presented in Table 3 where a HR of 0.95 (higher limit of 95% confidence interval) was reported for PFS when compared to afatinib and gefitinib (statistically significant) - all other HRs were not statistically significant.

<sup>^</sup> The analysis was weighted 70% erlotinib: 30% gefitinib.

DPMQ = dispensed price for the maximum quantity; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival

Note: multivariate analysis was not presented for #1 and #2 and #3 and #4, as assuming HR of OS and PFS for afatinib compared with erlotinib =1 implies that the weighting of time spent in post-progression treatment is equal for afatinib and erlotinib

Source: Constructed during the evaluation from Afatinib EGFR & Del-19 NSCLC Economic Evaluation (FINAL).xism,

**Drug cost/patient/course: \$ [REDACTED]**

- 6.48 The cost modelled per month of afatinib, gefitinib and erlotinib are presented in the table below. One tablet is taken per day. As TKI treatment continues until disease progression, the modelled cost per treatment course is derived from the modelled cost per month, multiplied by the modelled PFS.

**Table 9: Drug cost per patient per month and per treatment course, based on modelled costs**

|                  | DPMQ (pack size)                        | Modelled cost per month <sup>a</sup> | Modelled PFS (months) | Modelled cost per treatment course |
|------------------|---|--------------------------------------|-----------------------|------------------------------------|
| <b>Afatinib</b>  | \$ [REDACTED] <sup>b</sup> (28 tablets) | \$ [REDACTED]                        | [REDACTED]            | \$ [REDACTED]                      |
| <b>Gefitinib</b> | \$ [REDACTED] (30 tablets)              | \$ [REDACTED]                        | [REDACTED]            | \$ [REDACTED]                      |
| <b>Erlotinib</b> | \$ [REDACTED] <sup>c</sup> (30 tablets) | \$ [REDACTED]                        | [REDACTED]            | \$ [REDACTED]                      |

<sup>a</sup> (modelled DPMQ / pack size) × (365/12)

<sup>b</sup> Proposed DPMQ weighted by observed use at the end of treatment in the LUX Lung 3 and 6 trials

<sup>c</sup> PBS items 10022L, 10019H, 10014C, 10028T, 10020J and 10025P weighted by PBS item statistics, Feb – Nov 2014

Source: compiled during the evaluation

The cost per month and cost per treatment course of afatinib (40 mg), gefitinib (250 mg) and erlotinib (150 mg) are presented in the table below. These reflect the costs of the doses considered previously by the PBAC to be equi-effective.

**Table 10: Drug cost per patient per month and per treatment course, based on the cost of the equi-effective doses**

|                  | DPMQ (pack size)                        | Cost per month <sup>a</sup> | Modelled PFS (months) | Cost per treatment course |
|------------------|---|-----------------------------|-----------------------|---------------------------|
| <b>Afatinib</b>  | \$ [REDACTED] <sup>b</sup> (28 tablets) | \$ [REDACTED]               | [REDACTED]            | \$ [REDACTED]             |
| <b>Gefitinib</b> | \$ [REDACTED] (30 tablets)              | \$ [REDACTED]               | [REDACTED]            | \$ [REDACTED]             |
| <b>Erlotinib</b> | \$ [REDACTED] <sup>c</sup> (30 tablets) | \$ [REDACTED]               | [REDACTED]            | \$ [REDACTED]             |

<sup>a</sup> (DPMQ / pack size) × (365/12)

<sup>b</sup> Proposed DPMQ 40 mg afatinib

<sup>c</sup> DPMQ of PBS item 10014C (erlotinib 150 mg)

Source: Compiled during the evaluation

### **Estimated PBS usage & financial implications**

6.49 This re-submission was not considered by DUSC. The re-submission used an epidemiological approach to estimate the financial implications associated with the proposed listing of afatinib. The estimates of the projected incident cases of lung cancer were sourced from an AIHW report. The number of patients eligible for afatinib treatment, i.e. patients with Stage IIIb or IV non- squamous or not otherwise specified NSCLC with exon 19 deletion EGFR mutation(s) who have good performance status (WHO performance status of 2 or less) and are willing to receive treatment, was determined based on a variety of data sources, including AIHW data, epidemiological studies and previous DUSC advice. It was assumed that the uptake of afatinib would increase from 25% in Year 1 of listing to 70% in Year 5. The estimate of uptake of afatinib, if it is listed in the PBS for the proposed restriction, has not been justified in the re-submission. The number of patients having already been treated with afatinib, erlotinib or gefitinib in previous years who would stay on TKI treatment in each subsequent year was determined using the PFS curve modelled in the economic evaluation, by assuming that patients would continue TKI therapies until disease progression.

6.50 The estimated net costs to the PBS/RPBS presented in the table below were based on the proposed effective prices for afatinib.

**Table 11: Estimated use and financial implications**

|   | Year 1    | Year 2    | Year 3    | Year 4    | Year 5    |
|---|-----------|-----------|-----------|-----------|-----------|
| <b>Estimated extent of use</b>            |           |           |           |           |           |
| Number treated                            |           |           |           |           |           |
| Scripts <sup>a</sup>                      |           |           |           |           |           |
| <b>Estimated net cost to PBS/RPBS/MBS</b> |           |           |           |           |           |
| Net cost to PBS/RPBS <sup>b</sup>         | \$        | \$        | \$        | \$        | \$        |
| Net cost to MBS                           | \$0       | \$0       | \$0       | \$0       | \$0       |
| <b>Estimated total net cost</b>           |           |           |           |           |           |
| <b>Net cost to PBS/RPBS/MBS</b>           | <b>\$</b> | <b>\$</b> | <b>\$</b> | <b>\$</b> | <b>\$</b> |

<sup>a</sup> Assuming 12.72 scripts per year as estimated by the re-submission.

<sup>b</sup> Costs to the PBS/RPBS excluding the patient co-payments and incorporating the proposed effective prices for afatinib.

- 6.51 The number of patients likely to receive afatinib could be higher than the estimates used in the re-submission to calculate the financial implications to the PBS/RPBS. The re-submission assumed that 33% of patients with Stage IIb disease and 38% of patients with Stage IIIa at diagnosis would progress to Stage IIIb/IV and, subject to their exon 19 deletion EGFR mutation status, might become eligible for afatinib treatment. The submission assumed that no patients diagnosed with Stages I-IIa would experience a risk of disease progression. The re-submission's assumptions were unreasonable as patients diagnosed with earlier stages of lung cancer would reach Stage IIIb/IV disease later on unless they died from other causes first. The afatinib submission considered at the July 2013 PBAC meeting assumed that all patients with Stages I-IIIa lung cancer at diagnosis would progress to Stage IIIb/IV 2 years later.
- 6.52 The results of the financial implications to the PBS/RPBS relied on the comparative treatment effect of afatinib versus erlotinib and gefitinib in terms of PFS, which was the major clinical and economic uncertainty of the re-submission. Most (70%) of the patients expected to be treated with afatinib would otherwise receive erlotinib. For these patients, the use of afatinib instead of erlotinib would result in fewer patients staying on treatment in subsequent years and, thus, favour afatinib, given the modelled shorter PFS following afatinib treatment.
- 6.53 The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net cost to the PBS/RPBS/MBS would be less than \$10 million.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Financial Management – Risk Sharing Arrangements**

- 6.54 The re-submission stated that "Boehringer Ingelheim remains willing to enter into a risk sharing arrangement with the Commonwealth, and is able to accept the other terms and conditions of the risk sharing arrangements for the other PBS listed EGFR tyrosine kinase inhibitors (EGFR TKIs), to the limited extent that these have been disclosed by the DoH to date". A key aim of the re-submission was to request an SPA for afatinib.

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the more restricted listing of afatinib demaleate in patients with locally advanced or metastatic non-small cell lung cancer characterised by exon 19 deletion mutations of the epidermal growth factor receptor (EGFR) gene. In making this recommendation, the PBAC considered that the data provided in the submission did not provide sufficient evidence to demonstrate that afatinib is associated with improved clinical outcomes for the EGFR exon 19 deletion subgroup, in comparison with gefitinib and with erlotinib. Accordingly, the PBAC reiterated its advice to the Department that it does not accept that afatinib has unique characteristics compared to other available therapies for the treatment of any particular set of patients with advanced or metastatic non-squamous non-small-cell lung cancer, in order to inform the judgement of whether afatinib meets the required criteria for a SPA.
- 7.2 The PBAC agreed with ESC that there were significant limitations with the data presented in the indirect comparisons including:
- lack of trial exchangeability, due to varying eligibility criteria and PFS measurement;
  - lack of stratified randomisation by mutation subtype or pre-specification of subgroup analyses;
  - imbalances between treatment arms for the small mutation subgroups in some of the trials; and
  - the unknown rate of treatment switching after disease progression.
- 7.3 The PBAC agreed with ESC that the cost-effectiveness approach used for the economic evaluation could not confidently estimate the quantified differences in efficacy and safety that were proposed by the submission, noting that:
- the model relied on the point estimates of hazard ratios for PFS and OS obtained from indirect comparisons of non-exchangeable trials; and
  - the majority of the results were not statistically significant and there were wide confidence intervals around the point estimates.
- 7.4 Accordingly, the PBAC considered that the available evidence for afatinib compared with gefitinib and with erlotinib was not sufficiently strong to clearly support a case for improved clinical outcomes (or “uniqueness”) of afatinib compared with gefitinib and with erlotinib in patients with exon 19 deletion mutations.
- 7.5 In considering the clinical place of therapy, the PBAC recalled its previous recommendation that definition of the biomarker in NSCLC should not be restricted to specific activating EGFR mutations.
- 7.6 The PBAC considered that, given the aforementioned limitations of the data and analyses, further confirmatory studies are required that are better designed to clearly assess any superiority of afatinib over each of its two alternatives in the exon 19 deletion subgroup.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**  
Rejected.

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.