Proposal for the inclusion of the EGFR tyrosine kinase inhibitors gefitinib, erlotinib, afatinib in the WHO Model list of ESSENTIAL MEDICINES for the treatment of EGFR mutation positive Non-Small Cell Lung Cancer.

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1. Name of the focal point in WHO submitting or supporting the application
N/A

2. Name of the organization(s) consulted and/or supporting the application
Asian Clinical Oncology Society (Name will be changed to Asian Oncology Society).

3. International Nonproprietary Name (INN, generic name) of the medicine
3.1 Gefitinib
3.2 Erlotinib
3.1 Afatinib

Three medicines belong to the class of medicines representing epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).

4. Formulation proposed for inclusion; including adult and pediatric (if appropriate)
4.1 Gefitinib (trade name Iressa and approved generics) is available in 250 mg capsules and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of gefitinib for the treatment of non-small cell lung cancer (NSCLC) is 250 mg per day.
4.2 Erlotinib (trade name Tarceva and approved generics) available in 100 mg and 150 mg capsules and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of erlotinib for the treatment of NSCLC is 150 mg per day.
4.3 Afatinib (trade name Giotrif and approved generics) available in 20 mg, 40 mg and 50 mg capsules, and is prescribed for daily use for as long as the drug continues to be effective and tolerated. The typical dose of afatinib for the treatment of NSCLC is 40 mg per day.

5. International availability - sources, if possible manufacturers and trade names
5.1 Gefitinib (Iressa) approved by the U.S. Food and Drug Administration (FDA) for first-line treatment of advanced EGFR mutation-positive NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by a FDA-approved test (13 July 2015); the European Commission has granted marketing authorisation for gefitinib for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR across all lines of therapy (1 July 2009): many countries in Asia including Japan, Korea, Taiwan, China, India and Thailand approved gefitinib since 2003 as second or third line after chemotherapy. Later on the drug was approved as first line. India had several generic versions of gefitinib available.
5.2 Erlotinib (Tarceva) received regular approval as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen November 18, 2004, regardless EGFR mutational status. After approval as maintenance.
October 18, 2016, the FDA modified the indication for erlotinib for treatment of NSCLC by limiting its use to patients whose tumors have specific \textit{EGFR} mutations. The labeling change applies to patients with NSCLC receiving maintenance or second or later line of treatment. These indications will be limited to those patients whose tumors have \textit{EGFR} exon 19 deletions or exon 21 L858R substitution mutations as detected by a FDA-approved test. The first-line indication previously was limited to patients with \textit{EGFR} exon 19 deletions or exon 21 substitution mutations. Many countries in Asia including Japan, Korea, Taiwan, China, India and Thailand approved the drug erlotinib since 2004 as second or third line. Later on, the drug was also approved as first line.

5.3 Afatinib (Giotrif) FDA was initially approved in 2013 for the treatment of patients with metastatic NSCLC whose tumors have \textit{EGFR} exon 19 deletions or exon 21 (L858R) substitution mutations as detected by a FDA-approved test and in 2016 for metastatic, squamous NSCLC progressing after platinum-based chemotherapy (histology- oriented indication regardless \textit{EGFR} mutational status). January 12, 2018, the FDA broadened the indication to first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant \textit{EGFR} mutations as detected by a FDA-approved test. Afatinib is approved in several markets, including the EU, Japan, Taiwan and Canada under the brand name Giotrif, in the US under the brand name Giotrif and in India under the brand name Xovoltib for patients with distinct types of \textit{EGFR} mutation-positive NSCLC.

6. Whether listing is requested as an individual medicine or as an example of a therapeutic group?
Therapeutic group.

Treatment details (requirements for diagnosis, treatment and monitoring)
In the US 15% patients with NSCLC have mutations in \textit{EGFR-TK}. This occurs more frequently in non-smokers. In Asian populations the incidence of \textit{EGFR} mutation is higher, namely up to 62% (Prospective molecular epidemiology study of RGFR mutations in Asian patients with advanced NSCLC of adenocarcinoma histology (PIONEER)\textsuperscript{1}. Although \textit{EGFR} mutations are more common in non-smokers, the incidence in smokers is still 37%. Presence of \textit{EGFR} mutation confers a favorable prognosis and strongly predicts for sensitivity to 

EGFR-TKIs. Whenever feasible patients with advanced NSCLC which contains even an element of adenocarcinoma should have their tumor assessed for \textit{EGFR} mutation regardless of clinical characteristics of patient. Mutation analysis is also performed in patients with squamous cell lung cancer who are light or never smokers. The mutation analysis is performed on the primary tumor or metastatic disease by polymerase chain reaction (PCR). Liquid biopsies from blood by circulating tumor (ct) DNA analysis can also be performed however these are not readily available in low-middle income countries. Specific activating mutations include exon 19 deletions, L858R-point mutation in exon 21. First line therapy EGFR-TKIs are recommended in patients with advanced NSCLC with the above-mentioned driver mutation. If however, the patient is unstable before the mutational analysis is available chemotherapy can be started. Chemotherapy is continued for 4 cycles as long as therapy is tolerated and there is no evidence of disease progression. Treatment plan should be reassessed. There are no clinical trials directly addressing the optimal approach when a driver mutation is identifies after chemotherapy is started.

While on treatment, the patients require clinical monitoring to assess the safety and activity profile; however, the need to perform laboratory biochemical and hematologic test is generally more limited than chemotherapy, where a closer hematological biochemical monitoring is required, to assess the
eligibility to receive the cytotoxic agents for the higher rates of hematological toxicity i.e. anemia, neutropenia, thrombocytopenia. The disease monitoring does not differ from the chemotherapy standard for cancer treatment response assessment and is based on the RECIST 1.1 criteria.

The schedules recommended per guidelines and tested in the approval clinical trials are the following ones:
- Erlotinib 150 mg daily in a single administration, to be taken 30 minutes before one of the principal meals or 2 hours after it;
- Gefitinib 250 mg daily;
- Afatinib 40 mg daily, to be taken without food.

Patients receive the treatment on daily basis up to disease progression or unacceptable toxicity, where no safety signals require to withdrawn.

The three EGFR-TKIs are approved and recommended for the treatment of EGFR mutated NSCLC for the frontline treatment of advanced and not resectable disease and metastatic cancer or after the failure of frontline chemotherapy, as a second line treatment.

The identification of actionable mutations of EGFR in NSCLC requires a molecular pathology capacity of pathology laboratories, as it is performed by PCR, to be performed on histology (surgical specimen e.g. surgical biopsy or tru-cut biopsy) or cytology (fine-needle aspiration) specimen. EGFR mutation assays have evolved from a single-gene test (Sanger DNA sequencing) to multiplex hotspot mutation tests (eg, PCR-based) to next-generation sequencing (NGS). All EGFR mutation assays can be performed on fresh, frozen, formalin-fixed paraffin-embedded (FFPE), or alcohol-fixed tissue samples, including surgical resection specimens or various cytological preparations (samples from fine-needle aspiration or smears).

EGFR testing is recommended for adenocarcinomas and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade. In the setting of more limited lung cancer specimens (i.e., biopsies or cytology) where an adenocarcinoma component cannot be completely excluded, EGFR testing may be performed in cases showing squamous or small cell histology but clinical criteria (e.g., young age and lack of smoking history) may be useful in selecting a subset of these samples for testing. The test can be performed on specimen from the primitive tumor or a metastatic site.

The schedules and the indications for use are recommended as reported by the ESMO clinical guidelines for the management of NSCLC EGFR mutated, NCCN NSCLC guidelines, American College of Chest Physicians (ACCP) guidelines.

**Health system impact:** the prescription and monitoring of EGFR-TKI treatment requires a specialized physician, namely a medical oncologist. EGFR-TKI monitoring requires clinical and laboratory analysis for the assessment and early detection of tolerance and toxicity. The recommendation of EGFR-TKI is restricted to NSCLC harboring an EGFR sensitive mutation, stating the need to access quality and timely diagnostic facility (e.g. molecular pathology service) for the molecular assay (polymerase-chain reaction) and a trained pathologist in molecular diagnostics. In term of costs of the medicines, the availability of generics has increased the accessibility and affordability, ensuring more value for money and offering a reliable strategy for the patients’ financial risk protection.

7. **Information supporting the public health relevance.**
Lung cancer is the most diagnosed and the first cause of death due to cancer in the world, with estimated 2 million new cases and 1.7 related deaths in 2018, according to GCO 2018 (IARC). Lung cancer is a highly lethal malignancy, with an economic impact estimated around $8 billion productivity lost in the BRICS countries, according to the estimates provided by IARC in 2018\(^5\). Moreover, in the absence of a wide coverage effective screening program in place on global scale, lung cancer diagnoses occur in advanced stage (III and IV, TNM \(^7\)) in more than 60% of cases, with highly regional variability\(^6,7\). The mutational pattern of NSCLC varies across the different regions, with a higher prevalence in Asia-Pacific (up to 76% of patients) and the lowest registered in Oceania (12%). Interestingly, Africa, Europe and North America registered the same rate of \(EGFR\) mutated NSCLC, around 20%\(^8-10\).

Non-squamous NSCLC has been linked to gene mutations in \(EGFR\). This disease, given its incidence, comprises a high burden and leads to a high dead rate. However, with the advanced in cancer gene directed treatment, the outcome of the disease has improved. The response rate doubled as compared to chemotherapy, the progression free survival (PFS) doubled and the median survival time increased to nearly 3 years if patient received both the targeted medicines and chemotherapy together (the median survival time for patient receiving chemotherapy only is \(~10\) months, in the historical series).

8. **\(EGFR\)-TKIs gefitinib, erlotinib and afatinib for non-squamous NSCLC**

The three \(EGFR\)-TKIs are classified in first and second generation \(EGFR\)-TKI, according to the pharmacodynamic profile. In particular, first generation \(EGFR\)-TKIs (erlotinib, gefitinib) are reversible inhibitors and second generations (afatinib) work as irreversible inhibitors. However, these pharmacodynamic differences failed to show a meaningful clinical difference in a head-to-head comparison clinical trial\(^11\), concluding that the three drugs provide the same magnitude of benefit, with no relevant differences.

The three medicines all have demonstrated benefit with regards to increased efficacy, safety and quality of life (QoL) and prolonged survival in patients who have \(EGFR\) mutation. These medicines used worldwide, are even more important in Asia where NSCLCs have a high incidence of \(EGFR\) mutation (more than 50%)\(^12-15\).

\(EGFR\) testing may be done in all countries using DNA sequencing; though the sensitivity may be less compared to the commercial diagnostic kit; however, the specificity is high.

**Selected cases of squamous NSCLC and small cell lung carcinoma.**

The use of \(EGFR\)-TKIs is contemplated also in the context of mixed histology NSCLC or when an adenocarcinoma component cannot be ruled our (poor histology or cytology specimen) and in special clinical scenarios e.g. diagnosis of small cell lung carcinoma (SCLC) or squamous NSCLC in young age and lack of smoking history.

9. **Treatment details**

All three medicines were evaluated in:
- First line in NSCLC with \(EGFR\) mutation.
- Second/ third line NSCLC previously receiving chemotherapy.

However, the current proposal recommends the EML listing mostly for first-line treatment.

The addition of \(EGFR\)-TKI to chemotherapy is not approved for the use in clinical setting and is not endorsed by clinical guidelines as data are not conclusive (IMPRESS Trial).
10. Summary of comparative effectiveness in a variety of clinical settings:

10.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data).

Treatment of EGFR-mutated NSCLC partly as described in the ESMO NSCLC Guideline, 2018.

First-line treatment. EGFR mutation is the best established, oncogenic target for management of advanced stage NSCLC. The predictive power of EGFR mutation is confirmed in multiple randomized phase 3 studies comparing first- (gefitinib or erlotinib i.e. reversible inhibitors) or second-generation (afatinib i.e. irreversible inhibitors) EGFR-TKIs with standard platinum-based chemotherapy. The improvement in response rate (ORR) and PFS is consistent across all age groups, genders, smoking status and performance status (PS). Notably, none of the above studies have shown any benefit in OS for an EGFR-TKI over platinum-based chemotherapy, likely due to the high level of crossover. EGFR-TKIs represent the standard of care as first-line treatment for advanced EGFR-mutated NSCLC. Patients with PS 3–4 may also be offered an EGFR-TKI as they are likely to receive a similar clinical benefit as patients with good PS. Patients who have benefited from EGFR-TKI treatment may continue to receive the same therapy beyond initial radiological progression as long as they are clinically stable. The choice between first- and second-generation EGFR-TKIs was investigated in two randomized studies. The LUX-Lung 7 randomized phase 2B study compared afatinib with gefitinib. The study reported similar tumor ORR and a modest nonclinically meaningful difference in PFS (mPFS 11.0 vs 10.9 months; HR 0.73, 95% CI 0.57–0.95, p = .0165). The other co-primary endpoint for this study was OS, which was not statistically different. More specifically, there was no difference in OS in patients with EGFR exon 19 mutation, which is contrary to the earlier claim of benefit in this subgroup from the pooled analysis of LUX-Lung 3 and LUX-Lung 6 studies.

ARCHER 1050 is a randomized phase 3 study that compared dacomitinib with gefitinib in stage IV EGFR-mutated lung cancer patients without CNS metastasis. The study showed an improved PFS in the dacomitinib arm (mPFS 14.7 vs 9.2 months; HR 0.59, 95% CI 0.47–0.74, p < .0001). The mOS was 34.1 months with dacomitinib vs 26.8 months with gefitinib (HR 0.76, 95% CI 0.58–0.993, p < .04). The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively.
Erlotinib, gefitinib and afatinib are recommended as first-line therapy in patients with advanced NSCLC who have active sensitizing EGFR mutations, regardless of their performance status. Dacomitinib will be added to the list when the drug is approved by regulatory agencies, the United States FDA and the EMA [not EMA approved]. There is no consensus preferring any of the three currently available first-line EGFR-TKIs over others and the choice is generally related to the safety profile, according to the patients’ comorbidities.

The outcomes of First-SIGNAL, NEJ002 and WJTOG3405 trials in NSCLC patients carrying positive EGFR mutation through comparing gefitinib with doublet chemotherapy as first-line therapy, all showed longer PFS translating in no apparent OS gain; however, it is largely recognized a confounding effect of the high cross-over rates from chemotherapy to EGFR-TKI arm, resulting in a dilution of the net benefit, explaining the failure to achieve a statistically different OS. For instance, the crossover rates from chemotherapy to afatinib in LUX-Lung 3 (74%) and LUX-Lung 6 (54%) were generally similar to the crossover rates in the erlotinib and gefitinib trials (74% on average) and generally more than 50%. Moreover, the use of EGFR-TKI frontline showed a wider benefit gain than in second line, after chemotherapy in term of PFS (9.0 months, 95% CI, 7.7–10.2, HR: 0.78, p = .034), ORR (67.8% (159/233) and 55.6% (94/169), p = .001). and OS (HR: 0.69, p = .02).

Osimertinib is a third-generation EGFR-TKI that targets both sensitizing EGFR mutation and the resistant exon 20 T790M mutation. The drug was compared with gefitinib or erlotinib in the FLAURA phase 3 study. Improvement in PFS was observed (mPFS 18.9 versus 10.2 months; HR 0.46, 95% CI 0.37–0.57, p < .0001). More importantly, a similar degree of improvement was observed in the subgroup of patients with CNS metastasis (mPFS 15.2 vs 9.6 months; HR 0.47, 95% CI 0.30–0.74, p < .0009). OS data were immature. First-line osimertinib is now considered one of the options for NSCLC patients with sensitizing EGFR mutations, regardless T790M exon 20 resistance mutation, which is rare in EGFR-TKI naïve EGFR mutated NSCLC and is acquired in around a half of the patients receiving a first or second generation EGFR-TKI frontline.

The combination of chemotherapy with gefitinib, at progression with gefitinib, has not shown any clinical benefit (IMPRESS Trial). The NEJ009 trial evaluated the efficacy of a combination of gefitinib and carboplatin/pemetrexed in untreated advanced NSCLC patients with EGFR mutations. Carboplatin/pemetrexed/gefitinib demonstrated better PFS (mPFS: 20.9 vs 11.2 months, HR 0.49, 95% CI 0.39–0.62) and OS (mOS: 52.2 vs 38.8 months, HR 0.69, 95% CI 0.52–0.92) compared with gefitinib, in advanced EGFR mutated NSCLC, representing a first-line therapy option [not EMA-approved].

Gefitinib, erlotinib and afatinib are all scored 4 per MCBS v1.1 for the indication of frontline use in EGFR mutated NSCLC, supporting them as priority medicines in the effectiveness-safety assessment. Toxicity profile is generally clinically manageable, with 6% of toxicity-related treatment discontinuation, in one pooled analysis. Importantly, the use of EGFR-TKI favored EGFR-TKI over chemotherapy in the QoL analysis, reporting a longer time to clinical deterioration and maintained overall QoL. For afatinib, an extensive investigation of patient-reported symptoms and health-related QoL benefits have been provided, showing that afatinib delayed the time to deterioration for cough (HR, 0.60; 95% CI, 0.41 to 0.87; p = .007) and
dyspnea (HR, 0.68; 95% CI, 0.50 to 0.93; \( p = .015 \)), with more patients on afatinib (64%) versus chemotherapy (50%) experienced improvements in dyspnea scores (\( p = .010 \)), the cardinal symptom for lung cancer patients\(^{46}\). For erlotinib, a secondary analysis from OPTIMAL (CTONG-0802) phase 3 clinical trial, showed that patients receiving erlotinib experienced clinically relevant improvements in QoL compared with the chemotherapy group, across different scales to assess general outcome (FACT-L, TOI) and lung specific subscales\(^{47}\). Data for gefitinib are still consistent with the findings for the other two EGFR-TKIs: time to deterioration in physical and life well-being favored gefitinib over chemotherapy (HR of time to deterioration, 0.34; 95% CI, 0.23-0.50; \( p < .0001 \) and HR, 0.43; 95% CI, 0.28-0.65; \( p < .0001 \), respectively)\(^{43}\).

**Beyond first-line treatment**

Almost all patients who benefit from EGFR-TKIs will eventually develop clinical resistance. About half of the resistance is explained by the acquired *EGFR* exon 20 T790M mutations\(^{48}\).

**Osimertinib** and several other third generation EGFR-TKIs were developed targeting the T790M mutation. To date, the only approved medication for patients with T790M mutation is osimertinib. The randomized phase 3 AURA3 study compared osimertinib with pemetrexed/platinum in patients with proven T790M mutation at time of progression on first-/second-generation EGFR-TKI\(^{49}\). Tumor ORR was 71% and 31%, respectively (HR 5.39, 95% CI 3.46–8.48, \( p < .001 \)). The primary endpoint of PFS was also different (mPFS 10.2 vs 4.4 months; HR 0.30, 95% CI 0.23–0.41, \( p < .0001 \)). Osimertinib also showed a longer CNS PFS (11.7 months) and higher CNS ORR (70%, 95% CI 51–85) compared with chemotherapy (CNS PFS 5.6 months, CNS ORR 31%, 95% CI 11–59) in patients with CNS metastases at baseline\(^{50}\). The probability of experiencing a CNS progression event was lower for osimertinib than for chemotherapy at both 3 months (2.7% vs 8.2%, respectively) and 6 months (11.5% vs 28.2%, respectively).

This study has established a new paradigm: all patients with clinical resistance to first-/second-generation EGFR-TKIs should be tested for the presence of *T790M* mutation and osimertinib should be offered as standard treatment for patients who test positive\(^{51}\).
Table 1. This table shows the ESMO-MCBS scores for these medicines in NSCLC. Scores ≥4 is substantial. (mut=mutation)

<table>
<thead>
<tr>
<th>Tested Agent</th>
<th>Control arm</th>
<th>Treatment setting</th>
<th>Primary outcome</th>
<th>PFS Control</th>
<th>PFS Gain</th>
<th>PFS HR (95% CI)</th>
<th>OS Control</th>
<th>OS Gain</th>
<th>OS HR (95% CI)</th>
<th>QoL</th>
<th>Toxicity</th>
<th>ESMO-MCBS v1.1</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Carboplatin gemcitabine</td>
<td>1st line stage III or IV non-squamous, with EGFR mut</td>
<td>PFS</td>
<td>4.6 months</td>
<td>8.5 months</td>
<td>0.16 (0.10-0.26)</td>
<td></td>
<td></td>
<td></td>
<td>12% &lt; serious adverse events</td>
<td>4</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Platinum-based chemotherapy doublet</td>
<td>1st line stage III or IV non-squamous, with EGFR mut</td>
<td>PFS (crossover allowed)</td>
<td>5.2 months</td>
<td>4.5 months</td>
<td>0.37 (0.25-0.54)</td>
<td>19.35 months</td>
<td>NS</td>
<td>15% &lt; severe adverse reactions</td>
<td>4</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Placebo</td>
<td>Stage III or IV disease maintenance after responding to 4-6 cycles platinum doublet</td>
<td>PFS</td>
<td>11.1 weeks</td>
<td>1.2 weeks</td>
<td>0.71 (0.62-0.82)</td>
<td>11.0 months</td>
<td>1.0 month</td>
<td>0.81 (0.70-0.95)</td>
<td>1</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Carboplatin + paclitaxel</td>
<td>1st line stage III or IV adenocarcinoma with EGFR mutation</td>
<td>PFS (crossover allowed)</td>
<td>6.3 months</td>
<td>3.3 months</td>
<td>0.48 (0.34-0.67)</td>
<td></td>
<td>Improved</td>
<td>Reduced toxicity</td>
<td>4</td>
<td>19, 54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afatinib</td>
<td>Cisplatin + pemetrexed</td>
<td>1st line stage III/IV adenocarcinoma + EGFR mut</td>
<td>PFS (crossover allowed)</td>
<td>6.9 months</td>
<td>4.2 months</td>
<td>0.58 (0.43-0.78)</td>
<td></td>
<td>Improved</td>
<td></td>
<td>4</td>
<td>23, 46</td>
<td></td>
<td></td>
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<tr>
<td>Afatinib</td>
<td>Cisplatin + pemetrexed</td>
<td>1st line stage III or IV adenocarcinoma with EGFR mutation (Del19/L858R)</td>
<td>PFS</td>
<td>6.9 months</td>
<td>6.7 months</td>
<td>0.47 (0.34-0.65)</td>
<td></td>
<td>Improved</td>
<td></td>
<td>4</td>
<td>23, 46</td>
<td></td>
<td></td>
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<tr>
<td>Afatinib</td>
<td>Erlotinib</td>
<td>Squamous cell NSCLC who progressed on platinum-based doublet chemotherapy</td>
<td>OS</td>
<td>6.8 months</td>
<td>1.1 month</td>
<td>0.81 (0.69-0.95)</td>
<td></td>
<td>Improved</td>
<td></td>
<td>2</td>
<td>11</td>
<td></td>
<td></td>
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<tr>
<td>Osimertinib</td>
<td>Platinum / pemetrexed</td>
<td>2nd line for EGFR mut NSCLC after TKI with new T790M mut</td>
<td>PFS (crossover allowed)</td>
<td>4.4 months</td>
<td>5.7 months</td>
<td>0.30 (0.23-0.41)</td>
<td></td>
<td>Reduced toxicity</td>
<td></td>
<td>4</td>
<td>49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osimertinib</td>
<td>Gefitinib or erlotinib</td>
<td>1st line stage IIIb or IV non-squamous, with EGFR mut</td>
<td>PFS</td>
<td>10.2 months</td>
<td>8.7 months</td>
<td>0.46 (0.37-0.57)</td>
<td></td>
<td></td>
<td>Reduced</td>
<td>4</td>
<td>38</td>
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11. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group

- **Cost-effectiveness analysis (CEA):** Compared to standard cisplatin-containing chemotherapy, the EGFR-TKI is more cost-effective; the result was consistent with an analysis performed in the population unsuitable for chemotherapy vs. palliative care\textsuperscript{55,56}. More specifically, a CEA performed by the Comparative Effectiveness Public Advisory Council showed that the use of each of the first-line EGFR-TKI regimens resulted in a 0.84 life-year gain in survival relative to CT. On a quality-adjusted basis, Quality-adjusted life-year (QALYs) gained versus CT were also very similar, ranging from 0.60 for gefitinib to 0.62 for afatinib and erlotinib. Incremental costs versus CT were lower for gefitinib (~$66,000) than for the other EGFR-TKIs, as a function of a shorter duration of time spent in the progression-free state (and a consequently shorter duration of treatment). Cost-effectiveness estimates were similar across the EGFR-TKIs, ranging from approximately $110,000 - $130,000 per QALY gained\textsuperscript{57}. In another CEA, two different strategies were compared: the 'EGFR testing strategy', in which EGFR mutation testing was performed before treatment and patients with EGFR mutations received gefitinib while those without mutations received standard chemotherapy, to the 'no-testing strategy,' in which genetic testing was not conducted and all patients were treated with standard chemotherapy. The combination use of gefitinib and EGFR testing can be considered a cost-effective first-line therapy compared to chemotherapy such as carboplatin-paclitaxel for the treatment for NSCLC in Japan\textsuperscript{58}. The guidance document issued by NICE in the UK on 28 July 2010 states that 'Gefitinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the EGFR mutation and the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme'.

- December 1, 2008 — Erlotinib is now recommended for use in the second-line treatment of NSCLC by NICE. This means that this use of the drug is now covered by the UK National Health Service. The decision was reached after lengthy deliberations on cost effectiveness, and only after the manufacturer offered to supply the drug at a discounted price.

- ESMO Guideline recommends for use of the EGFR-TKIs the following. This figure illustrates the advised use of EGFR-TKI in the ESMO Guidelines
12. Conclusions

i. EGFR-TKIs (gefitinib, erlotinib, afatinib) should strongly be considered to be listed in the WHO list of ESSENTIAL MEDICINES for the frontline treatment of advanced EGFR mutated NSCLC because of the higher efficacy, improved survival and quality of life with high MCBS scores.

ii. Moreover, other EGFR-TKIs can be considered in case of acceptable costs including availability of generic versions.

iii. The inclusion as a priority medicine is supported by the burden of disease, with relevance both at global (most incident cancer and first cause of death for cancer in the world and in males in low-middle income countries, according to IARC 2018), regional (50% of new lung cancer diagnosis occurs in Asia, where half of the lung cancer patients are estimated to harbor an EGFR sensitive mutation, in some sub-regions) and national level, where EGFR-TKI offers a better therapeutic approach than chemotherapy, in term of sustained and longer disease control and tolerability, resulting in a better QoL.

iv. The use is intended as monotherapy in the frontline treatment of advanced EGFR mutated NSCLC, supported by consensual optimal supportive - palliative care in a comprehensive and patient-centered framework of care.

v. Eventually, the inclusion of EGFR-TKIs, both branded and generics, is considered in the facilitation process of access to safe, affordable, quality medicines for cancer: the inclusion in the WHO EML would stimulate a discussion around the negotiation and price-setting, providing matter to support the inclusion in the national EML – leaving no eligible lung cancer patients behind.

vi. Osimertinib (a 3rd generation EGFR-TKI), should also be discussed either for the frontline treatment of advanced EGFR mutated NSCLC or as a second line option for patients with at T790M mutation as the data are still progressing for the estimation of survival benefit.
References


Jiang T, Zhou C. EGFR-TKIs plus local therapy demonstrated survival benefit than TKIs alone in EGFR-mutant NSCLC patients with oligometastatic or oligoprogresive liver metastases. *J Thorac Oncol*. 2018; 13 (Suppl): S74 (abstr # 1290).


