Tyrosine kinase inhibitors or ALK inhibitors for the first line treatment of Non-small cell lung cancer

This application seeks the addition of tyrosine kinase inhibitor erlotinib (representative of class) and gefitinib and afatinib (alternatives) as well as ALK-inhibitor crizotinib to the list of the Essential Medicines List for the treatment of non-small cell lung cancer.

Introduction

In 2013, there were approximately 1.8 million incident lung cancer cases diagnosed worldwide and approximately 1.6 million deaths from the disease (1). Lung cancer had the second highest absolute incidence globally after breast cancer, and in 93 countries was the leading cause of death from malignant disease, accounting for one fifth of the total global burden of disability-adjusted life years from cancer. Men were more likely to develop lung cancer than women, with 1 in 18 men and 1 in 51 women being diagnosed between birth and age 79 years (1). Non-small cell lung cancer (NSCLC) is the most common form of the disease, accounting for 85–90% of all lung cancers (2)(43).

For patients with resectable disease, adjuvant chemotherapy improves the absolute 5-year survival rates in Stage II and III NSCLC (9,13,65,44-47). Acceptable adjuvant chemotherapy options include etoposide/cisplatin, docetaxel/cisplatin, gemcitabine/cisplatin, pemetrexed/cisplatin, and carboplatin/paclitaxel for patients with comorbidities or unable to tolerate cisplatin. In patients with non-metastatic but inoperable NSCLC or Stage III disease, concurrent chemoradiotherapy has been shown to improve overall survival (OS) and median survival (47-53).

However, most patients with NSCLC present with advanced stage disease – stage IV in particular – and half of all patients treated initially for potentially curable early-stage disease will experience recurrences with metastatic disease (3). Patients with stage IV disease are never curable, and chemotherapy, targeted therapy and radiation can only extend survival and palliate symptoms. Although NSCLC is generally regarded as a disease of the elderly, a third of cases are diagnosed in patients under 65 years of age (3). Platinum-based doublet chemotherapy is also the standard first-line treatment for patients with advanced (stage IV) disease.
Where high quality molecular diagnostics and targeted therapies are available, patients with activating mutations of epidermal growth factor receptor (EGFR) may benefit from treatment with EGFR (TKIs – erlotinib, gefitinib and afatinib), which have been shown to improve progression-free survival in patients with advanced disease, while being associated with greater tolerability than standard chemotherapy.

ALK gene rearrangements are found in 2-7% of NSCLC (64). Patients with driver oncogenes who failed to receive a targeted therapy previously may be treated with EGFR-TKIs or crizotinib as salvage therapy (29, 30).

Immunotherapy, specifically nivolumab and pembrolizumab (54-56,66), was discussed. The applicant is not proposing inclusion of these treatments on the EML at this time due to complex molecular testing requirements for first line use, and high costs versus modest benefits noted in the second- and third-line metastatic setting only to date.

**Public health relevance**

According to GLOBOCAN, lung cancer has been the most common cancer globally for several decades; estimated worldwide incidence in 2012 was 23.1 per 100 000 (age-standardized rate, ASR) (12.9% of all cancers) (4). Of the 1.8 million new cases in 2012, 58% occurred in less-developed regions. ASR incidence rates in 2012 were highest in central and eastern Europe (53.5 per 100 000) and in eastern Asia (50.4 per 100 000) and were 25% higher for men than for women (205 and 165 per 100 000 respectively). GLOBOCAN estimated the global mortality rate in 2012 to be ASR of 19.7 per 100 000.

**Requirements for diagnosis, treatment, and monitoring**

**Diagnostics**

Histopathological diagnosis from surgical sample, core- or fine-needle biopsies or cytology cell blocks from pleural effusion is essential. Adequate tissue must be obtained to permit the needed testing outlined here to be performed.
Immunohistochemistry (IHC) helps to subtype NSCLC: squamous cells are generally TTF1-negative and p40- and p63-positive, while adenocarcinomas are generally TTF1-positive and p40- and p63-negative (5, 6). Molecular testing is crucial for first-line treatment with molecular targeted therapy. This includes EGFR gene mutation analysis by Sanger sequencing or amplification refractory mutation system and anaplastic lymphoma kinase (ALK) gene rearrangement by break-apart fluorescent-in-situ hybridization (FISH) or IHC (7). Laboratories should use a validated mutation platform and participate in an external quality assurance programme.

**Testing**

Contrast-enhanced computerized tomography (CT) scan of the chest and upper abdomen, blood counts and blood chemistries for renal and hepatic function are required. CT scan or magnetic resonance imaging of brain or bone should be offered to patients with clinical symptoms suggestive of brain or bone metastases.

**Administration and care of patients**

CT scans are required to assess response to treatment. Access to laboratory facilities for monitoring adverse effects is also required. Clinicians should be proficient in recognizing and addressing the potential side-effects, and broad-spectrum antibiotics and transfusion facilities must be available to manage life-threatening events such as bone marrow suppression and neutropenic fever. Social well-being is inevitably affected by the diagnosis and treatment of NSCLC, and the financial burden of treatment may be particularly heavy for patients with metastatic NSCLC as many drugs are still on patent. Psychological and social support professionals are best integrated into multidisciplinary teams to care for patients with NSCLC.

**Overview of regimens**

The following basic information on administration and dosing for the proposed standard regimen options is provided; no details are given of ancillary medications pertaining to the management of adverse events.

*Standard regimen – TKI for metastatic NSCLC with activating EGFR mutations*

- erlotinib 150 mg/day orally

or
Alternative regimens – TKI for metastatic NSCLC with activating EGFR mutations

- gefitinib 250 mg/day orally
- Afatinib 40 mg/day orally

or

Standard first line therapy for metastatic NSCLC with activating ALK mutations

- Crizotinib 250 mg twice a day orally

Review of benefits and harms

Benefits - EGFR tyrosine kinase inhibitors / ALK inhibitor

Recent research shows that in regions where high quality molecular diagnostics are available, patients with targetable mutations may be eligible for targeted therapy with tyrosine kinase inhibitors.

EGFR sensitizing mutations (defined as in-frame deletions in exon 19 and L858R substitution in exon 21), are found in 10% of Caucasians with NSCLC and up to 50% of Asian patients (60). The incidence of mutation rates are still unknown in most parts of the world. Patients with tumors that harbor the EGFR gene mutations attain tumor response rate of 70-80%, progression free survival (PFS) of 10 to 14 months and improvement in overall survival of up to 33.3 (17-23) (24-26). Indirect comparisons showed that the three EGFR-TKIs have similar efficacy but they might differ within class in terms of toxicities (26, 27) (61-63). The contributors to the applications suggest that there are imminent price adjustments that will make the cost of the three TKIs comparable in the near future. All three are therefore being recommended for addition to the EML.

Patients receiving first-generation EGFR TKI will almost invariably develop resistance with time. EGFR T790 mutations account for 60% of resistance cases. The third-generation EGFR TKI, osimertinib, can achieve response rates of about 60% in patients with EGFR T790M mutations. Whilst the tumor responses clearly exceed that of chemotherapy in historical studies, survival data is not yet available (44, 45). This medicine is therefore not currently being recommended for addition to the EML.

For patients with ALK gene rearrangements, first-line crizotinib has been associated with a tumour response rate of 71% and PFS of 11.9 months (28). When compared with chemotherapy, there are improvements in quality of life and PFS, but no significant improvements in OS among patients given crizotinib. Prospective evidence for overall survival among patients on
crizotinib is immature, and will be difficult to obtain due to the confounding effects of crossover effects between the treatment arms (31, 32). However, there is robust retrospective evidence for improvement in overall survival when patients are treated with crizotinib as opposed to chemotherapy (30) and it is on that basis that the applicant is proposing that crizotinib is added to the EML.

Immunoetherapy

More recently, the development of immunotherapy approaches, specifically antibodies targeting the PD1/PDL1 axis, has shown promise. A recent phase III trial, KEYNOTE 024, showed that in patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, pembrolizumab significantly increased PFS from 6.7 to 10.3 months and improved OS at 6 months (66). Three earlier phase III trials have also confirmed superior clinical efficacy of pembrolizumab and nivolumab against docetaxel chemotherapy in the second and third line setting (54-56). All three trials to date have shown superior response rates compared to docetaxel (10% to 18-20%). A comparison of nivolumab to docetaxel as second line therapy in metastatic squamous NSCLC showed modest but statistically significant prolongation of PFS (2.8 months to 3.5 months) and overall survival benefit of 6 months to 9.2 months (54). Whilst promising, more mature data are required in this field. Immunotherapy is therefore not currently being recommended for addition to the EML.

Harms and toxicity considerations - EGFR tyrosine kinase inhibitors

Both EGFR tyrosine kinase inhibitors and the ALK inhibitor are well tolerated by many patients. Agents have similar toxicity profiles, although the incidence of toxicity depends on the drug. Diarrhoea is common, occurring in more than 60% of patients treated with EGFR-TKIs. Rarely, more severe gastrointestinal toxicity, including perforation, can occur, particularly with erlotinib. All agents are associated with characteristic dermatological toxicity and rash, and they may also cause hepatic toxicity and increased hepatic transaminases. Although the incidence is small, hepatic failure and hepatorenal syndrome have been reported in patients treated with erlotinib (24). (40-42). The common side effects for crizotinib are diarrhea, edema, vision changes and elevation in aminotransferase levels.

Recommendations

On the basis of the evidence presented in the application, the applicant recommends the addition of TKIs gefitinib, erlotinib and afatinib and the ALK inhibitor crizotinib to the complementary list of the EML for the treatment of non-small cell lung cancer. The contributors to the application believe that currently expanding access to high quality molecular testing will
not only increase access to potentially life-prolonging drugs, but also increase our understanding of the molecular epidemiology of these mutations worldwide.

The applicant continues to endorse the inclusion of etoposide, carboplatin, vinorelbine, gemcitabine, cisplatin and paclitaxel on the complementary list for use in the treatment of non-small cell lung cancer. The applicant notes that combination chemotherapy with the regimens possible with the current EML has been associated with modest improvements in overall survival and improved quality of life during extended survival.

The applicant does not recommend addition of the second line TKIs for resistant mutations and does not recommend immunotherapy, specifically nivolumab and pembrolizumab.

The applicant continues to support non-inclusion of pemetrexed based on a high cost/benefit ratio and bevacizumab based on the marginal benefit and significant costs and toxicity.

References


