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Abstract

Introduction

Non-small cell lung cancer (NSCLC) arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. Ceritinib is recommended as first-line treatment for adults with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC based on its' recent approval by the US Food and Drug Administration (FDA) and positive opinion by the European Committee for Medicinal Products for Human Use (CHMP). Ceritinib is also indicated for patients with disease progression or intolerance to crizotinib. By supressing the phosphorylation of ALK, ceritinib, a second-generation ALK inhibitor (ALKi), prevents the proliferation of ALK-positive NSCLC cells.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from ceritinib was evaluated based on, both the original and an adapted versions of, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the ASCEND-4 trial

Between 19 August 2013 and 11 May 2015, an intent-to-treat (ITT) population of 376 untreated ALK-rearranged NSCLC patients were randomly assigned to receive either ceritinib (n = 189) or platinum-based chemotherapy (n= 187). Ceritinib increased the primary endpoint of progression-free survival (PFS) in the ITT population by 8.5 months and duration of response (DOR) by 12.8 months, compared with chemotherapy. While overall survival (OS) data were immature at the time of analysis, the estimated OS rate at 24 months was 71% with ceritinib and 58% with chemotherapy. In patients with measureable brain metastases (BM) at baseline, 73% of ceritinib and 27% of chemotherapy recipients achieved an overall intracranial response (OIRR). Treatment-related adverse events (AEs) were more commonly reported in the ceritinib group; while 50 (28%) of dose adjustments or interruptions occurred due to gastrointestinal (GI) toxicity, ceritinib also increases the risk of hepatotoxicity, pancreatitis and cardiac arrhythmias.

Conclusion

Overall, ceritinib increases PFS and DOR in untreated ALK-positive NSCLC, regardless of the presence or absence of baseline BM, relative to platinum-based chemotherapy. Ceritinib also improved general quality of life (QoL) and prolonged time to deterioration of cancer-specific symptoms compared to chemotherapy. However, results from ASCEND-4 hold limited external validity as crizotinib is now standard care over chemotherapy for ALK-positive NSCLC and it is unclear whether increased PFS actually confers a meaningful change in OS. Even in the absence of head-to-head comparison trials and despite the lack of OS benefit, oncologists may chose ceritinib as first-line therapy for patients with advanced ALK-positive NSCLC if it is more active than other drugs even if it is less tolerable. Comparative studies of other second- and third-generation ALKi are ongoing which may offer further first-line options.

Table of Contents

List of Tables

1 Research questions

EUnetHTA
HTA Core Model®

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report[1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Element ID	Research question
Description of the technology	
B0001	What is ceritinib?
A0022	Who manufactures ceritinib?
A0007	What is the target population in this assessment?
A0020	For which indications has ceritinib received marketing authorisation?
Health problem and current use	
A0002	What is NSCLC?
A0004	What is the natural course of NSCLC?
A0006	What are the consequences of NSCLC for the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of NSCLC?
A0003	What are the known risk factors for NSCLC?
A0024	How is NSCLC currently diagnosed according to published guidelines and in practice?
A0025	How is NSCLC currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of ceritinib?
D0005	How does ceritinib affect symptoms and findings (severity, frequency) of NSCLC?
D0006	How does ceritinib affect progression (or recurrence) of NSCLC?
D0011	What is the effect of ceritinib on patients' body functions?
D0012	What is the effect of ceritinib on generic health-related quality of life?
D0013	What is the effect of ceritinib on disease-specific quality of life?
Safety	
C0008	How safe is ceritinib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying ceritinib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ceritinib?
A0021	What is the reimbursement status of ceritinib?

2 Drug description

Generic/Brand name/ATC code:

Ceritinib/Zykadia®/LDK378

B0001: What is ceritinib?

second-generation ALKi

In a subset of non-small cell lung cancers (NSCLC), a chromosomal rearrangement fuses the anaplastic lymphoma kinase (ALK) gene with the echinoderm microtubule-associated protein-like 4 (EML4) gene. The resulting EML4-ALK fusion oncogene produces a protein with constitutive kinase activity conferring uncontrolled cell growth [2, 3]. Ceritinib, a highly selective second-generation ALK inhibitor (ALKi), suppresses the phosphorylation of ALK thereby inhibiting proliferation of ALK-positive cancer cells [4, 5]. ALK-positive means that the cancer cells have certain defects affecting the gene responsible for the ALK protein.

750 mg orally once daily

Ceritinib is available as a 150 mg oral capsule. The recommended dose for ALK-positive metastatic NSCLC is 750 mg (five capsules) once daily until disease progression or unacceptable toxicity. Ceritinib is administered at least one hour before or two hours after a meal [6].

liver function/ lipase testing interrupt/reduce dose for safety/tolerability

Patients require monthly liver function tests and periodic lipase and/or amylase testing due to the risks for hepatotoxicity and pancreatitis. Dose interruption and reduction is recommended for individuals with hyperglycaemia or gastrointestinal (GI) adverse reactions. Ceritinib may be discontinued in patients with pneumonitis, cardiac arrhythmias, hepatotoxicity or intolerance at a dosage of 300 mg/day due to adverse drug reactions. Concomitant use of strong CYP3A inhibitors or inducers should be avoided [6].

A0022: Who manufactures ceritinib?

Novartis Pharmaceuticals

3 Indication

A0007: What is the target population in this assessment?

treatment naïve advanced ALK-rearranged (ALK-positive) NSCLC

Ceritinib (Zykadia®) is indicated as first-line therapy for patients with ALK-rearranged (ALK-positive) NSCLC.

4 Current regulatory status

A0020: For which indications has ceritinib received marketing authorisation?

FDA: licensed as 2nd-line in April 2014

In April 2014, the US Food and Drug Administration (FDA) granted accelerated approval of ceritinib for the treatment of patients with ALK-positive NSCLC with disease progression on or intolerance to the first-line ALKi crizotinib [7]. Initial approval was based on the results of the phase I, single-arm, open-label ASCEND-1 trial [8].

FDA: licensed as 1st-line in May 2017

In January 2017, the FDA granted ceritinib breakthrough therapy designation as first-line treatment for patients with ALK-positive NSCLC with brain metastases (BM), and priority review as first-line ALK-positive metastatic NSCLC. On May 26, 2017, the FDA expanded the use of ceritinib to include first-line treatment of patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test (Vysis ALK Break Apart FISH Probe Kit and Ventana ALK [D5F3] CDx assay) [9]. The first-line approval of ceritinib was based on results from the phase III ASCEND-4 trial [10].

EMA: marketing authorisation for ALK-positive NSCLC post crizotinib in May 2015; pos. CHMP for first-line treatment in May 2017

Ceritinib received marketing authorisation by the European Medicines Agency (EMA) in May 2015 for the treatment of adults with ALK-positive advanced NSCLC previously treated with crizotinib [11]. On May 18, 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending ceritinib monotherapy for the first-line treatment of adult patients with ALK-positive advanced NSCLC [12].

5 Burden of disease

A0002: What is NSCLC?

NSCLC accounts for 80–85% of all lung cancers

NSCLC is the most common epithelial lung cancer and accounts for approximately 80–85% of all lung cancers. Adenocarcinoma, the most common histological type, has a survival rate of approximately 5–6% at 5 years [13, 14]. ALK-positive tumours represent a subset of adenocarcinomas characterized by a solid growth pattern and signet ring cell cytomorphology or mucinous cribriform pattern. Radiologic features associated with ALK-positivity include central tumour location, lack of pleural tail sign, and pleural effusion [2].

ALK rearrangement in 5% of NSCLC patients

ALK rearrangements occur in approximately 4–5% of NSCLC patients, almost never co-occurring with epidermal growth factor receptor (EGFR) or Kirsten rat sarcoma viral oncogene (KRAS) mutations [15]. Multiple EML4-ALK variants have been identified with variations in truncations of EML4 on different exons but all include a functioning kinase domain [15]. Compared to EGFR-positive NSCLC, patients with ALK-positive tumours are most likely male, and are associated with larger-volume, multifocal thoracic lymphadenopathy [15-17].

A0004: What is the natural course of NSCLC?

staged I–IV by invasiveness

Lung cancer typically arises when epithelial cells lining the bronchial tubes undergo aberrant cell growth. To decide on the most appropriate treatment, lung cancer is staged from I through IV based on tumour size, and presence or absence of lymph node involvement and metastases (TNM). Stage I lung cancer is <3 cm and localized to one lobe; stage II has spread to other parts of the lung or lymph nodes; stage III may be large or spread to lymph nodes between the lungs; and stage IV has metastasized to the adjacent lung, brain, liver or bones [13, 18]. NSCLC patients harbouring EML4-ALK mutations typically have more advanced disease than unselected patients [19], with predilection for brain and liver metastases [20].

most commonly metastasize to brain and liver

A0006: What are the consequences of NSCLC for the society?

52–58% present with advanced cancer; relapse and metastasize early

Lung cancer is the second most frequently diagnosed cancer. While the implementation of smoking cessation programs and multidisciplinary treatments have reduced the incidence and mortality, 52–58% of lung cancer patients present with advanced-stage disease when curative treatment is no longer feasible. ALK-positivity is a poor prognostic factor in NSCLC [15], leading to a high rate of relapse and early formation of micro-metastases [21].

A0023: How many people belong to the target population?

4,716 Austrians were diagnosed with NSCLC in 2014

Lung cancer is the leading cause of cancer-related death in men and the second in women worldwide. The age standardized incidence rate for the European Standard Population was 56.9 per 100,000 persons per year in 2013. In Austria, 2,894 men and 1,822 women were newly diagnosed with lung cancer in 2014; and 3,908 men and 2,450 women died due to lung cancer (47.3 per 100,000 persons per year) [22]. Approximately 6.5% of people will be diagnosed with lung cancer during their lifetime and at least a third of newly diagnosed patients have distant metastases. While the average age at diagnosis is approximately 70 years in unselected patients [14], ALK-positive NSCLC patients are younger at onset with a median age of 52 years [15, 17]. In unselected NSCLC populations, defects in the ALK gene are relatively rare with an overall incidence of 4–7% [17].

ALK-positive NSCLC diagnosed at median age of 52 years

A0005: What are the symptoms and the burden of NSCLC?

NSCLC symptoms: cough, chest pain, weight loss, shortness of breath

Many lung cancers are not symptomatic until they have spread. Symptoms of NSCLC include incessant cough, bloody sputum, chest pain, wheezing or hoarseness, weight loss or loss of appetite, shortness of breath, fatigue, and recurrent bronchitis or pneumonia. ALK-positive NSCLC most commonly metastasizes to brain and liver causing pain, headaches, improper balance, seizures, or jaundice [13, 20].

A0003: What are the known risk factors for NSCLC?

The risk of lung cancer typically increases with age, tobacco use, radiation exposure, air pollution, and occupational exposure to asbestos, arsenic, chromium beryllium, nickel and other agents [13]. Despite a vast majority of NSCLC being associated with mutations induced through tobacco exposure, ALK-positive NSCLC is most prevalent in non-smokers [3, 15-17].

ALK-positive NSCLC is associated with never or light smoking (<10 pack-years)

A0024: How is NSCLC currently diagnosed according to published guidelines and in practice?

diagnosis: x-ray, CT and biopsy

While some lung cancers may be found through screening, most are identified when they become symptomatic. Following a clinical history and physical exam, a chest x-ray may be done to identify any abnormal areas in the lungs. A computed tomography (CT) scan may show the size, shape and location of any lung tumours or enlarged lymph nodes, and guide a needle biopsy if a suspected area is identified. Lung cancer is diagnosed by examining cells derived through biopsy or sputum sampling for the presence of cancer cells [18].

ALK status: FISH or IHC

Diagnostic methods most commonly used to identify ALK gene rearrangements in biopsy samples include fluorescence *in situ* hybridization (FISH) and immunohistochemistry (IHC) [2, 23]. Due to the ability to visualize rearrangements using dual colour, FISH with break-apart probes has become a reference standard for assessing ALK-positive NSCLC [2, 15]. IHC is rapid and relatively inexpensive, however the sensitivity and specificity of IHC ALK testing ranges from 67-100% and 93-100%. A two-tiered approach may be used where patients undergo initial IHC screening; those with moderate or intense staining may undergo further testing with FISH to confirm ALK positivity [2]. Next generation sequencing (NGS) may identify ALK rearrangements not previously identified through FISH and co-occurring driver mutations that may provide further clinical value [16, 24]. FISH and IHC are approved by the US FDA as companion diagnostic tests to identify ALK-positive NSCLC (Vysis ALK Break Apart FISH Probe Kit; Ventana ALK (D5F3) CDx assay) [25]. In Europe, IHC is widely used to detect ALK rearrangements [17].

NGS identifies rearrangements missed by FISH and co-occurring mutations

6 Current treatment

A0025: How is NSCLC currently managed according to published guidelines and in practice?

treatment by stage: surgery, radiation therapy, chemotherapy

Depending on the tumour stage, histology, and the patient's overall health, surgery, radiation therapy and/or platinum-based chemotherapy may be used alone or in combination to treat NSCLC [18].

- Stage I and II NSCLC patients typically undergo surgery to remove the cancer. Stage II patients may benefit from postoperative adjuvant chemotherapy.

- Patients with stage I or II cancers that are not surgical candidates, due to co-morbidities or limited lung function, may undergo local radiation therapy.
- Stage III NSCLC patients are highly heterogeneous and may undergo a combination of treatments depending on the extent and localization of disease as well as prior treatments.
- Patients with stage IV disease are treated with systemic therapy or a symptom-based palliative approach.

In appropriately selected patients, chemotherapy, molecularly targeted therapy, and/or immunotherapy may extend survival. Patients with adenocarcinoma should be assessed for EGFR and ALK mutations to identify subsets likely to respond to inhibitors [18]. ALKi treatment is limited to patients with ALK-positive tumours as demonstrated by FISH or IHC using FDA-approved tests [17].

- Combination chemotherapy with a platinum-based doublet or immunotherapy may be used as initial systemic treatment for patients with advanced NSCLC whose tumour does not have a driver mutation.

premetrexed: preferred chemotherapy

- While an ALKi is preferred as first-line therapy for ALK-positive NSCLC, some countries restrict ALKi to patients who have progressed following chemotherapy [18]. When ALK-positive advanced NSCLC patients require chemotherapy, most patients appear to benefit more from pemetrexed than taxanes.

first-line ALKi recommended over chemotherapy in ALK-positive NSCLC without CNS disease

- First-line treatment with ALKi crizotinib is recommended over chemotherapy for patients with advanced ALK-positive NSCLC without central nervous system (CNS) disease.
- In the US and Japan, initial treatment with the second-generation, CNS-penetrable ALKi alectinib is used to treat patients with advanced ALK-positive NSCLC with CNS disease at diagnosis. Radiation or surgery may also be indicated for BM.

second-generation ALKi alectinib for ALK-positive NSCLC with CNS disease

- Second-generation ALKi alectinib or ceritinib may be used to treat ALK-positive NSCLC patients who develop resistance or intolerance to crizotinib. While preference may be given to alectinib given CNS and systemic efficacy and tolerability, any second-generation agent may be used in the absence of head-to-head comparisons [17].

7 Evidence

systematic literature search in 5 databases: 295 hits

A literature search was conducted on 12 May 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “Ceritinib”, “Zykadia”, “NSCLC”, “non-small cell lung cancer”, “first line” and “advanced”. The manufacturer was also contacted and submitted four references (all of which had already been identified by systematic literature search). A manual search yielded three FDA reports [6, 9, 25], two EMA reports [11, 12], four clinical guidance documents [13, 17,

18, 21], two statistical documents [14, 22], and a cost document [26]. Ongoing trials information was found on clinicaltrials.gov and EU Clinical Trials Register. Overall, 296 references were identified.

Included in this reported are: **included: 3 studies**

- ASCEND-4, phase III [10, 27-29]
- ASCEND-1, phase I [8, 30, 31]
- ASCEND-3, phase II [32]

To assess the risk of bias at the study level the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [33]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. **study level risk of bias assessed based on EUnetHTA internal validity for RCTs**

To evaluate the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [34]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [35]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3. **magnitude of clinically meaningful benefit assessed based on ESMO-MCBS**

7.1 Clinical efficacy and safety – Phase III studies

ASCEND-4 (NCT01828099) [10, 29] is an open-label, randomized, phase III multicentre study involving 376 untreated patients with advanced ALK-positive non-squamous NSCLC. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved 364 patients who received at least one dose of study drug. **ASCEND-4: ceritinib versus chemotherapy in 375 treatment naïve ALK-positive NSCLC patient**

Study participants were adults with histologically or cytologically confirmed stage IIIb/IV non-squamous ALK-positive NSCLC; untreated, with measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1); World Health Organization (WHO) performance status 0–2; and asymptomatic or neurologically stable BM. ALK-rearrangement was determined centrally by the Ventana anti-ALK (D5F3) IHC assay. Patients were excluded if they had a hypersensitivity to ceritinib or platinum-containing drugs or a history of interstitial lung disease, concurrent malignancy, uncontrolled heart disease, radiotherapy-related toxicity or impaired GI function. Eligible patients were stratified by WHO performance status, previous neo-adjuvant or adjuvant chemotherapy, and presence of BM. **ITT stratified by WHO PS, previous therapy, and BM**

Patients were randomized 1:1 to receive either oral ceritinib (750 mg/day, fasted) or platinum-based chemotherapy (cisplatin 75 mg/m^2 or carboplatin AUC 5-6 plus pemetrexed 500 mg/m^2) IV every 3 weeks for four cycles followed by maintenance pemetrexed 500 mg/m^2) until unacceptable toxicity or disease progression. The median duration of treatment exposure was 66.4 weeks (IQR 30.0–83.7) for ceritinib and 26.9 weeks (13.0–62.3) for chemotherapy. **ceritinib 750 mg/day vs chemotherapy IV every 3 weeks, 4 cycles, with pemetrexed maintenance**

primary endpoint: PFS secondary endpoints: OS, ORR, DOR, TTR, OIRR, DIOR, ICBR, PROs, and safety

The primary endpoint was progression-free survival (PFS) as assessed by the blinded independent review committee (BIRC) according to RECIST 1.1 or death due to any cause. Should the primary outcome be met, the secondary outcome of overall survival (OS) would be evaluated. Other secondary endpoints included overall response rate (ORR), duration of response (DOR), time to response (TTR), overall intracranial response rate (OIRR), duration of intracranial response (DIOR), intracranial clinical benefit rate (ICBR), patient reported outcomes (PROs), and safety. Tumours were assessed at baseline, every 6 weeks after cycle 1 day 1 through month 33, every 9 weeks, and at the end of treatment.

ITT: median age 54 years, 97% had adenocarcinoma, 61% had never smoked

The ITT population (n = 376) had a median age of 54 years (range 22–81), 43% were male, 54% were Caucasian, 97% had adenocarcinoma, 96% were stage IV NSCLC at entry and 61% had never smoked. Approximately 17/376 (5%) of participants had prior adjuvant chemotherapy, 77/376 (21%) had radiation therapy, and 50/121 (41%) had brain radiation. Detailed patient characteristics, including inclusion and exclusion criteria are reported in Table 4 and study quality is described in Table 5 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and adverse events (AEs) are listed in Table 2.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of ceritinib on mortality?

OS: not mature; only 42% of required events for final analysis

24-month OS rates: 70.6% for ceritinib vs 58.2% for chemotherapy

At the time of analysis, June 24, 2016, the OS data were not mature with 107 OS events (48 events in the ceritinib group and 59 events in the chemotherapy group representing 42% of the required events for the final OS analysis. The median OS was not reached in the ceritinib group (95% CI 29.3–not estimable [NE]) and was 26.2 months (22.8–NE) in the chemotherapy group (hazard ratio [HR] 0.73 [95% CI 0.50–1.08]; p = 0.056). At 24 months, the estimated OS rates were 70.6 (95% CI 62.6-77.5) for ceritinib recipients and 58.2% (95% CI 47.6–67.5) for chemotherapy recipients. The study did not cross the efficacy stopping boundary for OS (-3.2546 [Z-scale] corresponding to p = 0.0006 on the p-value scale). Approximately 105/145 (72% of) patients received an ALKi after discontinuing chemotherapy, including 80 patients who received ceritinib after crossing over to ceritinib in the extension phase of the study [10].

D0006: How does ceritinib affect progression (or recurrence) of NSCLC?

median PFS in ITT: 16.6 months for ceritinib vs 8.1 months for platinum-based chemotherapy

Ceritinib patients had a median PFS of 16.6 months (95% CI 12.6–27.2) compared to 8.1 months (95% CI 5.8–11.1) for ALK-positive NSCLC patients treated with pemetrexed-platinum chemotherapy with pemetrexed maintenance, as assessed by BIRC [10]. Compared to platinum-based chemotherapy, ceritinib improved PFS, as assessed by the BIRC, with an estimated relative risk reduction of 45% in PFS (HR 0.55 [95% CI 0.42–0.73]; p < 0.00001) [10].

median PFS in patients with BM: 10.7 months for ceritinib vs 6.7 months for platinum-based chemotherapy

The PFS benefit of ceritinib over chemotherapy was also reported in patients with or without baseline BM. The median PFS, as assessed by the BIRC in patients without BM (n = 126, 34%) was 26.3 months (95% CI 15.4–27.7) in ceritinib patients versus 8.3 months (95% CI 6.0-13.7) in chemotherapy patients (HR 0.48 [95% CI 0.33-0.69]). The BIRC-assessed

median PFS in patients with BM (n = 121, 32%) was 10.7 months (95%CI 8.1-16.4) in the ceritinib group versus 6.7 months (95% CI 4.1-10.6) in the chemotherapy group (HR 0.70 [95% CI 0.44-1.12]) [10].

D0005: How does ceritinib affect symptoms and findings (severity, frequency) of NSCLC?

The whole body ORR, as assessed by the BIRC, was recorded in 72.5% (95% CI 65.5-78.7) of ceritinib recipients versus 26.7% (95% CI 20.5-33.7) of chemotherapy recipients [29]. The median TTR was 6.1 weeks (interquartile range [IQR] 5.9-6.7, n = 137) for ceritinib and 13.4 weeks (IQR 11.1-29.7, n = 50) for chemotherapy. The median DOR was 23.9 months (95% CI 16.6-NE) in the ceritinib group and 11.1 months (95% CI 7.8-16.4) in the chemotherapy group [10].

ORR
ceritinib: 72.5%
chemotherapy: 26.7%

median DOR
ceritinib: 23.9 months
chemotherapy: 11.1 months

OIRR in patients with measurable BM at baseline (n = 44) was 72.7% (95% CI 49.8-89.3) for ceritinib recipients versus 27.3% (95% CI 10.7-50.2) for chemotherapy recipients. The median DOIR was 16.6 months (95% CI 8.1-NE) in the ceritinib group and it was not estimable in the chemotherapy group because four of six patients had not progressed at the time of analysis. The ICBR at 24 weeks or longer was reported in 19 (86.4%) of 22 patients (95% CI 65.1-97.1) with ceritinib and 11 (50.0%) of 22 patients (95% CI 28.2-71.8) with platinum-based chemotherapy [10, 28].

OIRR
ceritinib: 72.7%
chemotherapy: 27.3%

median DIOR
ceritinib: 16.6 months
chemotherapy: NE

D0011: What is the effect of ceritinib on patients' body functions?

Ceritinib may induce liver function abnormalities in some patients. Elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyltransferase (GGT) were reported in a total of 60%, 53%, and 37% of ceritinib recipients, respectively. Increases in amylase and lipase were also observed in 37% and 13% of patients receiving ceritinib, respectively. Ceritinib may prolong the QTc interval and lead to an increased risk for ventricular tachyarrhythmia or sudden death. Prolonged QTc intervals were observed in 12% of patients treated with ceritinib [6, 10].

increased risk of hepatotoxicity, pancreatitis, cardiac arrhythmias

D0012: What is the effect of ceritinib on generic health-related quality of life?

Ceritinib recipients reported improvements in overall health status according to the EQ-5D-5L index (p = 0.0006) and a non-significant improvement in the EuroQol five dimensions questionnaire visual analogue scale (EQ-5-L VAS) (p = 0.053) compared with those treated with platinum-based chemotherapy [10].

ceritinib improved overall health status compared to chemotherapy

D0013: What is the effect of ceritinib on disease-specific quality of life?

PROs in disease-specific symptoms were improved for ceritinib versus chemotherapy as assessed by LCSS and QLQ-LC13. Patients receiving ceritinib had a longer time to definitive deterioration versus chemotherapy for the composite endpoint of lung cancer-specific symptoms of pain, cough, and shortness of breath (LCSS, HR 0.61 [95% CI 0.41-0.90]; p = 0.0055 and QLQ-LC13, HR 0.48 [95% CI 0.34-0.69]; p < 0.0001). All QLQ-LC-13 symptom scores improved with eight of ten improving significantly versus chemo-

ceritinib increased the time to deterioration and improved PROs versus chemotherapy

therapy. According to the QLQ-C30 instrument, four of five functional domains and six of nine symptom scales improved significantly with ceritinib versus chemotherapy. However, two scales related to diarrhoea and nausea and vomiting showed less favourable outcomes for ceritinib [10, 28].

Table 1: Efficacy results of ASCEND-4 [10, 27, 28]

Descriptive statistics and estimate variability	**Treatment group**	**Ceritinib**	**Chemotherapy**
	Number of subject	189	187
	OS events, n (%) Median OS, months (95% CI) 24-month OS rate, % (95% CI)	48 (25) NR (29.3-NE) 70.6 (62.2-77.5)	59 (32) 26.2 (22.8-NE) 58.2 (47.6-67.5)
	PFS events, n (%) Median PFS, months (95% CI) Without BM (n = 126) With BM (n = 121)	89 (47) 16.6 (12.6-27.2) 26.3 (15.4-27.7) 10.7 (8.1-16.4)	113 (60) 8.1 (5.8-11.1) 8.8 (6.0-13.7) 6.7 (4.1-10.6)
	ORR (CR+PR) events, n (%, 95%CI) CR, n (%) PR, n (%) SD, n (%) PD, n (%) UNK, n (%)	137 (72.5, 65.5-78.7) 1 (0.5) 136 (72.0) 23 (12.2) 19 (10.1) 10 (5.3)	50 (26.7, 20.5-33.7) 0 (0) 50 (26.7) 88 (47.1) 26 (13.9) 23 (12.3)
	Median TTR weeks (range)	6.1 (5.1-61.7)	13.4 (5.1-90.1)
	DOR Median DOR, months (95% CI) 21-month EFR, % (95% CI)	n = 137 23.9 (16.6-NE) 59.0 (49.3-67.4)	n = 50 11.1 (7.8-16.4) NE
	OIRR by BIRC neuro-radiologist OIRR events, n (%, 95% CI) CR, n (%) PR, n (%) SD, n (%) PD, n (%) UNK, n (%)	n = 22 16 (72.7, 49.8-89.3) 2 (9.1) 14 (63.6) 3 (13.6) 1 (4.5) 2 (9.1)	n = 22 6 (27.3, 10.7-50.2) 2 (9.1) 4 (18.2) 14 (63.6) 1 (4.5) 1 (4.5)
	Median DOIR months (95% CI)	16.6 (8.1-NE)	NE (1.5-NE) [27]
	ICBR at ≥24 weeks, n (%, 95% CI)	19 (86.4, 65.1-97.1)	11 (50.0, 28.2-71.8)
Effect estimate per comparison	**Study endpoint**	**Patient population**	**HR (95% CI), p-value**
	PFS by BIRC (primary endpoint)	ITT (n = 376) Without BM (n = 126) With BM (n = 121)	0.55 (0.42-0.73), p < 0.00001 0.48 (0.33-0.69) 0.70 (0.44-1.12)
	24-month OS rate, % (95% CI) (secondary endpoint) Data immature at interim analysis (42.3% of required events)	ITT (n = 376) 105/145 (72%) patients received an ALKi after discontinuing chemotherapy	0.73 (0.50-1.08), p = 0.056
	QoL data (secondary endpoint)	EQ-5D-5L EQ-5D-5L VAS LCSS QLQ-LC13	0.04 (0.02-0.07), p = 0.0006 2.3 (-0.03-4.59), p = 0.053 0.61 (0.41-0.90), p = 0.0055 0.48 (0.34-0.69), p < 0.0001

Abbreviations: BM = brain metastases, CI = confidence interval, CR = complete response; DOR = duration of response, ED = effect difference, EFR = event-free rate, EQ-5D-5L = EuroQol Group 5-dimension self-report questionnaire, HR = hazard ratio, ICBR = intracranial benefit rate, LCSS = lung cancer symptom scale, NE = not estimable, NR = not reached, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, QLQ-LC13 = lung cancer module, QoL = quality of life, SD = stable disease, UNK = unknown, VAS = visual analogue scale

7.1.2 Safety

C0008: How safe is ceritinib in relation to the comparator(s)?

most common AEs: diarrhoea, nausea, vomiting, hyperglycaemia, fatigue, and cough

The most common AEs associated with ceritinib use were diarrhoea (85%), nausea (69%), vomiting (66%), hyperglycemia (53%), decreased appetite (34%), fatigue (29%), abdominal pain (25%), and cough (24%). AEs suspected to be treatment-related were reported in 184 (97% of) ceritinib recipients and 156 (89% of) patients treated with platinum-based chemotherapy; of those 65% (123/189) in the ceritinib group and 40% (70/175) in the chemotherapy group were reported as having grade 3 or 4 treatment-related AEs. Of these, the most common grade 3 or 4 AEs occurring in >15% of ceritinib recipients were increase in ALT (30%), AST (16%) and GGT (26%). Pneumonitis was reported in 4 (2%) of patients in the ceritinib group and one (1%) of patients in the chemotherapy group. While 11 ceritinib recipients and six chemotherapy recipients died during the on-treatment phase, none were suspected to be drug-related [36, 37].

C0002: Are the harms related to dosage or frequency of applying ceritinib?

80% of certitinib vs 45% of chemotherapy patients required dose adjustment or interruption due to GI or hepatotoxicity

AEs requiring dose adjustment or interruption were reported in 80% of patients receiving ceritinib and 45% of chemotherapy recipients. Dose adjustment or interruption was primarily due to GI toxicity or liver function abnormalities. GI toxicity accounted for 52 (28%) of 189 patients in the ceritinib group, including vomiting (29 [15%]), diarrhoea (24 [13%]), nausea (22 [12%]) and led 2 patients to discontinue treatment. Most diarrhoea events were managed by dose interruption and supportive medication [36, 37].

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of ceritinib?

susceptible patient groups: long QT syndrome, CHF, arrhythmias, hepatic impairment

Patients with congenital long QT syndrome should avoid using ceritinib. Patients with congestive heart failure (CHF), bradyarrhythmias, electrolyte abnormalities and those on medications that prolong the QT interval should undergo periodic electrocardiogram and electrolyte monitoring. As the liver metabolizes ceritinib, patients with hepatic impairment may have increased exposure. Dose adjustment may be considered for patients with moderate to severe hepatic impairment. Patients who develop QT interval prolongation in combination with serious arrhythmia, severe hepatotoxicity, inadequate hyperglycemic control or pneumonitis while taking ceritinib should permanently discontinue use [37].

ceritinib may cause genotoxicity and foetal harm

Females are advised to use effective contraception during ceritinib treatment and for 6 months following completion of therapy based on the potential for foetal toxicity. Women are also advised not to breastfeed during treatment and for 2 weeks the last dose. Due to the risk of genotoxicity, males are advised to use condoms during treatment and for 3 months following therapy [37].

Table 2: Most frequent adverse events regardless of study drug relationship of ASCEND-4 [6, 10, 27]

Adverse Event (according to CTCAE version 4.03)	**Ceritinib** (n = 189)		**Chemotherapy** (n = 175)	
	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Any AE	189 (100)	148 (78)	170 (97)	108 (62)
Diarrhoea	160 (85)	10 (5)	19 (11)	2 (1)
Nausea	130 (69)	5 (3)	97 (55)	9 (5)
Vomiting	125 (66)	10 (5)	63 (36)	10 (6)
ALT increased	114 (60)	53 (31)	38 (22)	5 (3)
AST increased	100 (53)	32 (17)	34 (19)	3 (2)
Hyperglycaemia	100 (53)	19 (10)	117 (67)	18 (10)
Increased amylase	70 (37)	15 (8)	75 (43)	9 (5)
GGT increased	70 (37)	54 (29)	18 (10)	3 (2)
Decreased appetite	64 (34)	2 (1)	55 (31)	2 (1)
Blood ALP increased	55 (29)	14 (7)	8 (5)	1 (1)
Fatigue	55 (29)	8 (4)	52 (30)	5 (3)
Abdominal pain	47 (25)	4 (2)	13 (7)	0 (0)
Cough	46 (24)	0 (0)	28 (16)	0 (0)
Weight decrease	45 (24)	7 (4)	26 (15)	1 (1)
Blood creatinine increased	42 (22)	4 (2)	17 (10)	0 (0)
Upper abdominal pain	39 (21)	3 (2)	10 (6)	0 (0)
Non-cardiac chest pain	38 (20)	2 (1)	17 (10)	1 (1)
Back pain	36 (19)	3 (2)	32 (18)	4 (2)
Constipation	36 (19)	0 (0)	38 (22)	0 (0)
Pyrexia	34 (18)	0 (0)	24 (14)	2 (1)
Asthenia	33 (18)	5 (3)	36 (21)	6 (3)
Headache	31 (16)	0 (0)	21 (12)	2 (1)
Thrombocytopenia	31 (16)	1 (1)	67 (38)	9 (5)
Dyspnoea	29 (15)	4 (2)	35 (20)	11 (6)
Anaemia	28 (15)	4 (2)	62 (35)	13 (7)
Increased lipase	25 (13)	11 (6)	13 (7)	2 (1)
Prolonged QT interval	23 (12)	5 (3)	2 (1)	2 (1)
Neutropenia	9 (5)	1 (1)	38 (22)	19 (11)
WBC count decreased	7 (4)	0 (0)	31 (18)	7 (4)
Pericarditis	7 (4)	3 (2)	4 (2)	2 (1)

Abbreviations: AE = adverse event, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = common terminology for cancer adverse events, GGT = gamma-glutamyltransferase, WBC = white blood cell

7.2 Clinical effectiveness and safety – Further studies

ASCEND-1 (NCT01283516) is a multicentre, open-label, phase 1 trial investigating the efficacy of critinib (750 mg/day until disease progression or toxicity) in 255 patients, of whom 246 had ALK-rearrangements [8, 30, 31]. Approximately 67% of ALK-positive NSCLC patients had received at least two prior treatment regimens, and 66% had received prior ALKi treatment.

ASCEND-1: 83 ALKi-naïve and 163 ALKi-pre-treated ALK-positive patients

At a median follow up of 11.1 months (IQR 6.7–15.2), an overall response was reported in 60 (72% [95% CI 61–82]) of 83 ALKi-naïve patients and 92 (56% [95% CI 49–64]) of 163 ALKi-pre-treated patients. Median DOR was 17.0 months (95% CI 11.3–NE) in ALKi-naïve patients and 8.3 months (95% CI 6.8–9.7) in ALKi-pre-treated patients. Median PFS was 18.4 months (95% CI 11.1–NE) in ALKi-naïve patients and 6.9 months (95% CI 5.6–8.7) in ALKi-pre-treated patients. Of 94 patients with retrospectively confirmed BM and at least one post-baseline magnetic resonance imaging (MRI) or CT tumour assessment, intracranial disease control (IDCR) was reported in 15 (79% [95% CI 54–94]) of 19 ALKi-naïve patients and 49 (65% [95% CI 54–76]) of 75 ALKi-pre-treated patients. Of the 94 patients, 11 had measurable brain lesions and no previous brain radiotherapy, six achieved a partial intracranial response. Serious AEs were reported in 117 (48%) of 246 patients. The most common grade 3 or 4 events were increased ALT (73 [30%]), increased AST (25 [10%]), diarrhea (15 [6%]) and nausea (15 [6%]). Two on-treatment deaths occurred, one due to interstitial lung disease and one from ischaemic hepatitis [30].

median ORR: 72% of ALKi-naïve and 56% of ALKi-pre-treated patients; DOR 17 months vs 8.3 months

median PFS: 18.4 months in ALKi-naïve and 6.9 months in ALKi-pre-treated patients

ICDR: 79% of ALKi-naïve and 65% of ALKi-pre-treated patients

ASCEND-3 (NCT01685138) is a multicentre, open-label, phase II trial that evaluates the safety and efficacy of ceritinib (750 mg/day) in 124 ALKi-naïve patients with ALK-rearranged NSCLC [32]. Study participants had a median age of 56 (27–82), 40.3% were male, 59.7% were Asian and 38.7% were Caucasian; 40.3% had BM, of which 46% had no prior brain radiation. The median time from diagnosis to treatment was 13.5 (1.0–283.1) months; median exposure duration was 8.0 (0.1-16.2 months; and median follow-up was 8.3 (0.6-16.3) months.

ASCEND-3: 124 ALKi-naïve ALK-positive NSCLC patients given ceritinib 750 mg/day

At baseline, 10 patients had investigator-assessed measurable BM; IDCR was 80% (95% CI 44.4-97.5). Ceritinib showed brain response in six patients with BM without prior brain radiotherapy. Overall response was reported in 29 (58.0% [95% CI 43.2–71.8]) of patients with and 50 (67.6% [95% CI 55.7–78.0]) without BM. Whole body disease control rate (DCR) was 43 (86.0% [73.3–94.2] in patients with and 68 (91.9% [95% CI 83.2-97.0]) in those without BM. Median DOR was 9.1 (95% CI 7.5–NE) months in patients with BM and 10.8 (95% CI 9.3–10.8) months in those without. Median PFS was 10.8 (95% CI 7.3–NE) months in patients with and 11.1 (95% CI 9.2–12.8) months in those without BM. The most common AEs were diarrhoea (83%), nausea (74%) and vomiting (66.9%); 7.3% of patients discontinued due to AEs

IDCR: 80%

ORR: 58% of patients with and 67.6% of patients without BM; median DOR: 9.1 vs 10.8 months

median PFS: 10.8 months in patients with and 11.1 months in those without BM

8 Estimated costs

A0021: What is the reimbursement status of ceritinib?

€ 3,748.71 per 21-day cycle

In Austria, ceritinib is available as 150-mg hard capsules in packages of 150 pieces. One package of 150 150-mg capsules is available for € 5,355.30 (ex-factory price). At the recommended dose of 750 mg daily, the cost for ceritinib treatment would be € 3,748.71 per 21-day cycle [26]. A median duration of 16.6 months (IQR 7.5–20.9 months) of ceritinib treatment would cost approximately € 62,230.00. Since ceritinib is indicated for ALK-positive NSCLC patients, additional costs in the range of approximately $US 68.89 for IHC or $US 279.46 for parallel FISH and IHC will be incurred for ALK-testing [38].

9 Ongoing research

25 registered trials; 2 industry-sponsored phase III studies

Several studies are ongoing to investigate ceritinib as monotherapy following pre-treatment with chemotherapy or ALKi, and in combination with immune checkpoint inhibitors or other anticancer agents used to treat advanced NSCLC. A search of clinicaltrials.gov using search terms "ceritinib" and "NSCLC" yielded 18 registered studies (two phase III, seven phase II, three phase I/II, four phase I, an observational study and an expanded access protocol). A search of the EU Clinical Trials Register yielded six studies (three were already identified in clinicaltrials.gov, (one phase IV, two phase III, one phase II, and two phase I/II). Most studies are industry-sponsored or conducted in collaboration with industry.

Selected ongoing phase IV, III and II studies for ALK-arranged NSCLC patients:

- **NCT02584933:** A phase IV, open-label, roll-over study in patients with ALK-positive malignancies who have completed a prior Novartis-sponsored ceritinib study. Estimated primary completion date is December 2020.
- **NCT02450903:** A phase II, interventional study to investigate ORR, DOR, PFS and OR to ceritinib in ALK-positive NSCLC patients previously treated with the ALKi alectinib. Estimated primary completion date is August 2017.
- **NCT01964157:** A phase II, open-label study of ceritinib in 32 patients with ROS1-rearranged NSCLC. Estimated primary completion date is December 2017.
- **NCT01828112:** ASCEND-5 is a phase III, randomized, open-label trial comparing ceritinib versus chemotherapy in ALK-positive patients previously treated with platinum-based chemotherapy and crizotinib. Estimated primary completion date is August 2018.
- **NCT02292550:** A phase I/II, non-randomized study of ceritinib in combination with the CDK4/6 inhibitor LEE011 in patients with

ALK-positive NSCLC. Estimated primary completion date is October 2018.

- **NCT02336451:** ASCEND-7 is a phase II, interventional trial to evaluate the efficacy and safety of ceritinib in patients with ALK-positive metastatic NSCLC to the brain and/or to leptomeninges. Estimated primary completion date is December 2018.
- **NCT02513667:** A phase II, open-label, interventional study investigating ceritinib in combination with sterotactic ablative radiation-for metastatic lung adenocarcinoma. Estimated primary completion date is August 2019.
- **NCT03087448:** A phase I/II, interventional study to investigate ceritinib plus trametinib in patients with advanced ALK-positive NSCLC. Estimated primary completion date is March 2021.

10 Discussion

indication approved by the FDA

In 2014–2015, ceritinib was approved, by the EMA [11] and the US FDA [7], for the treatment of adults with ALK-positive advanced NSCLC previously treated with crizotinib. Initial approval was based on the results of the phase I, single-arm, open-label ASCEND-1 trial [8]. In January 2017, ceritinib was granted FDA-breakthrough therapy designation as first-line treatment for ALK-positive NSCLC with BM. On May 18, 2017, CHMP provided a positive opinion on ceritinib monotherapy as first-line treatment for adults with ALK-positive advanced NSCLC [12]. Similarly, on May 26, 2017, the FDA expanded use of ceritinib as first-line treatment for patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test [9]. The first-line approval of ceritinib was based on results from the phase III ASCEND-4 trial [10].

positive CHMP opinion

ASCEND-4: improvement in PFS (+8.5 months), improved ORR, immature OS data

ASCEND-4, a randomized, open-label, phase III multicentre study compared the safety and efficacy of ceritinib (750 mg/day, fasted) versus platinum-based chemotherapy in 376 untreated patients with advanced ALK-positive non-squamous NSCLC [10]. Compared with chemotherapy, ceritinib increased median PFS by 8.5 in the ITT population as assessed by the BIRC. The PFS benefit of ceritinib over chemotherapy was reported in patients regardless of the presence or absence of baseline BM. Compared with chemotherapy, ceritinib improved median PFS by 4 months in patients with BM, and by 17.5 months in those without. The ORR was 72.5% for ceritinib versus 26.7% for chemotherapy, where ceritinib conferred an increase of 12.8 months in DOR. At the time of analysis, OS data were not mature having accrued 107 (42%) of the required events for final OS analysis. Estimated OS rates at 24 months were 70.6% for ceritinib and 58.2% for chemotherapy recipients. Ceritinib significantly improved the general QoL and prolonged time to deterioration for cancer-specific symptoms compared with chemotherapy.

treatment-related AEs any grade were more common in the ceritinib group

The most common AEs were diarrhoea, nausea, vomiting and increased ALT in ceritinib recipients and nausea, vomiting and anaemia in chemotherapy recipients. AEs requiring dose adjustment or interruption were reported in 80% of ceritinib patients versus 45% of patients receiving chemotherapy. GI toxicity accounted for 50 (28%) of dose adjustments or interruptions in the ceritinib group including vomiting (15%), diarrhoea (13%), nausea (12%), and treatment discontinuation in 2% of patients.

consistent efficacy and safety results with former studies

The clinical efficacy and safety results of ASCEND-4 are consistent with phase I and II data, from the ASCEND-1 [8, 30, 31] and ASCEND-3 trials [32], where ceritinib prolonged the median PFS to 18.4 months in each study. Consistency in the PFS benefit of ceritinib over subgroups regardless of the presence or absence of baseline BM observed in ASCEND-4 is in keeping with similar findings from ASCEND-3. However, none of these trials confirm whether the increase in PFS actually confers a meaningful change in OS. Diarrhoea, nausea, vomiting, and elevated ALT were also commonly reported AEs in phase I and II trials.

high risk of bias: unclear allocation concealment, open-label study, possible selective outcome reporting

Several methodological limitations of the ASCEND-4 trial compromise internal and external validity. While patients were randomized 1:1 to ceritinib or chemotherapy via an interactive response system, allocation concealment was not maintained and may influence how participants were assigned to a given group. Internal validity may be compromised in an open-label study where patients and treating physicians are aware of treatment allocation introducing potential for bias in the estimate of effect of an intervention. While endpoints were assessed by the BIRC, the outcome of ICBR was added post hoc leading to possible selective reporting.

ESMO-MCBS

original: grade 4
adapted: grade 3

Given the non-curative setting of ceritinib and the statistically significant primary endpoint PFS we applied Form 2b of the ESMO-MCBS in order to assess whether ceritinib satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5). Both the original as well as the adapted version of the MCBS were applied [34, 35]. The application of the ESMO-MCBS to the ASCEND-4 study resulted in a grade 4 and 3 in the original and the adapted version of the ESMO-MCBS, respectively. Therefore, ceritinib only leads to a meaningful clinical benefit in the original scale, but not in the adapted framework. This difference occurs due to the higher implication of toxicities in the adapted ESMO-MCBS.

limitations due to comparator

Results of the ASCEND-4 study hold several limitations. While first-line platinum-based chemotherapy was standard of care for advanced NSCLC at inception of this study, crizotinib has since been approved as first-line treatment for patients with ALK-positive NSCLC based on results from the PROFILE 1014 study [39]. As crizotinib is now standard care for ALK-positive NSCLC, it may have been a more appropriate comparator for the study. In the ASCEND-4 study, 78% of ceritinib patients experience grade 3 or 4 AEs, and 80% required dose adjustment or interruption. In contrast 54% of crizotinib-treated patients in PROFILE experienced grade 3 or 4 AE of which 41% required dose interruption and 6% required dose reduction. Due to the potential for drug toxicity, patients may lend preference to initial treatment with crizotinib before transitioning to ceritinib following disease progression. Sequential treatment with crizotinib followed by ceritinib was associated with a comparable median PFS of 17.4 months in a retrospective analysis [40].

direct comparisons to alectinib needed

The ALEX trial is currently underway to compare the second-generation ALKi alectinib versus crizotinib in patients with crizotinib-naïve, ALK-positive NSCLC [41]. At interim analysis, alectinib improved PFS compared to crizotinib with notable benefit in patients with BM in whom median PFS was not reached versus 10.2 months. At primary analysis, 12-month PFS was significantly higher with alectinib compared to crizotinib (68% [95% CI 61-76] versus 49% [95% CI 40-57]; HR for disease progression or death was 0.47 [95% CI 0.34-0.65; p<0.001); and median OS was not estimable in either group]. CNS progression was more common the cizotinib group than the alectinib group (68 patients (45%) vs 18 (12%); HR 0.16 [95% CI 0.10-0.28; p<0.001]) [42]. In ASCEND-4, median PFS with ceritinib in patients with BM was 10.7 months suggesting alectinib may offer greater brain permeability and less GI toxicities than ceritinib. However, a direct comparison would be necessary to evaluate the more beneficial efficacy and safety profile for ALK-positive NSCLC patients. Other second- and third-generation ALKi are under evaluation with broader activity than ceritinib or alectinib against ALK resistance mutations and greater CNS activity raising the possibility of more durable responses in the first-line setting.

new second- and third-generation ALKis are under investigation

€ 3,748.71 per 21-day cycle; € 3,748.71 per 16.6 months of treatment

The cost of one package of 150 150 mg capsules of ceritinib is € 5,355.30 (ex-factory price). At the recommended dose of 750 mg daily, the cost for ceritinib treatment would be € 3,748.71 per 21-day cycle. In contrast, crizotinib treatment for 21 days would amount about € 4,000 and alectinib approximately € 4,100 [26]. A median duration of 16.6 months (IQR 7.5–20.9 months) of ceritinib treatment would cost approximately € 62,230.00.

improved PFS & DOR regardless of BM

limited external validity

inappropriate comparator

ongoing studies of second- and third-generation ALKi

Overall, the ASCEND-4 phase III randomised study reports that ceritinib improves PFS and DOR in patients with advanced ALK-positive NSCLC regardless of the presence or absence of baseline BM, relative to platinum-based chemotherapy. While ceritinib also improved general QoL and prolonged time to deterioration of cancer-specific symptoms compared to chemotherapy, higher rates of treatment-related clinically relevant AEs may incur higher cost with continuous treatment. However, results from the ASCEND-4 study hold limited external validity as crizotinib is now standard care over chemotherapy for ALK-positive NSCLC and it is unclear whether the increase in PFS actually confers a meaningful change in OS. Even in the absence of head-to-head comparison trials and despite the lack of OS benefit, oncologists may chose ceritinib as first-line therapy for patients with advanced ALK-positive NSCLC if it is more active than other drugs even if it is less tolerable. Comparative studies of other second- and third-generation ALKi are ongoing which may offer further first-line options with broader activity against resistant mutations, lesser toxicity and greater CNS activity than ceritinib.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [34, 35]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Ceritinib	NSCLC (1st-line)	Not curative	PFS	2b	>6 months	+8.5	0.55 0.42–0.73	HR ≤0.65 AND Gain ≥3 months	3	+16% grade 3–4 AEs (-1)[A]	impr. QoL (+1)[B]	-1/+1	**3**
Original ESMO-MCBS	Ceritinib	NSCLC (1st-line)	Not curative	PFS	2b	>6 months	+8.5	0.55 0.42–0.73	HR ≤0.65 AND Gain ≥3 months	3	x	impr. QoL (+1)[B]	+1	**4**

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, NSCLC = non-small lung cancer, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, PFS = progression-free survival, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[A] Downgrade due to a negative difference of at least 10% in grade ≥3 AEs

[B] Upgrade due to statistically significant positive difference in QoL

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12 Appendix

Table 4: Characteristics of the ASCEND-4 trial

Title: First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged NSCLC [10, 27, 29]			
Study identifier	NCT01828099, CLDK378A2301, EudraCT2013-000319-26, ASCEND-4		
Design	Multicentre (28 countries, 134 centres), randomised, open-label, interventional, phase III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		August 19, 2013-May 11, 2015: assessed eligibility of 425 patients; randomized 376 patients Interim analysis: March 23, 2015 85 PFS events Data cut-off: June 24, 2016 when 202 PFS events were observed by BIRC Median duration of follow-up: 19.7 months (randomization to cut-off) not applicable ET phase for 80 patients that crossed over to ceritinib after discontinuing chemotherapy: cycle 1 (28 days), subsequent cycles (21 days), end of treatment visit
Hypothesis	Superiority The study was designed to evaluate the efficacy, safety and PROs of ceritinib versus platinum-pemetrexed doublet followed by pemetrexed maintenance in untreated, advanced ALK-rearranged NSCLC patients.		
Funding	Novartis Pharmaceuticals Corporation		
Treatment groups	Ceritinib (n=189 full analysis; 189 treated, n=189 safety analysis)		750 mg/day orally (given in a fasted state) until disease progression or unacceptable toxicity
	Platinum-based chemotherapy (n=187 full analysis; 175 safety analysis) n=87 pemetrexed + cisplatin n=88 pemetrexed + carboplatin n=127 pemetrexed maintenance		Cisplatin 75 mg/m² or carboplatin AUC 5-6 plus pemetrexed 500 mg/m² IV every 21 days for 4 cycles followed by maintenance pemetrexed (500 mg/m²) every 21 days until disease progression according to RECIST 1.1 (confirmed by BIRC) or unacceptable toxicity
	Notes		Treated beyond progression if patients continued to derive investigator-assessed clinical benefit Ceritinib patients were allowed a maximum of three dose reductions (150 mg per reduction to 300 mg/day) Chemotherapy patients (n=80) were crossed over to ceritinib when they had BIRC-confirmed, RECIST-defined progressive disease [27]
Endpoints and definitions	Progression-free survival (primary endpoint)	PFS	Time from date of randomization first radiologically documented disease progression (as assessed by BIRC per RECIST 1.1) or death by any cause (33 months)
	Overall survival (secondary endpoint)	OS	Time from date of randomization to death by any cause (33 months)
	Overall response rate (secondary endpoint)	ORR	Proportion of patients with a best overall response defined as CR or PR (as evaluated by BIRC and by investigator assessment per RECIST 1.1) (33 month)
	Duration of response (secondary endpoint)	DOR	Time from date of first documented CR or PR to first documented disease progression or death by any cause (33 months)
	Time to response (secondary endpoint)	TTR	Time from date of randomization to first documented response (CR or PR) (as assessed by BIRC and investigator) (33 months)
	Overall intracranial response rate (secondary endpoint)	OIRR	Proportion of patients with a best overall confirmed response of CR or PR in the brain per modified RECIST 1.1 as assessed by BIRC neuro-radiologist
	Duration of intracranial response (secondary response)	DOIR	Among patients with confirmed intracranial response (PR or CR), DOIR is defined as the DOR based on target, non-target lesion (and new lesion, if applicable) assessments in the brain and calculated from time of first documented intracranial response (PR or CR) to date of first intracranial PD or death by any cause per modified RECIST 1.1 (33 months)

<table>
<tr><td colspan="5">Title: First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged NSCLC [10, 27, 29]</td></tr>
<tr><td>Study identifier</td><td colspan="4">NCT01828099, CLDK378A2301, EudraCT2013-000319-26, ASCEND-4</td></tr>
<tr><td rowspan="2"></td><td>Intracranial clinical benefit rate (secondary endpoint)</td><td>ICBR</td><td colspan="2">Proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or non-CR/non-PD (for patients with non-measurable disease) or better which lasts for a minimum time duration in the brain per modified RECIST 1.1 as assessed by BIRC neuro-radiologist. ICBR was added as post-hoc analyses to be calculated at 12 weeks, 18 weeks and 24 weeks after randomization among patients with measurable BM at baseline and separately in patients having measurable or non-measurable BM at baseline. (33 months)</td></tr>
<tr><td>Notes</td><td colspan="3">Tumour assessments were conducted at baseline, every 6 weeks after cycle 1 day 1 through month 33, every 9 weeks and at end of treatment. Patients who progressed were followed for survival every 12 weeks until death, loss to follow-up or consent withdrawal</td></tr>
<tr><td>Database lock</td><td colspan="4">Last updated: November 3, 2016</td></tr>
<tr><td colspan="5">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis
ITT: Primary endpoint was BIRC assessed PFS based on all randomly assigned patients (the full analysis set). Efficacy analyses were done based on the full analysis set. All safety analyses were done based on the safety set that included all patients who received at least one dose of study drug.
Given a median PFS of 8 months in chemotherapy patients, a 38% risk reduction in HR was expected with ceritinib. Assuming a HR of 0.62, about 205 PFS events were required for 90% power at a one-sided 2.5% level of significance to reject the null hypothesis using a log-rank test and a two-look group sequential design. Approximately 348 patients were needed for 1:1 randomization.
Interim analysis was planned for the primary endpoint PFS as per BIRC assessment when 72 PFS events of the targeted 205 (35%) PFS events were documented. At interim analysis March 23, 2015, 85 PFS events (41.4%) were observed. OS analyses were to be done if the primary endpoint was statistically significant using a group sequential design with three interim analyses and final analysis at approximately 253 deaths (one-sided 2.5% significance). A Cox regression model stratified by randomization stratification factors was used to estimate the HR, together with 95% CIs based on the Wald test. A stratified log-rank test (randomization stratification factors) was used for treatment comparisons of PFS and OS. The statistical basis for efficacy was the statistical significance (at the 2.5% one-sided level of significance) for PS in favour of ceritinib. Kaplan-Meier was used to analyse time-to-event endpoints.</td></tr>
<tr><td rowspan="4">Analysis population</td><td>Inclusion</td><td colspan="3">✪ Adults (aged ≥18 years) with histologically/cytologically confirmed LA or metastatic non-squamous ALK-rearranged NSCLC assessed by the Ventana anti-ALK (D5F3) IHC test (performed at Novartis designated central laboratory)
✪ Newly diagnosed stage IIIB (non-candidates for definitive multimodality therapy) or stage IV NSCLC or relapsed LA or metastatic NSCLC untreated with any systemic anti-cancer therapy (e.g.. cytotoxic drugs, monoclonal antibody therapy, crizotinib or other ALK inhibitors, or other targeted therapies, either experimental or not), except for neo-adjuvant or adjuvant therapy
✪ Measurable disease as per RECIST 1.1, WHO performance status 0-2
✪ Asymptomatic or neurologically stable BM (≥2 weeks)</td></tr>
<tr><td>Exclusion</td><td colspan="3">✪ Hypersensitivity to any excipients of ceritinib
✪ Hypersensitivity to platinum-containing drugs, pemetrexed or any known excipients of these drugs.
✪ History of interstitial lung disease or pneumonitis, including radiation pneumonitis; carcinomatous meningitis, concurrent malignancy or malignant disease other than NSCLC diagnosed or requiring therapy within the past 3 years (except resected basal cell, squamous cell, or carcinoma in situ); uncontrolled heart disease or cardiac event (within 6 months); impaired gastrointestinal function or gastrointestinal disease that could alter ceritinib absorption.
✪ Thoracic radiotherapy to lung fields ≤4 weeks before starting the study and radiotherapy-related toxicities
✪ Major surgery within 4 weeks before (2 weeks for resection of BM) starting study treatment or recovering from side-effects
✪ Symptomatic CNS metastases, neurologically unstable or requires increasing doses of steroids within the 2 weeks prior to screening</td></tr>
<tr><td>Characteristics</td><td>Ceritinib
(n = 189)</td><td>Chemotherapy
(n = 187)</td><td>All patients
(n = 376)</td></tr>
<tr><td>Median age, years (range)</td><td>55 (22–81)</td><td>54 (22–80)</td><td>54 (22–81)</td></tr>
</table>

Title: First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged NSCLC [10, 27, 29]				
Study identifier	NCT01828099, CLDK378A2301, EudraCT2013-000319-26, ASCEND-4			
Analysis population *(continuation)*	Male sex (%)	87 (46)	73 (39)	160 (43)
	Race Asian Caucasian Other	 76 (40) 104 (55) 9 (5)	 82 (44) 98 (52) 7 (4)	 158 (42) 202 (54) 16 (4)
	WHO PS 0 1 2	 69 (37) 107 (57) 13 (7)	 70 (37) 105 (56) 11 (6)	 139 (37) 212 (56) 24 (6)
	Smoking history Current smoker Ex-smoker Never smoked	 15 (8) 66 (35) 108 (57)	 15 (8) 50 (27) 122 (65)	 30 (8) 116 (31) 230 (61)
	Histology/cytology, n (%) Adenocarcinoma	 180 (95)	 183 (98)	 363 (97)
	Stage at entry, n (%) LA stage IIIb Metastatic stage IV	 9 (5) 180 (95)	 5 (3) 182 (97)	 14 (4) 363 (96)
	Metastatic site Bone Brain Liver	 77 (41) 59 (31) 34 (18)	 80 (43) 62 (33) 39 (21)	 157 (42) 121 (32) 73 (19)
	Previous therapy Surgery Radiotherapy Brain radiotherapy BR to randomization ≤3 months	 44 (23) 37 (20) 24 (13) 22/24 (92)	 43 (23) 40 (21) 26 (14) 23/26 (89)	 NR 77 (21) 50 (13) 45/50 (90)
	Chemotherapy Adjuvant Neoadjuvant	 10 (5) 0	 7 (4) 2 (1)	 17 (5) 2 (1)
	Prior regimens of chemo-therapy 1	 10 (5)	 9 (5)	 19 (5)

Abbreviations: AE = adverse events, ALK = anaplastic lymphoma kinase; BIRC = blinded independent review committee, BM = brain metastases, BR = brain radiotherapy, CNS = central nervous system, CR = complete response, CTDAE = Common Terminology Criteria for Adverse Events, DCR = disease control rate, DOIR = duration of intracranial response, DOR = duration of response, ET = extension treatment, HR = hazard ratio, ICBR = intracranial clinical benefit rate, IDCR = intracranial disease control rate, IHC = immunohistochemistry, IV = intravenous, LA = locally advanced, NR = not reported, NSCLC = non-small cell lung cancer, OIRR = overall intracranial response rate; ORR = overall response rate, OS = overall survival; PD = progression of disease, PFS = progression-free survival, PR = partial response, PROs = patient reported outcomes, PS = performance status, RECIST = Response Evaluation Criteria in Solid Tumours , SD = stable disease, TTR = time to response

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomized controlled trials) [33]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: 1:1 ceritinib vs IV chemotherapy via interactive response technology; stratified by WHO performance status (0 vs 1-2), previous neoadjuvant or adjuvant chemotherapy (yes vs no), and BM as per investigators' assessment at screening (present vs absent)		unclear
Adequate allocation concealment		unclear
Blinding	**Patient:** open-label, patients unmasked to treatment assignment	yes
	Treating Physician: open-label, investigators were unmasked to treatment assignment	yes
	Outcome assessment: open-label, tumour response assessed by investigator and BIRC; intracranial response assessed based on images collected for the BIRC by and independent central neuro-radiologist (from BIRC) who was masked to treatment; sponsor personnel remained masked until database lock for primary analysis (except to view individual patient data on case report forms for pharmacokinetics data, study drug dose and concomitant medications)	no
Selective outcome reporting unlikely: outcomes reported as specified in protocol; withdrawals and drop-outs reported		no
No other aspects which increase the risk of bias: Industry funded the study, assisted with study design, contributed to data interpretation, writing, reviewing, revising report, medical writer employed by the funder.		high
Risk of bias – study level		high

Abbreviations: BIRC = blinded independent review committee, BM = brain metastases