

Erlotinib and Gefitinib: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of the tyrosine kinase inhibitors (TKIs), erlotinib and gefitinib, for the treatment of Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC).

Listing on the Pharmaceutical Benefits Scheme (PBS)

The PBS listings for erlotinib and gefitinib were extended from 1 January 2014 to include first-line monotherapy for patients with Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC cancer and who have evidence of epidermal growth factor receptor (EGFR) gene mutations known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors in tumour material (EGFR+). The listing includes patients with non-squamous type NSCLC or not otherwise specified type NSCLC.

The current listings for erlotinib and gefitinib do not specify line of therapy because the Pharmaceutical Benefits Advisory Committee (PBAC) considered that the data indicated no difference in progression-free survival or overall survival whether a TKI is given as first-line or second-line therapy to patients with EGFR mutation positive NSCLC.

Prior to this, gefitinib and erlotinib had been PBS subsidised only for locally advanced or metastatic NSCLC where disease progression had occurred following chemotherapy and/or further chemotherapy was not an option. Gefitinib was available only for patients with activating mutation(s) of the EGFR gene in tumour material whereas the erlotinib listing did not specify EGFR status. From 1 January 2014 erlotinib was restricted to EGFR+ patients because the PBAC considered that use of this targeted therapy in the group of patients in which the target is absent was not appropriate. The PBAC did not consider that the net benefits would exceed its net harms in last-line EGFR mutation negative patients.^{1,2}

¹ Pharmaceutical Benefits Advisory Committee Public Summary Document for erlotinib July 2013: Available at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-07/erlotinib>

² Pharmaceutical Benefits Advisory Committee Public Summary Document for erlotinib March 2014: Available at <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-03/erlotinib>

Data Source / methodology

The analyses used data from the Department of Human Services (DHS) prescriptions database.

Key Findings

First line TKI use

- In 2014, 598 patients commenced erlotinib or gefitinib for first-line treatment of NSCLC harbouring EGFR mutations. Of these patients, 45% commenced PBS subsidised treatment within the first two months of the extension to listing. In 2015, only 347 patients commenced first-line erlotinib or gefitinib therapy.
- The number of people receiving first line TKIs was similar to expected in 2014 and lower than expected in 2015.
- Data available to date indicate that the median duration of TKIs for first-line treatment of NSCLC harbouring EGFR mutations is approximately 11 months. This is similar to the duration of treatment in the key clinical trials.
- A small proportion of patients have switched between TKIs (approximately 5%). The PBS restrictions allow switching if patients develop intolerance to one EGFR TKI of a severity necessitating permanent treatment withdrawal, and the disease has not progressed.
- A concern of DUSC and the PBAC was that the TKIs would continue to be used beyond disease progression. A limited analysis that examined patterns of treatment with a first-line TKI followed by chemotherapy (indicating progression) and then subsequent TKI use, suggests that at least 7.4% of patients may be using TKIs beyond progression.

Second or subsequent line TKI use

- Use of erlotinib as a second or subsequent line of treatment in the unselected population (EGFR gene mutation positive, wild-type EGFR gene, or unknown) peaked in 2011 with 1,175 patients initiating therapy. Use has been declining since. The key factor driving the reduction in use was the PBS requirement for any new patients treated with erlotinib to be EGFR mutation positive (from 1 August 2014). The decline in use in 2012 and 2013 suggests that clinical practice was changing ahead of the PBS restriction.
- EGFR status for patients using erlotinib prior to 2014 cannot be ascertained from PBS data.
- Use of gefitinib following chemotherapy in patients with EGFR mutations had been low prior to 2014 (less than 50 patients per year).

Prevalence of EGFR

- In 2015-16, there were 2,959 services for MBS item 73337³ and 530 new patients initiated erlotinib or gefitinib through the PBS. This indicates the prevalence of activating EGFR mutations in the tested and treated NSCLC population is 17.9%, which is similar to the predicted estimate of 15%.

³ A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Purpose of analysis

To compare the predicted and actual utilisation of the tyrosine kinase inhibitors, erlotinib and gefitinib, for the treatment of Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC).

Background

Pharmacology

Erlotinib and gefitinib are tyrosine kinase inhibitors (TKIs). They bind to the epidermal growth factor receptor (EGFR) and prevent activation of tyrosine kinase, which inhibits cell replication and growth.

Therapeutic Goods Administration (TGA) approved indications

Erlotinib (Tarceva[®]) is currently TGA registered for:

- first-line treatment of patients with advanced (Stage IIIB) or metastatic (Stage IV) NSCLC with activating EGFR mutations
- maintenance therapy* in patients with locally advanced or metastatic NSCLC with activating EGFR mutations who have not progressed on first-line chemotherapy
- locally advanced or metastatic NSCLC after failure of prior chemotherapy
- locally advanced, unresectable or metastatic pancreatic cancer in combination with gemcitabine.

**The original maintenance indication for locally advanced or metastatic NSCLC did not specify a requirement for patients to harbour an EGFR-activating mutation. The IUNO study found no demonstrable benefit of first-line maintenance treatment versus second-line treatment with erlotinib for patients whose tumours do not harbour an EGFR-activating mutation. As a result of this finding, the maintenance indication was restricted to patients with EGFR mutations only from 16 December 2015 and a safety update was published in April 2016.⁴*

Gefitinib (Iressa[®]) is currently TGA registered for treatment of patients with locally advanced or metastatic NSCLC whose tumours express activating mutations of the EGFR tyrosine kinase.

The original indication for gefitinib, approved by the TGA on 22 April 2003, was for the treatment of patients with locally advanced or metastatic NSCLC who have previously received chemotherapy.

⁴ Medicines Safety Update April 2016. Therapeutic Goods Administration.
<https://www.tga.gov.au/sites/default/files/medicines-safety-update-volume-7-number-2-april-2016.pdf>

Dosage and administration

Gefitinib: usual dose is 250 mg once a day, taken with or without food. Gefitinib needs to be swallowed whole or dispersed in water (without crushing – see Product Information for further details).

Patients with poorly tolerated diarrhoea or skin-related adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose.

Erlotinib: usual dose for NSCLC is 150 mg taken at least one hour before or two hours after food. Treatment should be continued until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond disease progression is beneficial.

When dose adjustment is necessary, reduce in 50 mg steps.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information). Refer to the PI for full details.

Clinical situation

Lung cancer is the fifth most common cancer in Australia.⁵ In 2015, lung cancer was the fourth leading cause of death overall in Australia and accounted for the most cancer deaths (8,466).⁶ Most lung cancers are advanced at diagnosis and prognosis is generally poor. Lung cancers are classified into two main groups, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC, the most prevalent lung cancer, has three common forms - adenocarcinomas, squamous cell carcinomas and large cell carcinomas. Some NSCLCs have certain mutations in the EGFR gene. These are more common in females, people with no prior history of smoking, and those of Asian descent. The EGFR TKI medicines are targeted therapies used for treatment for NSCLC in patients with evidence of activating EGFR gene mutations.

PBS listing details (as at December 2016)

There have been a number of PBS items and changes to the restrictions for erlotinib and gefitinib over time. An overview is provided in Appendix A. The current PBS listings are provided in Table 1 and a summary of the PBS restriction criteria are below.

For full details of the current PBS-listing refer to the PBS website.

⁵ [AIHW](#), Commonwealth of Australia 2016

⁶ [Australian Bureau of Statistics](#), Commonwealth of Australia, 2016.

Table 1: PBS listing of erlotinib and gefitinib

Item	Name, form & strength, pack size	Max qty packs	Max qty units	Rpts	DPMQ	Brand name and manufacturer
8769M	Gefitinib 250 mg tablet, 30	1	30	3	\$1432.97	Iressa® AstraZeneca Pty Ltd
10022L, 10028T	Erlotinib 25 mg tablet, 30	1	30	3	\$329.04	Tarceva® Roche Products Pty Ltd
10019H, 10020J	Erlotinib 100 mg tablet, 30	1	30	3	\$1173.00	Tarceva® Roche Products Pty Ltd
10014C, 10025P	Erlotinib 150 mg tablet, 30	1	30	3	\$1432.97	Tarceva® Roche Products Pty Ltd

Source: the PBS website.

Restriction (abridged)

Erlotinib and gefitinib are Authority Required (telephone) PBS medicines.

The initial treatment restrictions (1014C, 10020J, 10022L) are:

- stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC; and
- non-squamous type NSCLC or not otherwise specified NSCLC; and
- must have evidence of an activating EGFR gene mutation known to confer sensitivity to treatment with an EGFR TKI material; and
- must not have received previous PBS-subsidised treatment with another EGFR TKI; or must have developed intolerance to another EGFR TKI of a severity necessitating permanent treatment withdrawal; and
- must have WHO performance status of 2 or less; and
- treatment must be as monotherapy.

The continuing treatment restrictions (1014C, 10020J, 10022L) are:

- patients must have been previously issued with a prescription for this drug; and
- must have evidence of an activating EGFR gene mutation known to confer sensitivity to treatment with EGFR TKI in tumour material; and
- must not have progressive disease; and
- treatment must be as monotherapy.

There is also a continuing erlotinib treatment restriction (10019H, 10025P, 10028T) for patients who had commenced treatment with erlotinib prior to 1 August 2014:

- stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC; and
- patient must have a wild-type EGFR gene; OR patient must have an EGFR gene of unknown type; and
- must not have progressive disease; and
- treatment must be as monotherapy.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (abridged)

The PBAC (in July 2004) recommended the listing of **gefitinib** for treatment, as monotherapy, of locally advanced or metastatic NSCLC in patients with a WHO performance status of two or less, where disease progression has occurred following treatment with at least one chemotherapy agent and there is evidence that the patient has an activating mutation(s) of the EGFR gene in tumour material. The recommendation was made on the basis of acceptable cost-effectiveness compared with docetaxel and best supportive care. Listing was effective from 1 December 2004.

At the March 2008 meeting, the PBAC considered a sponsor request to amend the **gefitinib** PBS restriction by removing the requirement for the activating EGFR mutation, and alignment with the TGA indication at that time, which specified two patient subgroups eligible for gefitinib: those who have never smoked and those taking gefitinib who have demonstrated some benefit. The PBAC considered that inadequate evidence was provided to allow an assessment to be made on the cost-effectiveness of gefitinib in the population that would be covered under the requested listing and that more detailed information from a recent clinical trial was required. PBAC therefore recommended no changes be made to the PBS listing for gefitinib pending a further submission from the sponsor.

At its November 2009 meeting, the PBAC recommended an amendment to the PBS restriction for **gefitinib** by removing the requirement that analysis of the DNA sequence of the EGFR gene must be used to detect a mutation in the EGFR gene. The PBAC noted that the analysis by DNA sequencing methodology was not MBS reimbursed and it was therefore considered reasonable to use other methodologies to detect the specific activating mutations in the EGFR gene.

After rejections in March 2006, November 2006 and a deferral in November 2007, at the March 2008 meeting, the PBAC recommended the Authority Required PBS-listing of **erlotinib** as monotherapy for patients with stage IIIB or IV NSCLC with a WHO performance status of three or less, after prior platinum-based chemotherapy, where disease progression has occurred following treatment with docetaxel or pemetrexed; or where treatment with docetaxel and pemetrexed is contraindicated or cannot be tolerated. The recommendation was made on the basis of acceptable cost-effectiveness compared with best supportive care. Continuation of treatment was recommended for patients who have not developed progressive disease. Erlotinib was PBS-listed on 1 August 2008 for this indication.

At the July 2013 meeting, the PBAC considered three submissions for use of TKIs for first-line locally advanced or metastatic NSCLC. The submissions included resubmissions for **gefitinib** (rejected at the November 2010, July 2012 and November 2012 meetings) and **erlotinib** (rejected at the July 2012 meeting) and a first submission for **afatinib**.

The PBAC deferred recommending listing for all three medicines.

The PBAC accepted that each of the three TKIs (gefitinib, erlotinib and afatinib) were more effective than platinum-based doublet chemotherapy in patients with EGFR mutation

positive NSCLC in terms of improving progression free survival (PFS), with the additional gain in median PFS varying between 1.7 and 5.4 months across the key randomised trials presented.

The PBAC considered that there was no difference to progression-free survival or overall survival whether a TKI is given as first-line or second-line therapy to patients with EGFR mutation positive NSCLC.

The PBAC noted that the three TKIs have slightly different toxicity profiles. Although the side effects are manageable overall, the PBAC considered that the PBS-listing of more than one TKI would allow greater choice for patients.

On balance, the PBAC considered that the three TKIs (afatinib, erlotinib and gefitinib) were clinically non-inferior to each other, and so should be cost-minimised against each other with the equi-effective doses being afatinib 40 mg daily, erlotinib 150 mg daily and gefitinib 250 mg daily (as per the key trials). In these circumstances, the PBAC determined the equi-effective doses of afatinib, erlotinib and gefitinib on the basis of the doses determined for their respective key trials without adjusting for any variations in dose intensity or treatment duration.

The PBAC noted a range of concerns with the economic models in each submission. For erlotinib and afatinib, the PBAC considered the base case ICERs of \$45,000-75,000 to be unacceptably high and uncertain. For gefitinib, the PBAC considered the cost-effectiveness uncertain and more likely to be in the upper range of \$45,000-\$75,000 per QALY rather than dominant as proposed.

The PBAC noted that the biggest financial risk was the duration of therapy, particularly due to use beyond disease progression, which could double the estimate of net costs, and advised that a risk-share arrangement should be negotiated to manage this risk in particular. The negotiated risk-share arrangement should also satisfactorily address the uncertain effectiveness of TKIs in the [REDACTED] of patients expected to have rare EGFR activating mutations, whilst accepting its effectiveness in the [REDACTED] of patients expected to have common EGFR activating mutations.

Subsequent to the July 2013 PBAC meeting, the sponsor of erlotinib offered to reduce its price for all use of erlotinib under the proposed restriction to patients with NSCLC who are EGFR mutation positive. The PBAC therefore recommended out-of-session the listing of erlotinib on the PBS as an Authority Required listing, as monotherapy, for the treatment of locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified NSCLC in patients with evidence of activating mutation(s) of the EGFR gene in tumour material. Erlotinib is to cease on progression.

The PBAC considered that, at the reduced price, erlotinib could be considered to be cost-effective in comparison with platinum-based doublet chemotherapy. This was based on erlotinib's superiority in terms of progression free survival and quality of life and different toxicity profile. This was despite the evidence showing no additional overall survival benefit for first-line erlotinib over chemotherapy in patients with NSCLC who are EGFR mutation positive.

The sponsor of gefitinib also offered a price reduction. The PBAC advised that in light of its out-of-session recommendation for the listing of erlotinib at an effective price lower than that of gefitinib, and the PBAC's previous conclusion that erlotinib and gefitinib are likely to be clinically non-inferior to each another, the PBAC considered that gefitinib would not be cost-effective under the sponsor's pricing proposal. The PBAC considered that the cost-effectiveness of gefitinib would be acceptable if gefitinib was cost-minimised against erlotinib.

The PBAC recommended a risk share arrangement be negotiated to satisfactorily address risks of excessive utilisation and the use in patients with rare EGFR activating mutations.

The listings for erlotinib and gefitinib were extended to allow first-line use in patients with EGFR mutation positive NSCLC from 1 January 2014. As at December 2016, afatinib has not been listed on the PBS for NSCLC. A subsequent submission for **afatinib** seeking listing under a special pricing arrangement for locally advanced or metastatic NSCLC characterised by exon 19 deletion mutations of the EGFR gene was not recommended by the PBAC. For further details, refer to the Public Summary Document from the July 2015 PBAC meeting.

In March 2014, the PBAC considered a submission for **erlotinib** to establish the effectiveness and cost-effectiveness of erlotinib in last-line use for the population of patients who are not selected on the basis of EGFR mutation testing. The PBAC had requested that the sponsor make a submission to establish the effectiveness and cost-effectiveness of erlotinib in the population defined by this restriction.

When recommending the first-line use of erlotinib in EGFR-positive patients, the PBAC had foreshadowed its intention to replace the existing erlotinib restriction with one which limits eligibility to erlotinib to those patients with an EGFR mutation, but which makes no reference to any line of therapy.

The PBAC rejected the submission and recommended the deletion of the current last-line PBS restriction of erlotinib because of uncertain net clinical benefit and unacceptable cost-effectiveness. The PBAC did not consider that it was appropriate to retain a listing on the PBS of a targeted therapy for a population in which the target is absent. In reaching this conclusion, the PBAC noted that it was difficult to conclude with confidence that erlotinib's net benefits over best supportive care would exceed its net harms in the population identified by the current last-line restriction.

For further details refer to the Public Summary Document by product or meeting.

Approach taken to estimate utilisation

DUSC provided advice to the PBAC at its July 2013 meeting for the resubmissions for erlotinib and gefitinib (and the first submission for afatinib).

There were some differences in the approaches and assumptions across the three submissions as outlined below. The common main issues raised by DUSC for estimating use of TKIs for first-line use of stage IIIb and IV NSCLC were:

- Considerable risk of use outside the restriction, particularly in earlier stage disease,

given that EGFR status would be known at diagnosis. Use in combination with chemotherapy was also identified as a potential use outside of the restriction.

- Uncertain prevalence of patients with activating EGFR mutation. 15% was considered the appropriate base case based on Medical Services Advisory Committee (MSAC) advice.
- Risk of use following progression, despite the PBS restriction precluding this.

Erlotinib resubmission (July 2013 PBAC)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Previous reviews

DUSC reviewed the utilisation of erlotinib for locally advanced or metastatic NSCLC at the February 2011 meeting. The review found that there were significantly more patients commencing therapy than predicted and consequently a higher number of prescriptions and expenditure. On average, patients were receiving fewer prescriptions than predicted. Three possible reasons were identified for the greater number of patients commencing therapy than predicted: an underestimation of the number of eligible patients opting to take up therapy; a higher proportion of patients diagnosed with NSCLC that undergo first-line treatment than predicted and are thus eligible for erlotinib; or prescribing outside of the authority restriction.

The sponsor provided a detailed response including revised estimates of use to support their view that the use, although higher than expected, was within the restrictions. DUSC accepted that the assumptions at the time of listing were uncertain and the estimates of patients were likely to have been underestimated; however, DUSC remained uncertain whether erlotinib was being used in patients not suitable for chemotherapy or whether the pattern of treatment of NSCLC had changed significantly following the introduction of erlotinib.

The PBAC agreed with DUSC and also noted that there was no EGFR test subsidised by the Medical Benefits Scheme (MBS) and that prescribers may be commencing patients on erlotinib for a short-term trial. The PBS-listing does not specifically require evidence of the activating mutation to be present, unlike the listing for gefitinib; and there were studies underway that showed benefits when used first-line (without prior trial of a platinum based therapy).

Methods

The Department of Human Services (DHS) prescription database was used for all analyses. Erlotinib and gefitinib prescriptions were extracted from the date of the first PBS-listing of gefitinib in December 2004 to the end of September 2016 (the most recent complete date of supply data).

Patients initiating to TKI therapy or a particular TKI drug were defined as those who have not been supplied a prescription since the PBS-listing of gefitinib in December 2004. Initiating and prevalent patients were counted by quarter of supply as both gefitinib and erlotinib have a median time to re-supply of approximately one month. Thus nearly all patients on therapy are likely to have at least one supply in a quarter and so quarterly supply prevalence is likely to be a good approximation of prevalence on therapy. Annual prevalence (a count of patients supplied at least one TKI prescription in each calendar year) was also determined.

To assess whether patients were using a TKI as a first or subsequent line of therapy, an assessment of prior chemotherapy was undertaken. This included all prescriptions for antineoplastics (WHO ATC=L01) supplied in the period January 2003 (the beginning of

reliable patient level data) to the end of September 2016 for all patients initiating TKI therapy in the period December 2004 to the end of September 2016. The classification of first line therapy (i.e. erlotinib, gefitinib or chemotherapy) was based the patient's first prescription in this data.

Length of Treatment Analysis

A Kaplan-Meier length of treatment analysis for TKI drugs was performed using the DHS supplied prescription data from the time of the expansion of the TKI listings to first-line therapy (January 2014) to the end of September 2016. The median time to resupply for gefitinib and erlotinib was 30 and 29 days, respectively. A break in treatment was defined as three times the median time to resupply or more between prescription supplies. A treatment episode was defined as the time from supply of the first prescription in the period, or the first prescription after a break, to the supply of the last prescription before a break, plus the drug specific median time to resupply to account for the coverage of the last prescription. A patient was deemed to be continuing treatment (i.e. censored for the purposes of the Kaplan-Meier analysis) if the supply of their last prescription was within three times the median time to resupply of the end of the data period. Apart from the length of drug treatment episodes, two episode aggregation measures were calculated:

- The length of treatment excluding breaks was defined as the sum of all treatment episodes.
- The length of treatment including breaks was defined as the time from supply of the first prescription to supply of the last prescription in the period plus the drug specific median time to resupply to account for the coverage of the last prescription.

As these analyses use date of supply prescription data, there may be small differences compared with publicly available DHS Medicare date of processing data.⁷

Results

Analysis of drug utilisation

Overall utilisation

The number of PBS/RPBS erlotinib and gefitinib prescriptions supplied per quarter since the listing of gefitinib in December 2004 is shown in Figure 1.

⁷ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

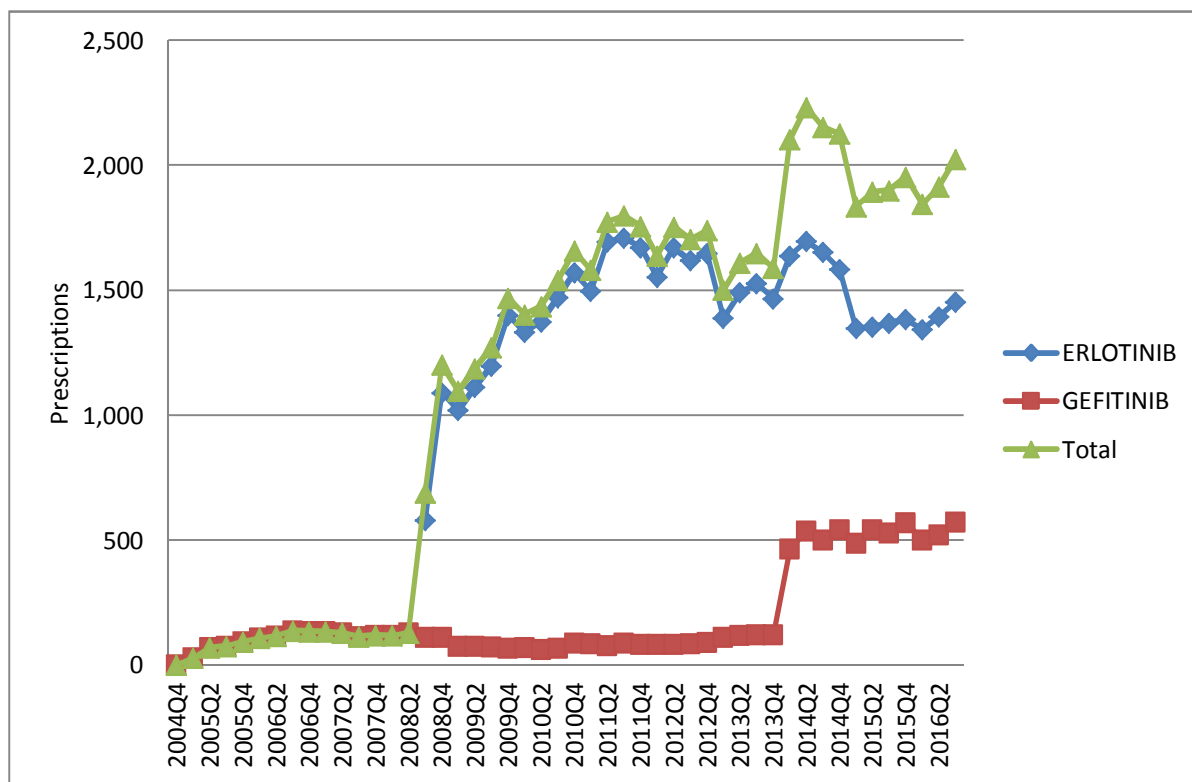


Figure 1: Number of PBS/RPBS erlotinib and gefitinib prescriptions supplied

Prescriptions by date of supply. Source: DHS prescription claims database, accessed November 2016.

Figure 1 shows that there was an increase in the use of gefitinib and erlotinib after the listing was extended to include first-line use on 1 January 2014. The use of erlotinib subsequently declined because the benefits and harms of erlotinib for patients without activating EGFR mutations was under review, and from 1 August 2014 erlotinib was no longer PBS-subsidised for this group (existing patients were able to continue erlotinib until progression).

Gefitinib is available only as a 250 mg tablet whereas erlotinib is available in three strengths. The use of erlotinib by strength is shown in Figure 2.

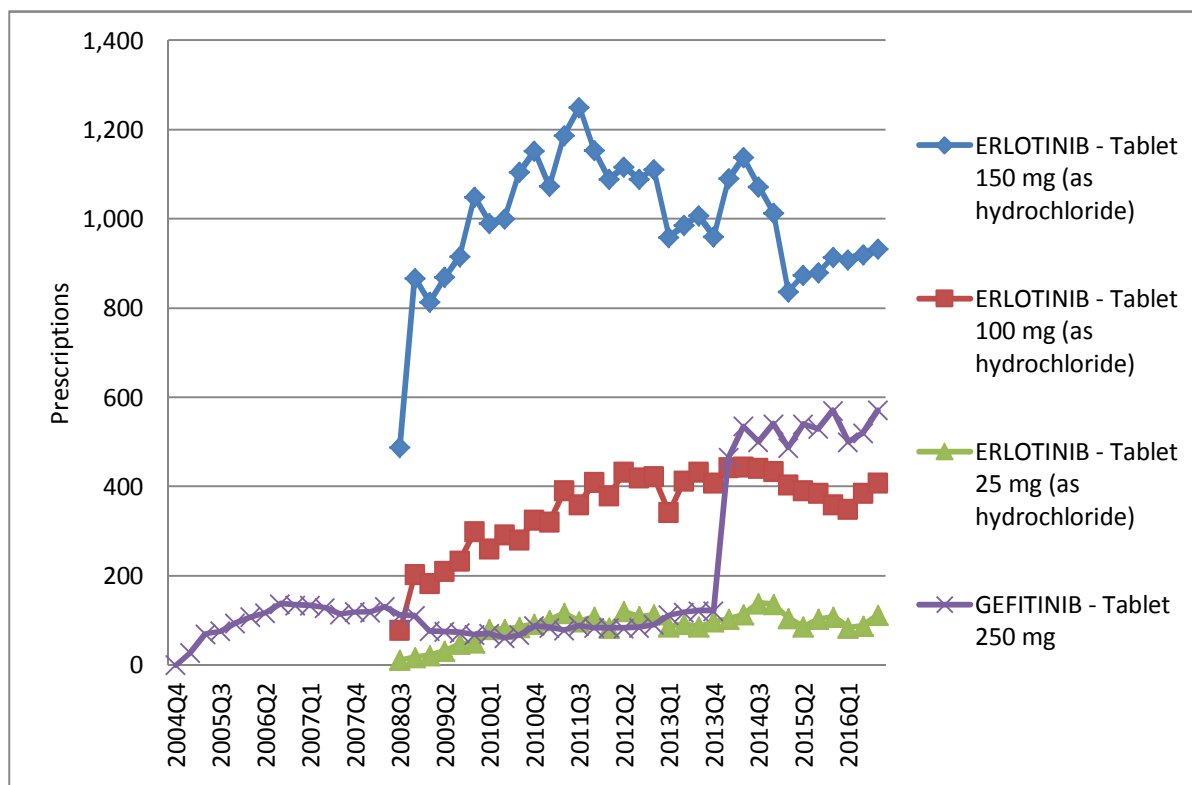


Figure 2: Number of erlotinib and gefitinib prescriptions by strength

Prescriptions by date of supply. Source: DHS prescription claims database, accessed November 2016.

Figure 2 shows that 150 mg is the most commonly supplied strength of erlotinib. Lower doses of erlotinib are used to manage toxicity, for patients using concomitant use of CYP3A4 substrates and modulators, or with hepatic impairment.

It was expected that approximately 89%, 9% and 2% of erlotinib for first-line use would be for the 150 mg, 100 mg and 25 mg strengths, respectively (erlotinib resubmission July 2013). For the second and subsequent line use it was expected that about three quarters of use would be with the 150 mg strength tablet (erlotinib resubmission March 2008).

Patients initiating and prevalent to TKI therapy

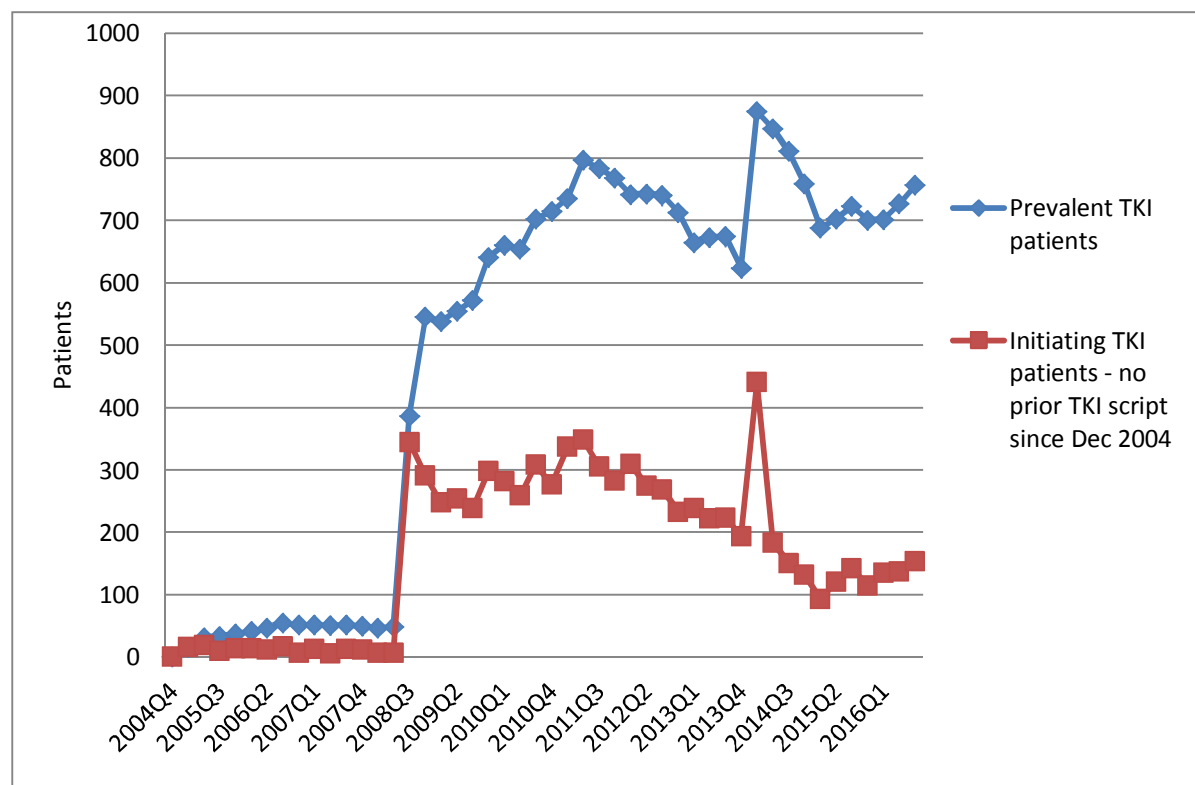


Figure 3: Number of prevalent and initiating patients on TKI therapy

Source: DHS prescription claims database, accessed November 2016.

Figure 3 and Table 4 show that the number of TKI patients peaked in 2011 and was in decline in 2012 and 2013. There was a sharp increase in the number of new patients commencing PBS treatment coinciding with the extension to allow first-line TKI use (1 January 2014).

Table 4: Patients initiating and prevalent to TKI therapy by year

Year	Initiating	Prevalent
2005	59	59
2006	50	79
2007	44	85
2008	650	691
2009	1,039	1,339
2010	1,127	1,527
2011	1,275	1,699
2012	1,087	1,550
2013	880	1,332
2014	908	1,366
2015	472	1,094
2016 (part year to end of Sep)	426	1,020

Source: DHS prescription claims database, accessed November 2016.

Figure 4 presents the market share of erlotinib and gefitinib for incident and prevalent patients.

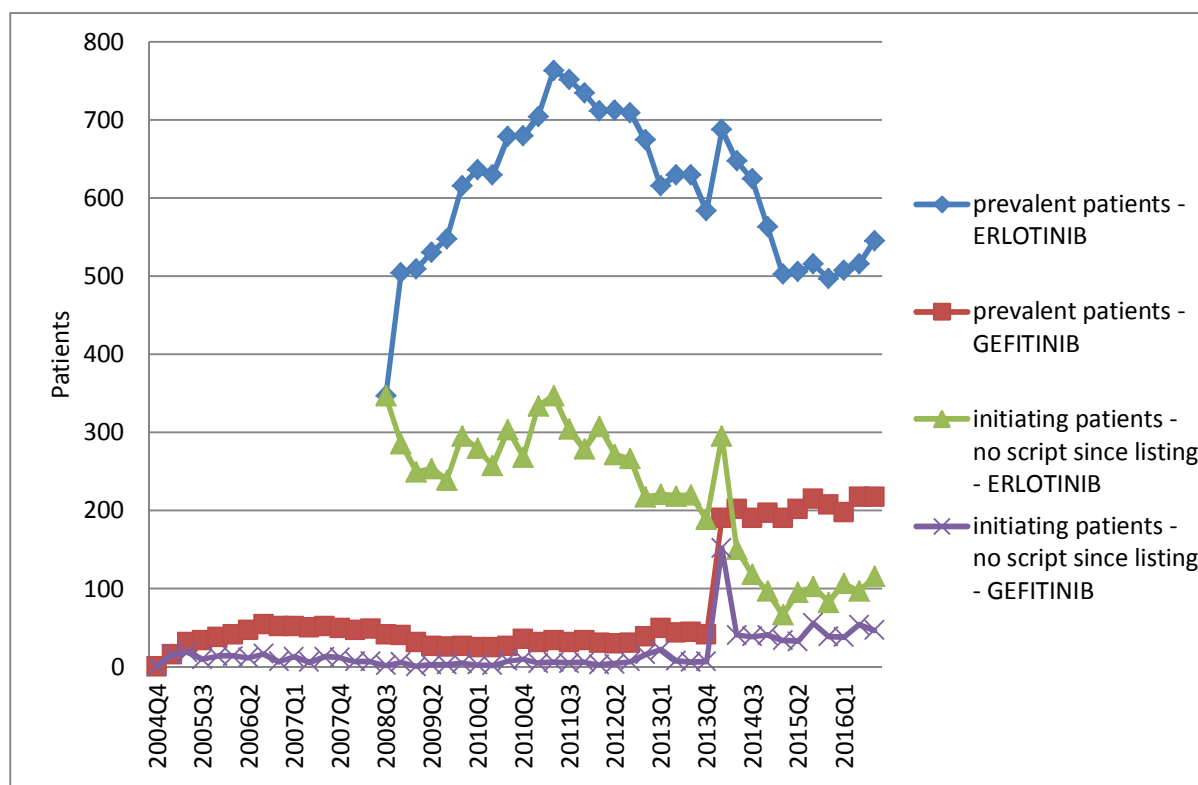


Figure 4: Number of prevalent and initiating patients by TKI drug

Source: DHS prescription claims database, accessed November 2016.

Overall, many more patients have commenced treatment with erlotinib than gefitinib, likely reflecting the broader listing of erlotinib until the end of July 2014 (not limited to mutation positive patients for second and subsequent lines). After the extension of listing to first-line treatment in January 2014, the number of patients commencing both gefitinib and erlotinib increased sharply before stabilising at lower levels.

Use of chemotherapy prior to commencement of a TKI

Figure 5 presents the number of patients commencing a TKI over time according to whether the TKI or chemotherapy was their first treatment. Chemotherapy was classified as any medicine within the ATC classification of L01 (antineoplastics), excluding the TKIs erlotinib and gefitinib.

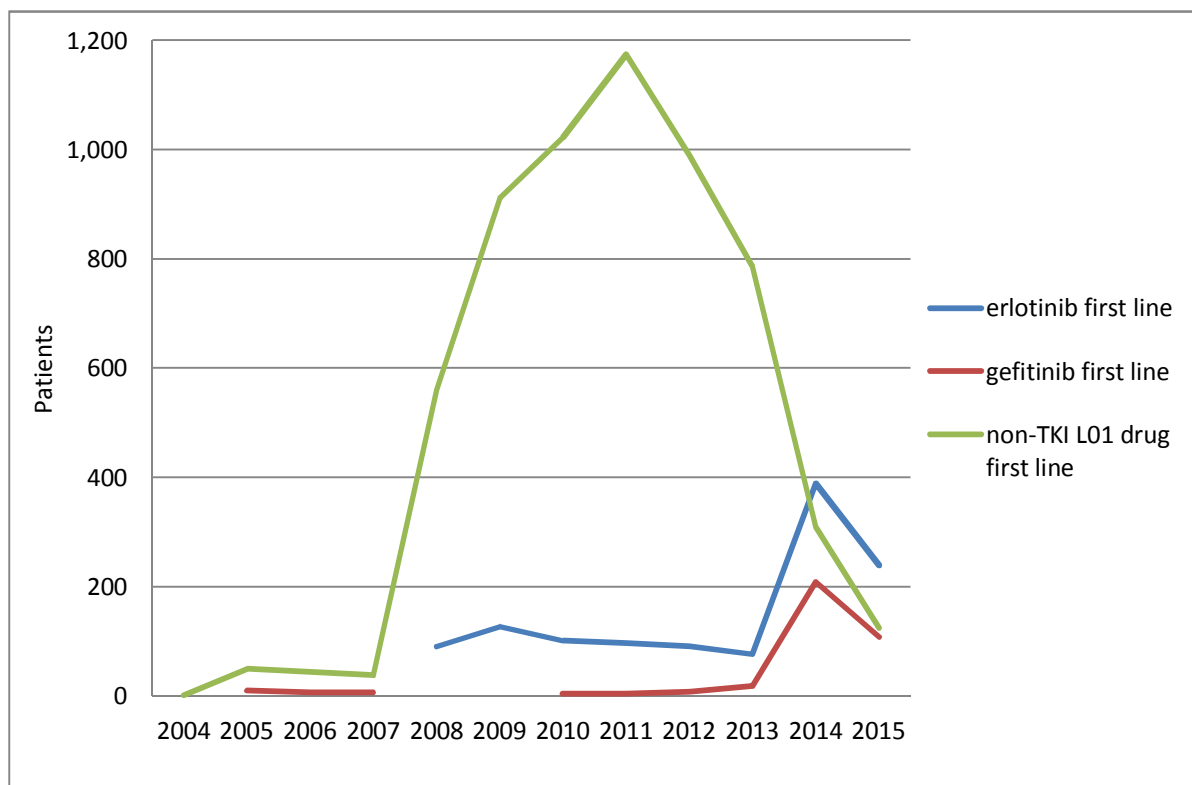


Figure 5: First line therapy for TKI patients by year of initiation to TKI therapy.

Source: DHS prescription claims database, accessed November 2016.

The vast majority of patients were using TKIs after chemotherapy prior to the extension to include first-line use in 2014. There were approximately 100 patients per year initiating erlotinib as first-line therapy prior to the expansion of listing. DUSC had noted in the last review of erlotinib (2011) the potential for use outside of the restriction in earlier lines. The data in Figure 5 indicated that use in first-line was a comparatively small proportion of total use, and was not a rapidly growing trend.

The use of prior chemotherapy is presented in more detail in Table 5.

Table 5: Use of anti-neoplastic agents prior* to initiation of TKI therapy

% Patients	TKI initiation year				
Antineoplastics taken prior to TKI initiation	2011	2012	2013	2014	2015
None	7.8%	9.0%	11.0%	66.1%	73.5%
Platinum doublet (no pemetrexed)					
carboplatin, gemcitabine	23.8%	23.2%	19.0%	5.8%	5.5%
cisplatin, gemcitabine	2.7%	3.8%	5.1%	1.5%	1.5%
carboplatin, paclitaxel	8.9%	8.0%	6.0%	3.0%	4.0%
cisplatin, paclitaxel	0.5%	0.2%	0.5%	0.0%	0.0%
carboplatin, docetaxel	1.3%	1.4%	1.8%	0.1%	0.4%
cisplatin, docetaxel	0.7%	0.6%	0.6%	0.0%	0.0%
carboplatin, vinorelbine	3.7%	2.6%	3.0%	0.9%	1.1%
cisplatin, vinorelbine	3.8%	2.2%	2.6%	3.0%	3.4%
carboplatin, other	0.3%	0.4%	0.2%	0.2%	0.2%
cisplatin, other	1.6%	1.5%	2.2%	1.7%	1.3%
Subtotal	47.3%	43.7%	40.9%	16.2%	17.4%
Platinum doublet (plus pemetrexed)					
carboplatin, gemcitabine	15.6%	20.9%	23.4%	7.7%	2.5%
cisplatin, gemcitabine	2.0%	1.9%	2.6%	0.7%	0.0%
carboplatin, paclitaxel	6.0%	5.7%	6.3%	1.5%	0.2%
cisplatin, paclitaxel	0.0%	0.1%	0.3%	0.0%	0.0%
carboplatin, docetaxel	0.9%	1.3%	0.9%	0.4%	0.2%
cisplatin, docetaxel	0.5%	0.3%	0.2%	0.1%	0.2%
carboplatin, vinorelbine	2.7%	2.8%	3.9%	1.3%	0.0%
cisplatin, vinorelbine	1.5%	1.4%	1.1%	1.0%	0.0%
carboplatin, other	0.0%	0.2%	0.0%	0.1%	0.4%
Subtotal	30.0%	35.2%	39.9%	13.1%	3.6%
Other					
carboplatin only	2.7%	1.0%	0.6%	0.0%	0.6%
cisplatin only	0.9%	0.7%	0.5%	0.3%	0.4%
gemcitabine only	2.0%	1.6%	1.1%	0.4%	0.2%
paclitaxel only	0.2%	0.2%	0.0%	0.0%	0.0%
docetaxel only	0.2%	0.0%	0.1%	0.1%	0.0%
vinorelbine only	0.5%	0.2%	0.6%	0.0%	0.0%
other (no pemetrexed)	2.2%	1.8%	1.1%	3.0%	3.6%
carboplatin, pemetrexed only	2.5%	3.4%	2.0%	0.6%	0.4%
cisplatin, pemetrexed only	0.6%	0.7%	0.6%	0.0%	0.0%
gemcitabine, pemetrexed only	0.9%	0.6%	0.7%	0.1%	0.2%
paclitaxel, pemetrexed only	0.1%	0.2%	0.0%	0.0%	0.0%
docetaxel, pemetrexed only	0.2%	0.1%	0.1%	0.0%	0.0%
vinorelbine, pemetrexed only	0.0%	0.3%	0.2%	0.0%	0.0%
pemetrexed only	1.1%	0.8%	0.5%	0.0%	0.0%
other (plus pemetrexed)	0.5%	0.4%	0.1%	0.1%	0.0%
Subtotal	14.8%	12.1%	8.2%	4.6%	5.5%
Total	100%	100%	100%	100%	100%
Patient count	1,275	1,087	880	908	472

*The analysis does not attempt to distinguish multiple lines of chemotherapy prior to initiation of the TKI.

Source: DHS prescription claims database, accessed November 2016.

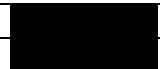
Note: The platinum doublets are constructed using the following rules:

- if more than one platinum (i.e. cisplatin and carboplatin) was supplied, then the doublet therapy is assigned according to the first platinum supplied.
- if more than one of gemcitabine, paclitaxel, docetaxel and vinorelbine was supplied, then the partner in the doublet is based on the first of the four drug supplied.
- if the partner in the doublet is 'other', this means any other antineoplastic drug (i.e. ATC = L01). There may be more than one 'other' drug.

Analysis of predicted versus actual utilisation

This analysis compares the predicted and actual use of gefitinib and erlotinib for first-line treatment of advanced or metastatic NSCLC for patients with activating EGFR gene mutation.

Table 6: Predicted versus actual comparison of first-line TKI patients

	Incident TKI patients (total)	Incident TKI patients (first-line)*	Incident TKI patients (second or subsequent line)
Actual			
Year 1 (2014)	908	598	310
Year 2 (2015)	472	347	125
Predicted			
Erlotinib submission			
			
Gefitinib submission			
Year 1 (2014)	NA	707	NA
Year 2 (2015)	NA	726	NA

*no prior chemotherapy medicines (ATC L01 –antineoplastics)

NA – not applicable for a comparison of first-line predicted and actual use.

Following the extension to listing, the number of first-line patients was similar to predicted in the first year but substantially lower in the second year.

The estimated median length of treatment for TKI first-line patients is presented in Table 7. The proportion of patients on either erlotinib or gefitinib, and patients switching between TKIs is presented separately.

The estimated median length of treatment in Table 7 is estimated using the Kaplan Meier (aka Product-Limit) method (see Methods section for details). The average follow-up period of patients in year 1 is greater than year 2, but this method is designed to allow for varying lengths of follow-up. The percentage of patients deemed to be continuing on treatment at the end of the period (i.e. censored) was 19.6% for the year 1 cohort and 47.0% for the year 2 cohort.

Table 7: Estimated median length of TKI treatment (excluding breaks) in months

	Initiating first-line cohorts		
	Year 1 (2014)	2014 minus first 2 months [^]	Year 2 (2015)
Patients treated with erlotinib only*	10.7 (n=375)	10.4 (n=224)	13.3 (n=224)
Patients treated with gefitinib only	10.3 (n=194)	10.2 (n=88)	10.2 (n=103)
Patients that switched between erlotinib and gefitinib or vice versa	12.3 (n=29)	18.9 (n=17)	7.7 (n=20)
All Patients on any TKI therapy	10.8 (n=598)	10.8 (n=329)	11.0 (n=347)

*irrespective of strength

[^] the year 1 cohort was assessed including and excluding the patients commencing PBS therapy in the first two months of listing to assess any difference in durations for patients that may have been grandfathered. Follow-up data available until the end of September 2016 (based on date of supply)

The erlotinib

The gefitinib submission assumed ten prescriptions per first-line patient based on the median PFS in IPASS trial. The median length on TKI treatment for first-line use has been similar to that predicted.

The number of patients switching between TKI drugs is low. Only 4.8% (n=29) and 5.8% (n=20) of patients in the year 1 and 2 cohorts, respectively, switched between TKIs. Although the median time on treatment in this group of patients appears to differ from the duration of use in patients using only erlotinib or gefitinib, this may be due to the small number of patients in the analysis.

A concern raised by DUSC and the PBAC was the potential for the TKIs to be used beyond progression or in combination with chemotherapy. An analysis examined patterns of treatment with a first-line TKI, followed by chemotherapy (indicating progression) and then subsequent TKI use. Of the 598 year 1 cohort patients that initiated first-line therapy on erlotinib or gefitinib, there were 44 (i.e. 7.4%) that had one or more supplies of chemotherapy (i.e. any non-TKI L01 prescription) between supplies of TKI prescriptions.

A further area of uncertainty raised by DUSC was the prevalence of NSCLC patients harbouring EGFR mutations. In 2015-16 there were 2,959 services for MBS item 73337⁸ and 530 new patients initiating erlotinib or gefitinib through the PBS. This indicates the prevalence of activating EGFR mutations in the tested and treated population is 17.9%, which is similar to the predicted estimate of 15%.⁹

⁸ A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

⁹ Based on MSAC advice.

DUSC consideration

DUSC noted that:

- The number of patients initiating erlotinib or gefitinib was similar to predicted in Year 1 and lower than expected in the Year 2 after the restriction extension on 1 January 2014 to include first-line patients.
- There were access programs prior to the change in listing on 1 January 2014, therefore higher “initial” use in 2014 was likely due to grandfathering arrangements. Median length on TKI treatment for first-line use was similar to predicted from data available to date.
- Observed prevalence of EGFR mutations (17.9%) was similar to predicted (15%).
- 7.4% of patients initiating TKI therapy in 2014 had supplies of chemotherapy between supplies of TKI indicating use beyond progression or in combination with chemotherapy. A Sponsor considered that the usage of TKIs beyond progression of disease is likely to have decreased since the report analysis was conducted because immunotherapies have become available (through trials and access programs) for previously treated NSCLC. DUSC noted that immunotherapies are not currently indicated for first line treatment of locally advanced or metastatic NSCLC in patients with tumour EGFR gene mutations but nivolumab may be used after progression on or after targeted therapy.

DUSC Actions

Refer the report, Sponsor responses and DUSC minutes to the PBAC.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

AstraZeneca Pty Ltd (Gefitinib): The sponsor has no comment.

Roche Products Pty Ltd (Erlotinib): The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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Appendix A: Listing History on PBS

Date	Medicine and PBS item codes	Listing, amendment or extension to listing (abridged).
1 Dec 2004	Gefitinib tablets (Iressa [®]) 250mg (8769M) Max Qty: 30 Max repeats: 1	Listed as monotherapy for patients with - locally advanced or metastatic NSCLC where: - disease progression has occurred following treatment with at least one chemotherapy agent; and - there is evidence that the patient has an activating mutation(s) of the EGFR receptor gene in tumour material. The mutation(s) must be demonstrated by analysis of the DNA sequence of the EGFR gene. - WHO performance status of 2 or less The Authority Required application was required to be made in writing until 1 July 2012, after which it was telephone approval.
1 August 2008	Erlotinib tablets (Tarceva [®]) 25 mg (9166K), 100 mg (9167L), 150 mg (9168M) Max Qty: 30 Max repeats:3	Listed* as monotherapy for patients with - locally advanced or metastatic (stage IIIB or IV) NSCLC after prior treatment with platinum-based chemotherapy, where: - disease progression occurred following treatment with docetaxel or pemetrexed; or - treatment with docetaxel or pemetrexed is either contraindicated or cannot be tolerated; and - Further cytotoxic chemotherapy is not appropriate and WHO performance status of 3 or less Written authority required
1 March 2010	Gefitinib	Removal of the criterion; The mutation(s) must be demonstrated by analysis of the DNA sequence of the EGFR gene. This change was recommended at the November 2009 PBAC meeting due to the availability of alternative methods (e.g. PCR-based targeted assays)
1 Jan 2014	Gefitinib	Expansion of listing to first line therapy i.e. removal of the criterion “where disease progression has occurred following treatment with at least 1 chemotherapy agent” Addition of the criteria; - 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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal. - The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC.

1 Jan 2014	Erlotinib 6 new items added, 25 mg (10022L,10028T), 100 mg (10014C,10025P), and 150 mg (10019H,10020J). The previous 3 items (9166K, 9167L, 9168M) continued until 1 August 2014	The same three criteria changes as for gefitinib (above), plus addition of the criteria; - Population criteria: Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors in tumour material. - Patient must have a WHO performance status of 2 or less. Written authority no longer required The items 10019H, 10025P, 10028T are continuing treatment items for grandfathered patients. That is, a patient must have previously been issued with an authority prescription for this drug prior to 1 January 2014. This allowed EGFR wild type patients or patients with unknown EGFR status and who started erlotinib prior to 1 January 2014 to receive continuing treatment. The restriction for items 9166K, 9167L and 9168M also changed on 1 January 2014 from having no reference to EGFR status to having the population criteria. - Patient must have a wild type epidermal growth factor receptor (EGFR) gene; OR Patient must have an epidermal growth factor receptor (EGFR) gene of unknown type. This change effectively removed assess to these items for EGFR positive patients. These patients would use the new items 10022L, 10014C and 10019H.
1 August 2014	Erlotinib Only the 3 continuing treatment items (10019H, 10025P, 10028T) had the following restriction change.	Addition of the criteria; - Patient must have previously been issued with an authority prescription for this drug prior to 1 August 2014 This was an extension of the grandfathering period cut-off date to 1 August 2014.

*There was also a grandfather restriction for patients who had accessed erlotinib through the access program prior to 1 August 2008.