Abemaciclib is a new drug for the treatment of a type of advanced lung cancer called non-small cell lung cancer (NSCLC) with a mutation in the KRAS gene. This cancer is considered difficult to treat disease and at present there are no targeted treatments. Abemaciclib is administered orally twice daily as a capsule or tablet. If licensed, abemaciclib could offer an additional treatment option for patients with this type of lung cancer after their initial treatments have stopped working.

NIHR HSRIC ID: 10539

Lay summary

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This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

• Non-small cell lung cancer (NSCLC): stage IV; KRAS mutation positive; for patients who have progressed after platinum-based chemotherapy.

TECHNOLOGY

DESCRIPTION

Abemaciclib (abemaciclib mesylate; bemaciclib; bemaciclib mesylate; CDK 4/6 dual inhibitor – Eli Lilly; LY-2835219) inhibits both cyclin-dependent kinase 4 and 6, which are key regulators of the cell cycle. Both kinases partner with cyclin D to phosphorylate retinoblastoma protein during the G1 phase of the cell cycle, which is important for normal progression to S phase. In phase III clinical trials, abemaciclib was administered orally at 200mg twice daily, with doses 12 hours apart.

Abemaciclib does not currently have Marketing Authorisation in EU for any indication.

Abemaciclib is also in phase III clinical trials for breast cancer, and in phase II clinical trials for other solid tumours, liposarcoma, and mantle-cell lymphoma.

INNOVATION and/or ADVANTAGES

If licensed, abemaciclib will provide an additional oral treatment option for this patient group, who currently have a poor prognosis.

DEVELOPER

Eli Lilly and Company Limited.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

NSCLC is the most common type of lung cancer, accounting for approximately 85-90% of all lung cancers. The most common NSCLC subtypes are squamous cell carcinoma (45%), adenocarcinoma (45%), and large cell carcinoma (10%). The subtype of NSCLC relates to the site of origin, reflecting the variation in respiratory tract epithelium from the bronchi to alveoli, with adenocarcinoma (the most common form) usually originating in peripheral lung tissue. The symptoms of NSCLC include cough, shortness of breath, haemoptysis, chest pain, loss of appetite, weight loss, and fatigue. Smoking is the main cause of lung cancer, responsible for more than 80% of cases.

KRAS is the most commonly mutated oncogene in NSCLC; mutations are more likely to be found in smokers and those from White ethnic groups, but are extremely rare in patients with
squamous histology\(^6\). They have also been associated with a poorer prognosis in the later stages of disease as well as resistance to chemotherapy\(^7,8\).

These mutations are mutually exclusive with respect to mutations of the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genes\(^7\).

**CLINICAL NEED and BURDEN OF DISEASE**

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cases\(^9\). In 2014, there were 37,419 new cases of lung cancer diagnosed in England\(^10\), equating to approximately 33,677 cases of NSCLC. Lung cancer is also the most common cause of cancer-related death in both men and women, accounting for 22% of all cancer deaths in the UK\(^11\).

Lung cancer survival is strongly related to the stage of disease at diagnosis, with the majority of new diagnoses presenting with advanced disease, around 75% are diagnosed at stage III or IV\(^12\) equating to 25,258 patients. In England, around 23% of patients with advanced NSCLC receive first line chemotherapy, which equates to 5,809 people\(^13\). Around 30-40% of these patients may subsequently become eligible for second-line chemotherapy (approximately 1,743 to 2,324 people)\(^14\). Median survival for patients with stage IV NSCLC treated with platinum-based therapy is 8-12 months\(^15\).

KRAS mutations can be detected in approximately 25% of all NSCLC tumours\(^16\). KRAS mutation does not predict for response, outcome or efficacy of EGFR tyrosine kinase inhibitors, even though EGFR mutations and KRAS mutations rarely occur in the same tumor\(^17\). Approximately 15 to 30% of lung adenocarcinomas harbor a KRAS mutation\(^18\).

In 2014-15, there were 89,247 hospital admissions in England due to neoplasm of the bronchus (ICD-10 C34), equating to 109,339 finished consultant episodes and 278,868 bed days\(^19\). In 2014, there were 30,851 deaths from lung cancer registered in England and Wales\(^20\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**

- NICE technology appraisal in development. Lung cancer (non-small cell, advanced, inoperable) - liposomal cisplatin, with chemotherapy (ID657). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Lung cancer (non-small cell, squamous, metastatic) – nivolumab (after chemotherapy) (ID811). Expected date of issue to be confirmed.
Horizon Scanning Research & Intelligence Centre

- NICE technology appraisal. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy (TA 374). December 2015.

NHS England Policies and Guidance


Other Guidance

- European Society for Medical Oncology. ESMO consensus guidelines; non-small cell lung cancer first-line/second and further lines in advanced disease. 201424.
CURRENT TREATMENT OPTIONS

The aim of treatment for advanced NSCLC is to prolong survival, improve quality of life, and control disease-related symptoms. Treatment strategies should take into account the tumour histology and molecular pathology, as well as the patient’s age, performance status, comorbidities, and preferences. Patients who smoke should be encouraged to cease, as cessation improves treatment outcomes.

Unlike EGFR and ALK, to date there have been no agents licensed that specifically target KRAS mutations. Chemotherapy should be offered to patients with stage IIIb or IV NSCLC (without activating mutations or whose activating mutation status is unknown) and good performance status (WHO 0 or 1, or a Karnofsky score of 80–100) to improve survival, disease control and quality of life. The following treatment options are recommended for the first line, maintenance and second-line treatments of treatment of advanced NSCLC that does not have EGFR or ALK mutations.

First-line
- Chemotherapy in the first-line setting for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. If patients cannot tolerate a platinum combination, single-agent chemotherapy with a third-generation drug should be offered.
- Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic NSCLC only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.

Maintenance
- Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non squamous non-small cell lung cancer in adults when, a) their disease has not progressed immediately after 4 cycles of pemetrexed and cisplatin induction therapy and, b) their Eastern Cooperative Oncology Group (ECOG) performance status is 0 or 1 at the start of maintenance treatment.
- Pemetrexed is recommended as an option for the maintenance treatment of people with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

Second-line
- Docetaxel monotherapy should be considered for second-line treatment of locally advanced or metastatic NSCLC when cancer has relapsed after previous chemotherapy.

Palliative care is usually considered the main goal of third-line treatment. However, in the absence of contraindications, patients progressing after chemotherapy (e.g. docetaxel) and maintaining a good performance status can be considered for third-line treatment. Only erlotinib is offered as a third-line option in unselected NSCLC patients after failure of first- and second-line chemotherapy.
### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>JUNIPER, NCT02152631, EudraCT2013-004662-33; abemaciclib vs erlotinib; phase III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Eli Lilly and Company.</td>
</tr>
<tr>
<td>Status</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry¹.</td>
</tr>
<tr>
<td>Location</td>
<td>EU (not incl UK), USA, Canada and other countries.</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised, active-controlled.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=550 (planned); aged &gt;18yrs; NSCLC; stage IV; KRAS mutation-positive (detectable mutations in codons 12 or 13); disease progression after platinum-based chemotherapy (with or without maintenance therapy) and have received one additional therapy, which may include an immune checkpoint inhibitor or other anticancer therapy, for advanced and/or metastatic disease or ineligible for further standard second-line chemotherapy; Eastern Cooperative Oncology Group (ECOG) scale 0 to 1; no unstable central nervous system metastasis.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Randomised to abemaciclib 200mg oral every 12 hrs plus best supportive care (BSC); or erlotinib 150mg oral every 24 hrs plus BSC.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment and follow-up continues until death or overall study completion.</td>
</tr>
<tr>
<td>Primary outcome/s</td>
<td>Progression free survival (PFS); overall survival (OS).</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Overall response rate (ORR); MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC) score; pharmacokinetics; European Quality of Life - 5 Dimensions - 5 Level (EQ-5D-5L) score.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as August 2019.</td>
</tr>
</tbody>
</table>

### ESTIMATED COST and IMPACT

**COST**

The cost of abemaciclib is not yet known. However, the cost of 30 tablets of erlotinib (150mg) is £1,600³².

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other
- ☐ No impact identified

**Impact on Health and Social Care Services**

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other
- ☐ None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- **Other: uncertain unit cost compared to current alternative treatment option.**
- None identified

Other Issues

- Clinical uncertainty or other research question identified
- None identified

REFERENCES


