REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND REIMBURSEMENT
OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Alunbrig 30 mg film-coated tablet x 28

Alunbrig 90 mg film-coated tablet x 7

Alunbrig 90 mg film-coated tablet x 28

Alunbrig 180 mg film-coated tablet x 28

INN Brigatinib

Therapeutic indications	monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with Crizotinib.
Start - end of the procedure	19.04.2019 – 27.12.2019
Final decision	Positive for an inclusion in Annex 2 for purchase by medical establishments with state and / or municipal participation and under Art. 5 of the Medical Establishments Act of the Positive Drug List (PDL) and payment by the National Health Insurance Fund (NHIF) beyond the value of the provided medical services.

Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Alunbrig

Health problem

Lung cancer is the second most common cancer in the world and the leading cause of death in cancer. Survival is very poor and only 13-18% of patients have a 5-year survival after diagnosis.
Lung cancer is classified according to histology, with the two main forms being small cell and non-small cell lung cancer. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases. Most patients, over 70%, are diagnosed with advanced disease. There are three main subtypes of non-small cell carcinoma: adenocarcinoma - about 40%, squamous cell carcinoma - 25-30%, and large cell carcinoma - 15-25%. There are some other, less common histological subtypes of NSCLC: adenosquamous, sarcomatoid, neuroendocrine and others. Approximately 5% of patients with NSCLC (mainly adenocarcinomas) showed positive for anaplastic lymphoma kinase (ALK) advanced non-small cell lung cancer (ALK + NSCLC). ALK + NSCLC occurs most often in young people, more often in men who do not smoke.
The most common risk factors for lung cancer are smoking, polluted air and working with various chemicals and substances. The early stages of the disease are usually asymptomatic. Clinical manifestations are non-specific and include chest pain, prolonged cough, haemoptysis, fatigue, loss of appetite and weight, shortness of breath, wheezing. Hoarseness or loss of voice, pain in the bones or joints, especially in the shoulder, difficulty swallowing may occur.
The diagnosis of NSCLC is made by imaging methods: X-ray of the lung, CAT of the thorax / abdomen, PET / CT, followed by histological verification by bronchoscopy, biopsy under CT / ultrasound control, thoracocentesis or VATS with biopsy. It is necessary to obtain a sufficient amount of tissue to subsequently perform molecular genetic analysis.
More than half of newly diagnosed patients with ALK + NSCLC progressed within 12 months of starting treatment with the current standard of care (Crizotinib).
ALK-positive patients have disease-specific clinical features: non-smokers, young age, adenocarcinoma histology, lack of EGFR or KRAS mutations, and high sensitivity to ALK inhibitor therapy. In addition, patients with ALK-positive NSCLC at diagnosis were more frequent in the advanced stage of the disease with metastases at different sites than other subtypes of NSCLC. Survival in patients with advanced NSCLC varies depending on the characteristics of the disease, but is usually low. Most often ALK + NSCLC metastasizes to the central nervous system (CNS) and in these cases the treatment of patients is complex. There are currently limited options for treating metastases in the central nervous system. During first-line treatment with crizotinib or chemotherapy, the incidence of CNS metastases may increase to 60%.

The main goal of treatment for ALK + metastatic NSCLC is to delay disease progression as long as possible, including CNS metastasis in newly diagnosed patients.
Alunbrig (INN Brigatinib), according to the marketing authorization, is approved as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK), advanced non-small cell lung cancer (NSCLC), previously treated with Crizotinib.

Epidemiological data

It is the second most common cancer in the world and the leading cause of death from cancer. The incidence in Bulgaria (since 2017) is 86.1 per 100,000 men and 16.2 per 100,000 women, and the mortality rate is 74.8 per 100,000 and 14.6 per 100,000, respectively.
Based on the increase in the incidence worldwide in connection with air pollution, the extrapolated data on newly diagnosed patients with lung cancer in Bulgaria for 2019 are about 4,728 people. Patients with advanced disease (stage III and IV) will be about 63.7%. Of these, those with NSCLC – about 78.4%. Patients with adenocarcinoma are about 46.6%. About 90% of patients with first-line treatment are tested for EGFR. About 88.2% of them are EGFR-negative. Patients tested for ALK mutation status from EGFR-negative patients were about 94%. Of these, patients with ALK-positive NSCLC were about 3.8%.
ALK + NSCLC occurs most often in young people, more often in men who do not smoke.

Efficacy data

The main clinical evidence for Brigatinib treatment is from two studies:

ALTA Study, Phase 2 - The ALTA Study (NCT02094573) is an ongoing, open-label, multicenter, international, two-arm, randomized, dose-determination study, a Phase 2 trial conducted in adult patients with locally advanced or metastatic ALK + NSCLC who have progressed with Crizotinib treatment. Randomized phase 2 is not intended for statistical comparisons between the arms. Efficacy and safety endpoints were evaluated by the investigator or by an independent cancer review committee (IRC) that were not directly related to the treatment of patients. However, subsequent comparisons of PFS (progression-free survival) and OS (overall survival) data were performed to support dose selection.

Limitations of the study. The ALTA study has some limitations:

- ALTA is open, two-phase study;

- ALTA does not include a reference arm (nor any other tyrosine kinase inhibitor or chemotherapy);

- The randomized selected design does not allow a formal statistical comparison of progression (PFS0) and median overall survival (OS) between the arms;

- In addition, the ALTA study has a relatively short follow-up (average 18.6 months)

- The ALTA study continues at the moment, and the results are announced at regular intervals.

Study 101, phase 1 and phase 2, involving 25 patients in the respective subgroup. The Phase 1/2 study is the first human, non-randomized, uncontrolled study of Brigatinib. It is not intended to statistically compare progression-free survival or overall survival through dosing regimens. A total of 137 patients with advanced lung cancer were included and dosed, including 79 patients with ALK + NSCLC, of whom 71 had previously been treated with Crizotinib. A total of 50 of the ALK + NSCLC patients had brain metastases at baseline. The 90 mg / 180 mg cohort includes 25 ALK + NSCLC patients previously treated with Crizotinib and is therefore relevant for this use. In this group, 19 of 25 patients (76.0%; 95% CI: 54.9%, 90.6%) had a confirmed objective response. The mean response time is 1.9 months (range 1.2 - 6.0 months). KM estimates the average duration of the response.

The main result in both studies was the researchers' assessment of the overall response using the criteria for assessing the response to solid tumors (RECIST v1.1). Secondary results in the studies included assessment of progression-free survival, overall survival, safety, tolerability, and duration of response. The median follow-up in ALTA was 24.3 months and the median overall survival was 34.1 months. The objective response rate was 56% in ALTA and 76% in Study 101. The median progression-free survival was 16 months in ALTA and Study 101. The median duration of response was 14 months (estimated by a researcher) and 16 months (estimated by an independent committee for evaluation) in ALTA, and 26 months in Study 101 (evaluated by a researcher). 74% of ALTA patients received chemotherapy and 67% had brain metastases before the start of the study.

Study AP26113-13-301 (study 301) is an ongoing, phase 3, randomized, multicenter study to evaluate the efficacy and safety of Brigatinib in patients with advanced ALK + NSCLC who received prior ALK-targeted therapy.
There are no studies or clinical trials to directly compare Brigatinib with Ceritinib and Alectinib, therefore an indirect comparison is used. Brigatinib compared with Ceritinib/Alectinib prolonged both overall and progression-free survival, and the difference between the two treatments was statistically significant.
Brigatinib provided significant improvements in PFS over the other two ALK inhibitors, Ceritinib and Alectinib (16.7 months versus 5.7-8.9 months, respectively, based on an indirect

comparison of treatments). The results showed that Brigatinib improved overall survival from 16 to 19 months and progression-free survival from 9 to 10 months compared with Ceritinib.
Brigatinib was associated with a significant improvement in median progression-free survival compared to Ceritinib (16.7 versus 5.7 months). The results of the study suggest a trend in improvement in median progression-free survival than in Alectinib treatment (16.7 versus 8.9 months) demonstrated in an indirect comparison of therapies.
While current second-line ALK inhibitors have a systemic PFS of less than 12 months, Brigatinib has demonstrated efficacy in a median PFS of 16.7 months. Patients with ALK + NSCLC have a very poor 5-year survival, and Brigatinib offers an improvement in overall survival in current treatments with a median OS of 27.6 months. Brain metastases lead to disabling symptoms for patients with ALK + NSCLC, and it is important for new treatments to limit or prolong these developments, and Brigatinib has a sustained intracranial response. The development of resistant mutations is common in patients with ALK + NSCLC who are currently taking available ALK inhibitors, and Brigatinib has been shown to be effective against resistant mutations.
The benefits of Brigatinib over Ceritinib and Alectinib include:
- better efficacy (PFS) and overall survival (OS) in the treatment of adult patients with positive anaplastic lymphoma kinase (ALK), advanced non-small cell lung cancer (NSCLC) previously treated with Crizotinib;
- better central nervous system efficacy than Crizotinib;
- better tolerability, with less need for dose reduction or discontinuation of the drug (especially with regard to gastrointestinal side effects);
- More convenient dosing for patients (ie one tablet, once daily with or without food, while ceritinib requires many capsules to be taken once daily with food).
Brigatinib is a highly selective CNS active next-generation inhibitor of ALK and RET tyrosine kinase receptors that, by binding to the ALK tyrosine kinase domain, prevents ATP binding and thus autophosphorylation of the ALK receptor, restoring apoptosis and inhibiting proliferation of the tumor.

The results of the studies show a clear and consistent clinical benefit in patients with locally advanced or metastatic ALK + NSCLC after Crizotinib and establish Brigatinib as a potent ALK inhibitor for effective development protection of CNS metastases and delaying their appearance in the CNS, as well as reducing the available target metastases. These results support the introduction of Brigatinib as a standard of care in patients who have progressed with Crizotinib.

Analysis of data reported by patients

Quality-of-life results were reported in the ALTA study. The secondary endpoint of the phase 2 of the ALTA study was the assessment of patient-reported symptoms and HRQOL (health-related quality of life) with EORTC QLQ-C30 (WHO European Quality of Life Questionnaire in Cancer Treatment). The questionnaire was administered at baseline, at the beginning of the scheduled visits and 30 days after the last dose of Brigatinib.
The mean QOL value is maintained higher than the baseline mean values and there is no significant difference between the dosing arms in the multivariate analysis.
The results of EORTC QLQ-C30 on cycle 5 for all patients are shown in the following table. In addition, in cycle 5, less than 15% of patients reported clinically significant worsening - nausea / vomiting and less than 5% - diarrhea, respectively.

Results of EORTC QLQ-C30 in Cycle 5:

	Patients with improvement or no change,%	**Patients with clinically significant improvement,%**
Overall health status/QOL	80	50
Result of the assessment of physical functions	80	50
Result of pain assessment	80	30
Result of dyspnea assessment	90	30

Safety data

The safety profile of Brigatinib is expected for ALK inhibitors, but is better than other ALK inhibitors. Most toxicities from drug administration are manageable, although gastrointestinal effects, fatigue, and neuropathy may affect quality of life. The discontinuation rate was only 6.4% and was considered relatively low in this group of patients with severe pre-treatment.

Data for comparators

Following disease progression during Crizotinib therapy, Brigatinib competed with second-generation ALK inhibitors (Alectinib and Ceritinib), which were used as second-line treatment.
Despite the initial benefit of Crizotinib treatment, patients usually relapse within one year of starting treatment. Ceritinib and Alectinib were approved as follow-up treatment in patients initially treated with Crizotinib. Currently, only INN Alectinib is paid with a public resource. INN Ceritinib is available on the market with an established marginal price and is included in the pharmacoeconomic analysis, but is not taken into account in determining the budget impact of the entry into the market of the new Brigatinib health technology.

Pharmacoeconomic indicators

Description of published assessments of health technology performed by state institutions for the purposes of another national health care system

In the indication for the treatment of ALK-positive advanced non-small cell lung cancer resistant to crizotinib, the United Kingdom gave a positive assessment when providing negotiated trade agreements, in France there are therapeutic alternatives for this indication, supported by compulsory social security schemes and an evaluation in Germany does not confirm the presence of additional therapeutic benefits from the use of brigatinib.

Applied analysis

Cost-effectiveness analysis (CEA) with outcome measure overall survival and cost-utility analysis (CUA) with outcome measure QALY (quality-adjusted life year) were used. Due to the lack of direct comparative randomized trials of Brigatinib versus Alectinib and Ceritinib, an indirect comparison of efficacy outcomes between therapies based on the relevant clinical trials was used. The analysis is directed to adult patients with anaplastic lymphoma kinase (ALK) positive advanced NSCLC who have previously been treated with Crizotinib.
The alternatives were selected from the recommendations for the treatment of NSCLC and the comparison was made with them. Brigatinib and Alectinib are second-generation ALK inhibitors developed for Crizotinib-resistant (CRZ) ALK + NSCLC. The perspective of the analysis is that of the paying institution - NHIF. The time horizon is 10 years (second line therapy, which has a low survival rate). At the end of the 10th year, 96.3% of the patients in the cohort died. A 3.5% discount for costs and benefits is applied. The results of the analysis are in favor of brigatinib, with an incremental ratio of less than 3 times GDP per capita in comparison to the both alternatives. Subgroup analysis is not applicable.

A standard, inhomogeneous Markov cohort model with three defined states is applied. No return from one condition to another is expected due to the number of patients and the nature of the disease. At any given time, the proportion of patients in a progressive disease is assumed to be the difference between OS (overall survival) and PFS (progression-free survival). The results presented show prolonged progression-free survival (PFS) and overall survival (OS) with brigatinib compared to alectinib or ceritinib.

Brigatinib adds an additional cost to the NHIF, but is also more effective than the available alternatives - it provides improvements in PFS over the other two ALK inhibitors Ceritinib and Alectinib (16.7 months versus 5.7-8.9 months, respectively).

Budget impact analysis

The analysis was conducted from the point of view of the paying public institution - NHIF for the time horizon of 5 years. The target population is patients previously treated with crizotinib. It is assumed a gradual increase in the target population from 3 to 11 people in 5 years. The budget impact of the introduction of the new technology is accompanied by an increase in costs compared to current therapeutic practice, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The results of the studies showed that Brigatinib was more effective in the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with Crizotinib, compared with the alternatives. Brigatinib is a potent ALK inhibitor for effective protection against the development of CNS metastases and delaying their occurrence in the CNS, as well as reducing existing target metastases and has better tolerability, with less need for dose reduction or discontinuation of the drug, and more convenient dosing for the patients. Brigatinib adds an additional cost to the NHIF, but is also more effective than the available alternatives, with the additional cost being less than 3 times GDP per capita, making Brigatinib therapy cost-effective.